ADVANCES IN SOCIAL COGNITION ASSESSMENT AND INTERVENTION IN AUTISM SPECTRUM DISORDER

EDITED BY: Soumeyya Halayem, Isabelle Reine Amado, Asma Bouden and Bennett Leventhal

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ADVANCES IN SOCIAL COGNITION ASSESSMENT AND INTERVENTION IN AUTISM SPECTRUM DISORDER

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Editorial: Advances in social cognition assessment and intervention in autism spectrum disorder

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Editorial on the Research Topic
Advances in social cognition assessment and intervention in autism spectrum disorder

Social cognition (SC) refers to all cognitive processes and skills involved in social interactions, that needs to be engaged in a perpetual changing environment. SC encompasses several domains: theory of mind (ToM), facial emotions processing, empathy, emotional regulation, and attributional style etc. Numerous are altered in patients suffering from autism spectrum disorders (ASD) resulting, in addition, or in combination with ASD core symptoms, as it will be discussed in this Research Topic, significant social impairments. These latter needs better assessment, new theoretical approaches as well as innovative interventions. Since 30 years, tools of assessment were created and adapted to cultural characteristics. Progressively, SC has been a crucial therapeutic target for this population leading to the development of therapies using technological advances. Interventions are now available with encouraging results that require confirmation. The goal of this Research Topic was to improve our understanding of SC deficits in people suffering from ASD and search for new methods of assessment. Relevant empirical and theoretical articles were selected. Subtopics include assessments considering assessment, contribution of new technologies in therapeutic interventions, and etiopathology of SC in ASD.

Assessment

New SC assessment tools and correlations with cognitive functioning

Three articles present new tools for assessment of SC. Two of them deal with the validation of a new facial emotion recognition tool for children, developed by a Tunisian team whose originality consists in the use of photos of three levels of difficulty and videos of the basic emotions of Ekman expressed by actors of different gender and age. The first reliability study (Taamallah et al.) showed good internal consistency for each subtest and normative references for typically developing (TD) children of 7–12 years. The second one (Jelili et al.) confirmed the clinical validation of the tool in children with high functioning autism.

Morel-Kohlmeyer et al. presented a new battery for adults SC evaluation named "ClaCoS," which allows testing: emotion recognition, ToM, attributional style, and social perception and knowledge; but also subjective complaints in SC. In this study, the ASD group showed deficits in all domains of SC and reported greater complaints regarding their social abilities, that were correlated to neuropsychological performances. Along the same lines, Peñuelas-Calvo et al. focused on the links between intelligence quotient using the WISC and Reading The Mind in the Eyes Test performances' in children and adolescents with Asperger's syndrome. Intelligence quotient and age were positively correlated to the performance in ToM.

Briot et al., systematically reviewed new technologies for the assessment of emotional facial expression in people with ASD through 20 studies. Authors found discrepancy between the expressed emotions and the expected ones with low coordination of facial muscles. The hypothesis of a poor correspondence between mental representations and facial emotion expressions underlined by an ≪ alteration of sensory-motor neural circuit involved in the processing of information ≫ was raised.

Eye attention to social stimuli

Four studies looked at the assessment of social attention through eye-tracking procedures. Bochet et al. explored the processing of emotional and neutral faces using an eye-tracking paradigm with pre-school aged children with ASD and age-matched TD children. Participants with ASD make fewer fixations to emotional faces than their TD peers, and equivalent duration of first fixation on emotional faces to that on neutral faces. Participants also demonstrated neither habituation nor increased interest in the changing emotional expressions over the course of the task. These results confirm literature reports of a lesser interest to emotional faces and a lack of sensitivity to changes in facial expression in children with ASD.

Mouga et al. compared visual attention to faces vs. objects, in ecological situations using three tasks from the ADOS. Participants with ASD's focused less and shorter on faces and their performances became similar to TD children when they were asked to tell a story from a photo. This study has a therapeutic interest in remedying deficits in spontaneous social attention.

Wang et al. used a preferential looking paradigm using eye gaze tracking devices when presenting to children with ASD at the same time two stimuli: a photo of eyes and a photo of objects alternating with a high attention attracting object in participants diagnosed with ASD (vehicle) vs. a low one (vegetable). The results showed that preference and interest in the eyes decreased among ASD patients' when the competitive stimulus was a high attracting object. This study has interesting therapeutic implications for improving eye contact in this population by using objects as stimuli to motivate joint attention.

The last two studies by Ioannou et al. compared social visual attention in four groups: patients with ASD, ASD and ADHD, ADHD, and a neurotypical group using a static medium with real social situations of low and high complexity. Authors found a significant lower duration of face fixation with a lengthening of the time of first fixation in the ASD-ADHD vs. the ASD group. The duration of face fixation was reduced in ASD vs. TD, especially for scenes with high social complexity. Regarding nonsocial clues, Iaonnou et al. found that there was no difference between the groups.

These two studies raise the hypothesis of possible biomarkers that can distinguish the different conditions (ASD, ADHD, ASD with ADHD and TD) with an interest for early diagnosis and specific therapeutic interventions.

Interventions in SC

The first article made a link between assessment and therapeutic effects on SC in ASD. In their perspective article, Yamamoto et al. examined the usefulness of visualizing face-to-face interaction in social skills learning scenes for children with ASD using a business microscope that can qualify and visualize face-to-face interactions automatically. This device's use may provide an objective measurement that complements the observer's evaluation in intervention's validation programs.

Dandil et al. conducted a synthesis of all studies of cognitive remediation interventions for adolescents and adults with ASD using the PRISMA statement. They concluded, on 13 studies, that cognitive remediation therapies and interventions could potentially be effective in improving SC and functioning. However, methodological challenges were a source of heterogeneity. This calls for double-blind randomized studies of longer duration, assessing the effect size and generalization of improvement in SC as well as social functioning and the possible linked effects between these latter.

Herbrecht et al. studied the two-years outcomes of a short-term, highly, intensive early 18-day family intervention in a case series study without control group. The therapy consists of up to 6 h of play sessions per day involving the family. Parents are intensively coached while playing with their child and while observing their child's behavior *via* video observation of play sessions. Authors found, for 32 children with a mean age of 44 months, presenting moderate to severe ASD, that ADOS total scores decreased significantly from baseline to 2-year follow-up. The DD-C-GAS, fullfilled by parents, showed significant improvements on all subdomains in areas of everyday functioning. There was a significant relationship between parents' treatment adherence and ADOS scores. These results invite to strengthen early intensive approaches within randomized studies.

In a perspective article, Bochet et al. brought some light on their clinical experience to adapt the PEERS© model for adolescents into French after reviewing its limitations and its positive aspects in generalizing SC competencies, when involving parents. Indeed, follow-up measures over up to 5 years have shown improved SC. This maintenance could be explained by the participation of parents as "social coaches" and needs randomized double blind studies for confirmation.

Dubreucq and Dubreucq conducted a systematic research following PRISMA guidelines, on autistic women's needs for care relating to romantic relationships and reproductive health. They found eight studies on interventions addressing the first domain and no study on reproductive health or parenting. Most interventions did not deal with gender-sensitive content though women with ASD face challenges in theses domains.

Fu et al. studied the predictors of change in a 12 weeks play-based communication and behavior intervention for 70 13–30-month-old toddlers at high-risk for ASD. Hierarchical regression analysis concluded that parenting stress, level of completion of training at home and mother-child dyadic synchrony were crucial factors in predicting the intervention's efficacy. These factors are working levers to improve the prognosis of early interventions involving parents.

In their systemic review, including 39 studies (N = 1,774 participants), Mayer-Benarous et al. explored music therapy for children with ASD and/or other neurodevelopmental disorders. Positive effects of educational music therapy on patients with ASD was reported in most controlled studies on speech production and of improvisational music therapy on social functioning. Authors concluded that improvisational music therapy appears relevant for individuals with both ASD and intellectual disability.

Etiopathology

Networks

Sato et al., using fMRI, showed that modulation from the amygdala to the neocortex during observation of dynamic facial expressions is reduced in an ASD group. Based on these findings and literature review, they hypothesized that weak modulation from the amygdala to the neocortex—through which emotion modulates various types of perceptual, cognitive, and motor processing functions—underlies the social atypicalities in people with ASD.

Pino et al. aimed to map the network of SC domains in 76 children with ASD matched for verbal age to TD children through graph analysis using three measures: Eyes Task-Simplified, Comic Strip Task and Social Information Processing Interview (SIPI). TD children exhibited a SC network characterized by a single domain, with nodes of higher closeness and strength compared to the ASD network. For instance, the node related to encoding in the SIPI was not connected in the ASD network. This suggests that people with ASD can encode social information, but that this latter would not be utilized by the entire network.

Looking for SC related biomarkers of ASD

Based on the finding that people with ASD show an atypical pattern of autonomic nervous system activation (ANS) induced by psychosocial stimulation, Doi et al. proposed a new assessment tool to evaluate the risk of ASD by measuring ANS activation in response to emotional stimulation. Authors video-recorded faces of 17 and 21 adult males with and without ASD while watching emotion-inducing video clips. Though the performance was modest, the gradient succeeded in classifying people with and without ASD. Taking into consideration the fact that the study recruited only high-functioning adults who may use compensatory strategies, ASD screening by measurement of pulse wave could be promising to evaluate ASD risk.

Bearing in mind that it is generally challenging to assess ASD individuals using task-based and fMRI paradigms, Yao et al. reviewed neuroimaging studies examining inter-hemispheric resting state functional connectivity (rsFC) abnormities. There are converging findings on reduced inter-hemispheric rsFC in brain networks particularly in posterior hubs and in the corpus callosum. Thus, the strength of inter-hemispheric rsFC may be a promising biomarker for assisting in ASD diagnosis.

All these results remain in the field of research, as biomarkers in functional imaging and ANS assessment are within the reach of few clinicians.

Unified theories

Crespi developed a theory unifying ASD semiology and etiology through pattern concept. Pattern is defined as ≪ a repeated configuration, with recurring, ordered, or predictable characteristics, and discernable interrelationships of components ≫. This concept is related to information processing, including ≪ sensory input, entropy, and predictability ≫. ASD involves enhanced ≪ pattern perception, recognition, maintenance, generation, processing, and seeking ≫. Restricted interests and repetitive behavior result from increased and imbalanced pattern-related perception and cognition, and social deficits result in part from the lack of clear pattern in social interactions, with non-pattern avoidance of social interaction, combined with the interference of restricted interests with social development. This approach has strong implications for research as well as personalized therapy.

Conclusion

This Research Topic helps highlighting new tools of SC assessment, with spot on facial emotion recognition, and deficits of interest to facial stimuli in ASD population. FMRI, ANS and eye tracking specificities were proposed as biomarkers calling to confirmatory works studying correlations with clinical phenotypes. The link between symptoms of ASD and SC deficits in the light of pattern conception may be an interesting framework to develop research approaches.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

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Short-Term and Highly Intensive Early Intervention FIAS: Two-Year Outcome Results and Factors of Influence

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Background: Comprehensive behaviorally or developmentally based early intervention programs have been shown to be effective in improving cognitive, social communicative, and adaptive skills of children with autism spectrum disorder (ASD). Besides the definition of relevant outcome predictors, the question of whether early intensive intervention positively changes core autism symptoms in children, as well as their long-term outcome, is an important issue for current research. The primary objective of the current study was to examine whether symptomatic and behavioral changes in children up to 4.5 years with ASD were sustained one and two years after an initial 18 days of intensive FIAS (Frühintervention bei autistischen Störungen) intervention.

Methods: We analyzed the data of 32 young children with moderately severe to severe ASD who had been treated at the FIAS center between January 2011 and July 2017 and who had completed their 2-year follow-up in summer 2019.

Results: ADOS total scores decreased significantly from baseline to the 1-year follow-up and from baseline to the 2-year follow-up ($p < 0.01$), with the most prominent change being from baseline to 2-year follow-up. The DD-C-GAS, a global scale used to assess four areas of everyday functioning, showed highly significant improvements on all subdomains. We found mostly significant correlations between results on both rating instruments at all time points, yet mostly no meaningful correlation between their changes over time. There was a close and statistically significant relationship between parents' treatment adherence and ADOS scores, indicating that the better parents' treatment adherence, the lower the children scored on the ADOS at 1- and 2-year follow-up. Overall, improvement on both scales was virtually independent of age and autism symptom severity at baseline, suggesting that older (>43 months) and more severely affected children (ADOS total score >20) may benefit from the FIAS intervention to the same extent as younger children do.

Conclusions: The results of the study indicate that the FIAS approach of providing an initial highly intensive 18-day intervention period, followed by 2 years of less intensive

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follow-up care had an impact on the core autism symptoms as well as the adaptive functioning of children with ASD.

Keywords: autism spectrum disorder, early intervention, FIAS, outcome, autism symptom severity

INTRODUCTION

Since 2011, we have applied FIAS (Frühintervention bei autistischen Störungen), a highly intensive treatment method derived from the Mifne approach (1), to young children with moderately severe to severe autism spectrum disorder (ASD). FIAS is a play-based early intervention used with children aged up to 5 years. Its aim is to encourage children to get involved in social interactions by increasing their shared enjoyment and social motivation. A distinctive feature of FIAS is an initial 18-day period of very intensive treatment of the child, together with his/her core family, in a specialized unit, followed by continued, professionally supervised, play interaction between the parents and the child in the family home.

Evidence from early intensive intervention research points to the effectiveness of comprehensive, behaviorally or developmentally based intervention programs on cognitive, social communication, and language functioning as well as adaptive skills (2–4). Outcomes across different studies have often shown significant treatment effects, albeit with usually small effect sizes (5); moreover, outcomes have generally been found to vary across studies, reflecting the heterogeneity of patient profiles, specific treatment approaches, and the diversity of outcome measures used (6). Most early intervention studies published in recent years have found pre-treatment intellectual ability, as well as language and adaptive behavior abilities, to be the most reliable predictors of positive outcomes (7). Conversely, the severity of autism symptoms and age at the start of intervention have shown rather inconsistent results in terms of outcome predictability (8). However, there is some evidence that interventions targeted at improving social communication may be most effective at around the age of 3-1/2 years (3).

The duration of most early interventions in the studies that have been published varies from between 1 and 2 years of intensive intervention. However, there is insufficient evidence concerning the role of intervention duration (4). Fossum et al. (9) showed that, standard measures of pre-treatment cognitive and language abilities aside, positive affect and level of appropriate toy contact significantly influenced children's expressive language outcome after one year of a community "Pivotal Response Treatment" program. In addition, less social avoidance and fewer repetitive vocalizations were among the larger benefits of the intervention. Variability in intervention outcomes has been repeatedly shown across different intervention approaches; and yet the sources of this variability are unclear, and whether and which developmental profiles benefit most from which kind of early intervention approach remain crucial questions (3, 9). In addition to identifying relevant outcome predictors, the question of whether early intensive intervention positively changes the long-term outcomes for children is another important issue in current research, as most studies have focused on outcomes immediately following the end of the intervention. Magiati et al. (4), who summarized a number of reviews and meta-analyses, concluded that children continue to make progress in terms of standard measures of cognitive and adaptive behavior after the end of an intensive intervention period. However, they also suggested that such gains often decrease during follow-up and argued that there is currently no evidence to suggest that early interventions reduce the need for special support with respect to long-term outcomes.

In a previous study (10) we reported positive short-term changes both in specific autism-related behaviors and in everyday functioning domains in 40 children after an 18-day period of FIAS early intervention. Changes in autism symptoms were captured by the Autism Behavior Coding System (ABCS), a video-based instrument to assess core autism symptoms during therapist-child interaction. We found the most relevant improvement in social cooperative behavior, expression of wishes, and eye contact. Additionally, the study reported on highly significant improvement of everyday functioning domains on the Developmental Disorders–Child–Global Assessment Scale (DD-C-GAS).

The present study set out to examine whether an early intensive FIAS intervention showed effects 1 and 2 years after the initial intervention period, by considering the following questions: (a) are the effects of FIAS interventions reflected in independently rated standard assessments of autism symptoms [(using the Autism Disorder Observation Scale or ADOS-2) (11); German version (12)] at 1 and 2 years after intervention? (b) is there a relationship between age and autism symptom severity at baseline and ADOS score changes after 1 and 2 years? (c) to what extent are the effects of FIAS interventions reflected in assessments made by clinicians using the DD-C-GAS? (d) what is the relationship between the ADOS and DD-C-GAS results? (e) is there a relationship between either the ADOS or DD-C-GAS results and parents' treatment adherence during the 2 years of follow-up care?

MATERIALS AND METHODS

The FIAS Approach

FIAS treatment consists of an initial 18-day intervention period with the core family at the FIAS center involving up to 6 h of play sessions per day with alternating therapists. Parents are intensively coached while playing with their child themselves and while observing their child's behavior *via* direct and video observation of therapist–child interactions during play sessions.

Sessions with the child are relation-oriented and include exploration, imitation, functional, and symbolic play as well as everyday activities as eating, clothing, or hygiene. Main intervention targets are sensory perception and processing, emotion and behavioral regulation, and development of autonomy. Parents are taught how to motivate their child to engage in social interaction and play without directly prompting or discouraging specific behaviors, and how to interpret their child's emotional expressions in order to facilitate reciprocal interactions. Therapists also teach the parents how to transfer these skills to their home situation. Instruction of parents also includes psychoeducation, training of behavioral observation focusing on social signals, video analysis of play interactions, and hands-on coaching regarding play and everyday activities.

The initial intervention period is followed by 2 years of follow-up care by a FIAS therapist (8 h per month on average), during which the therapist provides regular coaching, analyzes the parents' play interventions at home, and fosters exchange with other institutions involved, i.e. kindergarten, in order to follow the child's development. In contrast with other early intervention programs that usually last from 1 to 2 years, FIAS focuses on a very high-intensity treatment period of about 100 h during the first 18 days, followed by less intensive follow-up care. During the follow-up period, the parents are encouraged to provide their child with play sessions of 1 to 2 h of per day in order to consolidate and amplify the gains made during the initial period [for details, see Herbrecht et al. (13)].

FIAS demands high motivation and commitment from parents during both the initial 18-day period at the treatment center and the continuing regular play sessions at home. In this respect, families participating in the FIAS treatment program represent a "positive selection"; not all mothers and fathers of children with ASD are able and/or willing to stay away from home and to suspend their professional and other customary activities for 18 days and nights in order to spend up to 6 h per day, including weekends, in the confines of the FIAS center. The particular conditions of FIAS also mean that it is not possible to include matched control groups receiving some form of sham treatment. Consequently, properly controlled clinical trials of FIAS treatment are not feasible.

Participants

Between January 2011 and November 2018, 62 young children with autism according to DSM-IV/DSM-5 (14, 15) criteria were treated at the FIAS intervention center in Muttenz, Switzerland. By the end of June 2019, 32 of these children had full, 2-year follow-up data and these were the data used in the current analysis. The 32 children represent a sub-sample of the 40 patients whose 18-day outcomes have been described in a previous paper (Herbrecht et al., 2019). Three children having been treated at the FIAS center in 2011 had only 1 year of follow-up care, but still got their 2-year assessment. Diagnosis of ASD at baseline was based on direct observation and assessment by expert clinicians not involved in the subsequent interventions, using the Autism Diagnostic Observation Schedule (ADOS/ADOS-2 Module 1) and the Autism Diagnostic Interview-Revised ((ADI-R) (16); German version (17). None of the children had additional relevant neurological or somatic problems. All the families were currently living in Switzerland but were of various nationalities. All parents spoke either German or English. Parents of all children included in the study gave their written informed consent to the anonymized use of their data. During the 2-year follow-up period, according to their age, all children were integrated in regular or special education settings and followed additional occupational or speech therapy sessions.

Measures

Autism Symptoms

The ADOS-2 is a semi-structured, standardized interaction and observation tool that assesses social communication and interaction as well as restricted and repetitive behaviors during child–adult interaction (11, 12). Different modules are administered depending on expressive verbal language ability and age. ADOS Module 1 for pre-verbal- to single-word-using children was used to assess all children at baseline. For the 1-year assessments, Module 1 was used in most cases; however, for one child Module 2, which requires simple phrase speech, was more appropriate. At the 2-year assessments, four children switched to ADOS Module 2, while one child (the one assessed using ADOS Module 2 at the 1-year assessment) switched to Module 3 which requires fluent speech.

The ADOS-2 provides a total score resulting from coding behaviors during the ADOS assessment according to a strict algorithm. For most assessments, the ADOS-2 version was used. If the prior ADOS-version had been used (i.e. baseline assessments before 2013), we calculated the updated ADOS-2 algorithms for comparability of all ADOS results. The ADOS-2 severity score is intended to allow comparisons across different ages, language abilities, and modules. In this study, both the ADOS total and severity scores are reported. In addition, assessments of autism spectrum-related symptoms provided a further categorization in terms of symptom levels: "high," "moderate," "low," or "minimal-to-no-evidence."

Level of Functioning

As in our previous studies (10, 18), we used an ASD-adapted version of the Children's Global Assessment Scale, the DD-C-GAS (Developmental Disorders–Child–Global Assessment Scale) (19); German translation (20), as the reference measure of children's level of functioning in daily life. The DD-C-GAS comprises 10 levels of functioning, using a 0 to 100 scale in four domains: everyday functioning, intellectual performance, communication, and social behavior. Scores below 70 indicate that a child has important special needs in that particular domain. DD-C-GAS assessments were made by clinicians, based on parents' observations. In the current study, we used the DD-C-GAS as an independent instrument to assess changes in the four domains after the FIAS intervention. We also explored whether changes on this instrument corresponded to changes in ADOS scores. The DD-C-GAS ratings were made at baseline, directly after the 18-day intensive intervention period, at 1-year follow-up, and at 2-year follow-up. As this instrument was not used for all children (see below), the total number of DD-C-GAS data is smaller than the one of the ADOS.

Treatment Adherence

Adherence to treatment during follow-up intervention is crucial when non-clinicians are mediators of the intervention (3). During the 2 years of FIAS follow-up care, parents were regularly encouraged to provide play sessions of at least 1 to 2 h duration per day. To date, few studies have examined therapists' persistence in training parents or other intervention mediators, or parents' fidelity to the intervention. As follow-up care in the FIAS approach is notably long compared with the shorter, initial high-intensity period, we considered treatment fidelity during the 2 years of follow-up to be a relevant factor when interpreting the follow-up results. As part of FIAS procedures, the follow-up therapists allocated to each family were requested to provide an annual global judgment of parents' treatment adherence (using the four categories of minimal, low, sufficient, and excellent), taking into consideration the parents' observed and reported adherence to the therapists' inputs and their active co-operation in implementing the learned strategies during follow-up.

Procedures

Assessments were made at baseline and at 1 and 2 years after the initial intensive period (hereafter referred to as baseline, 1-year, and 2-year follow-up assessments), the 2-year time point coinciding with the end of the FIAS follow-up care. Autism symptom levels and follow-up levels of functioning were assessed by clinical psychologists at the special Autism Unit of the Child and Adolescent Psychiatry University Department in Basel. None of the evaluators was involved in the FIAS intervention. Baseline functioning levels were assessed by the lead FIAS therapist working with each child. Treatment adherence was evaluated by the follow-up reference therapist assigned to each family (see **Table 1** for an overview of the evaluation procedure).

Statistical Analyses

Data analysis was performed using non-parametric methods. Behavioral changes assessed by the ADOS and DD-C-GAS were evaluated using Friedman's rank sum test for repeated measurements and Wilcoxon signed rank tests for comparisons between two time points. If the Friedman test indicated significance, Wilcoxon signed rank tests with adjustment for multiple testing by Bonferroni–Holm were performed between each pair of two time points. The outcome measures were changes in ADOS total and severity scores, the DD-C-GAS subdomain scores, autism symptom level, and treatment adherence scores. In order to evaluate the impact of either age or autism symptom severity at baseline on outcome parameters, analyses of change were performed by age category (<=43 months; >43 months) and baseline ADOS total score category (</=20; >20) respectively. The extent of relationships between the DD-C-GAS findings and the ADOS scores at the three time points, as well as between changes from baseline to 1- and 2-year follow-ups for both instruments and treatment adherence scores were assessed by Spearman's rank correlation coefficients. The analysis was based on values as observed, except for one missing Year 1 ADOS observation which was replaced by the average of baseline and Year 2 values. The sensitivity analysis with imputed missing DD-C-GAS observations showed no relevant differences.

TABLE 1 | Evaluation procedures.

Assessment domain and instruments		Time point			Evaluator
		Base-line	1-year follow-up	2-year follow-up	
Autism symptoms	ADOS TS, SS	X	X	X	FIAS independent clinical psychologists
Level of functioning	DD-C-GAS	X			FIAS reference therapist
Level of functioning	DD-C-GAS		X	X	FIAS independent clinical psychologists
Treatment adherence			X	X	FIAS reference follow-up therapist

ADOS TS, ADOS Total Score; ADOS SS, ADOS Severity Score.

RESULTS

Background and Demographic Data

We analyzed the data of 32 children (28 males, 4 females) who had been treated at the FIAS center between January 2011 and July 2017 and who had completed their 2-year follow-up assessment. The children's mean age when the FIAS intervention started was 44.0 ± 8.3 months.

The mean ADOS total score at baseline was 20.0 ± 3.46, while the mean severity score was 7.0 ± 1.43 indicating moderate to high average levels of autism-related symptoms. Mean DD-C-GAS subdomain scores at baseline were similar for self-care (30.6 ± 14.21) and communication (31.0 ± 12.05), slightly lower for social behavior (27.0 ± 10.44), and higher for intellectual skills (42.1 ± 16.17). Scores at baseline indicated significant special needs in all four domains, especially in the areas of social behavior and communication.

After splitting the group into two according to median age (43 months), no relevant age-related differences were observed for any of the ADOS or DD-C-GAS variables at baseline (Mann-Whitney-U-test, data not shown), although ADOS severity scores were slightly higher in the older age group than in the younger group (7.4 ± 1.35 *vs.* 6.7 ± 1.45 respectively). We observed no differences in baseline scores between males and females. Because of the small number of females, we did not retain the sex category for analyzing changes in outcome parameters (see **Table 2**).

Core Autism Symptom Outcomes

ADOS Findings by Time Point and Changes From Baseline

Mean ADOS total scores decreased from 20.0 ± 3.46 at baseline to 18.5 ± 5.91 at 1-year follow-up and statistically significantly to 17.1 ± 6.16 at 2-year follow-up ($p = 0.031$). Mean severity scores decreased numerically from 7.0 ± 1.43 at baseline to 6.8 ± 2.01 at

TABLE 2 | Summary statistics of background and demographic data for all participants and by subgroups.

Parameter		Age		Sex		Baseline ADOS Total Score	
	All N = 32	≤43 mo. N = 17	>43 mo. N = 15	Male N = 28	Female N = 4	≤20 N = 17	>20 N = 15
Age							
mean (std)	44.0 (8.3)	37.9 (4.98)	50.9 (5.31)	44.1 (8.88)	43.5 (1.29)	42.5 (8.84)	45.8 (7.55)
med	43.0	39.0	48.0	42.5	43.5	42	44
min–max	25–60	25 –43	44–60	25–60	42–45	25–59	32–60
Age category n (%)							
≤43 mo.	17 (53.1)	–	–	15 (53.6)	2 (50.0)	10 (58.8)	7 (46.7)
>43 mo.	15 (46.9)	–	–	13 (46.4)	2 (50.0)	7 (41.2)	8 (53.3)
ADOS Total score							
mean (std)	20 (3.46)	19.4 (3.61)	20.7 (3.26)	20 (3.66)	19.8 (1.89)	17.1 (2.31)	22.9 (1.36)
med	20.5	20.0	22.0	20.5	20.5	17.0	23.0
min–max	11–26	11–24	16–26	11–26	17–21	11–20	21–26
ADOS Severity score							
mean (std)	7 (1.43)	6.7 (1.45)	7.4 (1.35)	7.1 (1.5)	6.5 (0.58)	5.8 (0.54)	8.3 (0.86)
med	6.5	6.0	8.0	6.5	6.5	6.0	8.0
min–max	4–10	4–9	6–10	4–10	6–7	4–6	7–10
		Age		**Sex**		**Baseline ADOS Total Score**	
	All N = 31	**≤43 mo. N = 17**	**>43 mo. N = 14**	**Male N = 27**	**Female N = 4**	**≤20 N = 17**	**>20 N = 14**
DD-C-GAS Self-care							
mean (std)	30.6 (14.21)	30.6 (15.08)	30.6 (13.65)	29.7 (11.34)	36.3 (29.26)	30.9 (12.55)	30.1 (16.49)
med	25.0	25.0	25.5	25.0	35.0	31.0	23.0
min–max	5–70	5–70	17–55	17–55	5–70	5–55	17–70
DD-C-GAS Communication							
mean (std)	31.0 (12.05)	32.5 (13.89)	29.1 (9.53)	31.3 (10.88)	29.3 (20.55)	32.1 (13.15)	29.7 (10.92)
med	29.0	32.0	28.5	29.0	31.0	30.0	25.0
min–max	5–55	5–55	17–51	17–55	5–50	5–51	17–55
DD-C-GAS Social behavior							
mean (std)	27.0 (10.44)	27.8 (11.74)	26.1 (8.96)	27.0 (9.43)	27.0 (17.87)	27.2 (12.28)	26.8 (8.11)
med	25.0	31.0	25.0	25.0	30.0	23.0	25.0
min–max	5–50	5–50	13–43	13–50	5–43	5–50	13–40
DD-C-GAS Intellectual skills							
mean (std)	42.1 (16.17)	39.1 (17.91)	45.7 (13.52)	42.2 (12.69)	41.8 (34.9)	44.7 (18.73)	38.9 (12.33)
med	41.0	35.0	43.0	41.0	40.5	50.0	38.5
min–max	5–81	5–65	21–81	19–65	5–81	5–81	21–60

No relevant group differences were observed for any of the ADOS or DD-C-GAS variables (Mann-Whitney-U test), except for the ADOS scores, as expected.

1-year follow-up and to 6.4 ± 1.83 at 2-year follow-up (see **Table 3**). The possible impact of age, total ADOS scores, and ADOS severity scores at baseline were estimated by comparing subgroups above and below the respective median values: no statistically significant or relevant subgroup differences were noted for any of these baseline variables (data not shown).

Change in Autism Symptom Level

In addition to ADOS total and severity scores, level of autism spectrum-related symptoms could be further categorized (Lord et al., 2012): "high" encompasses severity scores from 8 to 10; "moderate," scores from 5 to 7; "low," scores from 3 to 4; and "minimal-to-no-evidence," scores of less than 3. According to

TABLE 3 | Summary statistics for ADOS total and severity score by time point and change from baseline, and results of Friedman test and pairwise comparisons (N = 32).

				Friedman			Pairwise comparisons°	
	Baseline	Year 1	Year 2	Test p-value	Bsl-Year 1	Bsl-Year 2	Bsl-Year 1 p-value	Bsl-Year 2 p-value
ADOS Total score								
mean (std)	20 (3.46)	18.5 (5.91)	17.1 (6.16)	0.031*	1.5 (4.89)	2.9 (4.92)	0.171	0.006**
min–max	11–26	6–26	6–26		–6–13	–8–16		
ADOS Severity score								
mean (std)	7 (1.43)	6.8 (2.01)	6.4 (1.83)	0.236	0.2 (1.95)	0.6 (1.93)	n.a.	n.a.
min–max	4–10	3–10	2–10		–3–3	–5–5		

**p-value < 0.05; **p-value < 0.01. The significance level = 0.05.; °p-value from pairwise comparisons following significant Friedman test (Wilcoxon signed rank test adjusted by the Bonferroni–Holm correction for multiple testing. Bsl, baseline; n.a., not applicable.*

this categorization, in the present study 13 children had "high," 18 had "moderate" and 1 had "low" levels of autism symptoms at baseline. In the older age group the percentage was 53 and 47% for high and moderate autism symptom levels respectively, while in the younger group the respective figures were 30 and 65%. From baseline to 2-year follow-up, all but two children showed no change or a decrease in these levels of autism symptoms: one of these children changed from low to high levels and the other from moderate to high levels of autism symptoms at the 2-year follow-up; 11 children showed a decrease in these levels at the 2-year follow-up: 5 changed from high to moderate, 1 from high to low, 5 changed from moderate to low. We did not observe any other relevant differences by age or ADOS total score category at baseline (see **Table 4**).

Developmental Functioning Outcomes

DD-C-GAS Findings by Time Point and Changes From Baseline

For the analysis of changes from baseline, DD-C-GAS data from 25 children were available for all time points. Seven parents were unable to evaluate the subdomain intellectual level for their child. There were highly statistically significant changes (i.e. improvements) in all four DD-C-GAS domains from baseline to 1-year follow-up, as well as from baseline to 2-year-follow-up (see **Figures 1–4**). DD-C-GAS mean scores increased by an average of about 30 points, with relatively small changes between the 1- and 2-year follow-ups.

At baseline we observed slightly higher median scores in the younger age group compared with the older group for the domains of communication and social behavior. Changes over time were also somewhat greater in the younger age group, except for the domain of communication where changes were greater in the older group. There was a trend towards greater improvement on the DD-C-GAS intellectual skills domain in the lower ADOS total score category at baseline.

DD-C-GAS subdomain scores were highly intercorrelated. We observed moderately strong negative correlations between ADOS total scores and DD-C-GAS subdomain scores at baseline. At 1-year follow-up, there were highly significant negative correlations for all subdomains except self-care. At 2-year follow-up, negative correlations were moderately significant for ADOS total score and all DD-C-GAS subdomain scores (data not shown). In contrast, there were no relevant correlations between the two instruments in terms of change from baseline. Scatterplots of changes in ADOS total as well as ADOS severity

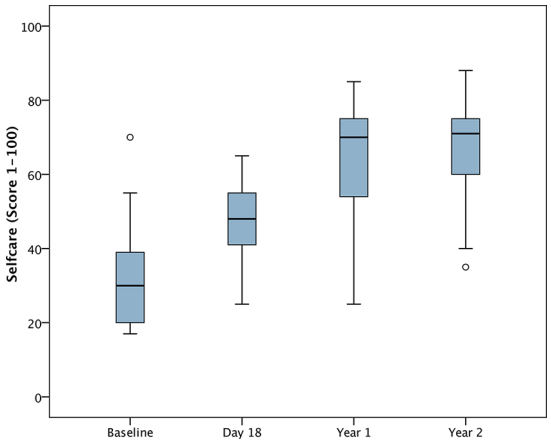

FIGURE 1 | Box plot: DD-C-GAS Self-care (N = 25). Non-parametric repeated measures ANOVA (Friedman test): p = 0.000***. Pairwise comparisons between time points (Wilcoxon signed rank test): p-values adjusted by Bonferroni-Holm were 0.000***, except for comparison Year 1 to Year 2 (p = 0.060).

scores *versus* DD-C-GAS subdomains illustrate the heterogeneity of the individual results (see **Figures 5** and **6**). Nevertheless, the vast majority of data points were consistently found in the upper right quadrant of all the scatterplots, indicating positive changes of varying magnitude in the behavioral and symptomatic areas investigated (DD-C-GAS and ADOS).

Treatment Adherence

Treatment adherence was rated as excellent in 18 of the 32 families at 1-year follow-up and in 14 of 29 families at 2-year follow-up (ratings were not done for three families treated in

TABLE 4 | Changes of ADOS symptom levels from baseline to Year 2.

ADOS symptom level autistic spectrum at baseline		ADOS symptom level autistic spectrum at Year 2		
		High	Moderate	Low
High	13	0	7	6
Moderate	18	5	6	7
Low	1	0	1	0
Total	32	5	14	13

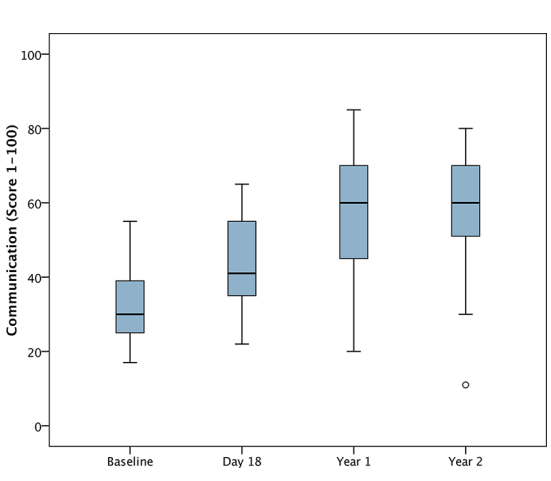

FIGURE 2 | Box plot: DD-C-GAS Communication (N = 25). Non-parametric repeated measures ANOVA (Friedman test): p = 0.000***. Pairwise comparisons between time points (Wilcoxon signed rank test): p-values adjusted by Bonferroni-Holm were 0.000***, except for comparisons Day 18 to Year 1 (p = 0.002**), and Year 1 to Year 2 (p = 0.460).

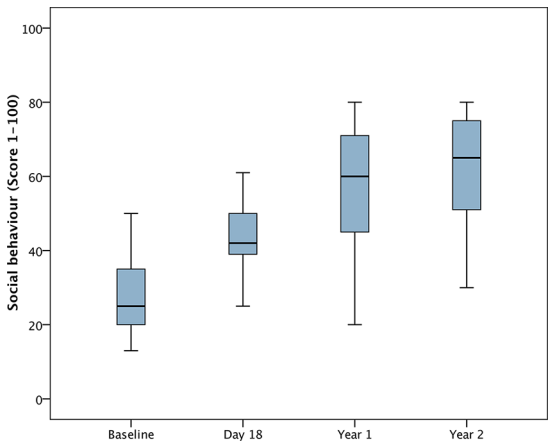

FIGURE 3 | Box plot: DD-C-GAS Social behavior (N = 25). Non-parametric repeated measures ANOVA (Friedman test): p = 0.000***. Pairwise comparisons between time points (Wilcoxon signed rank test): p-values adjusted by Bonferroni–Holm were 0.000***, except for comparison Day 18 to Year 1 (p = 0.002**), Year 1 to Year 2 (p = 0.145).

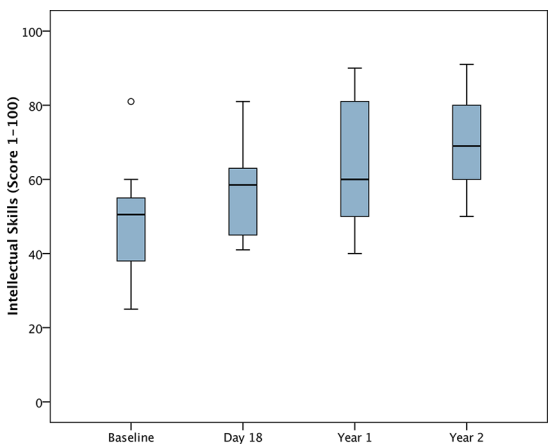

FIGURE 4 | Box plot: DD-C-GAS Intellectual skills—Subjects with all time points (N = 18). Non-parametric repeated measures ANOVA (Friedman test): p = 0.000***. Pairwise comparisons between time points (Wilcoxon signed rank test): p-values adjusted by Bonferroni–Holm were 0.000***for comparison Baseline (Bsl) to Year 2, <0.01** for comparisons Bsl to Day 18 and Year 1, and Day 18 to Year 2, <0.05* for Day 18 to Year 1 and Year 1 to Year 2.

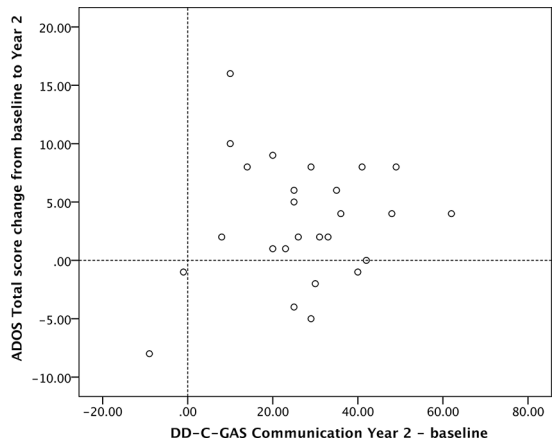

FIGURE 5 | Scatterplot: ADOS Total score change versus DD-C-GAS Communication change (N = 26). Changes for ADOS scores were calculated as differences baseline – Year 2 to present improvements as positive values.

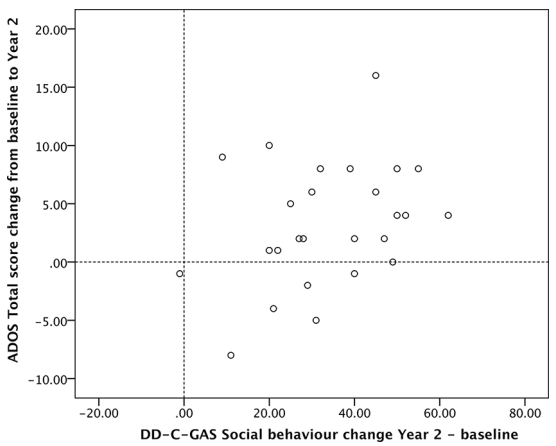

FIGURE 6 | Scatterplot ADOS Total score change versus DD-C-GAS Social behavior change (N = 26). Changes for ADOS scores were calculated as differences baseline – Year 2 to present improvements as positive values.

2011 whose follow-up care lasted one year only). Treatment adherence was rated as being minimal in three families at one-year and in four families at 2-year follow-up. There was a trend towards lower treatment adherence in the older age group compared with the younger age group, and overall, treatment adherence decreased slightly over time in both age groups. When analyzed by ADOS total scores at baseline, treatment adherence was significantly higher in the lower-score group at 1-year follow-up and still so, albeit less prominently, at 2-year follow-up (**Table 5**).

Correlations between treatment adherence and ADOS total scores were statistically significant ($p < 0.01$) at both 1-year and 2-year follow-up ($r = -0.45$, $r = -0.60$). Correlations between treatment adherence and ADOS severity scores were statistically significant ($p < 0.01$) at 2-year follow-up ($r = -0.50$). Significant positive correlations were found between treatment adherence and DD-C-GAS subdomain scores at 1-year follow-up (between 0.41 for intellectual skills, $p < 0.05$; and 0.50 for selfcare, $p < 0.001$). At 2-year follow-up, correlations were mostly low and not significant (see **Table 6**).

TABLE 5 | Summary statistics of treatment adherence findings, by baseline ADOS total score category.

Baseline ADOS Total score category	≤20 N = 16					>20 N = 16				
Treatment adherence	**Minimal**	**Low**	**Sufficient**	**Excellent**	**Total**	**Minimal**	**Low**	**Sufficient**	**Excellent**	**Total**
Year 1 - n (%)	0 (0.0)	2 (12.5)	2 (12.5)	12 (75.0)	16	3 (18.8)	1 (6.3)	6 (37.5)	6 (37.5)	16
Year 2 - n (%)	1 (7.1)	2 (14.3)	2 (14.3)	9 (64.3)	14	3 (20.0)	4 (26.7)	3 (20.0)	5 (33.3)	15

TABLE 6 | Correlations between treatment adherence, ADOS scores, and DD-C-GAS findings at both Year 1 and Year 2.

Spearman-rho			ADOS Total score	ADOS Severity score	DD-C-GAS Self-care	DD-C-GAS Communication	DD-C-GAS Social behavior	DD-C-GAS Intellectual skills
Year 1	**Treatment adherence**	**Corr. Coeff.**	–0.452**	–0.338	0.501**	0.483**	0.489**	0.411*
		N	32	32	28	28	28	24
Year 2	**Treatment adherence**	**Corr. Coeff.**	–0.595**	–0.504**	0.370	0.129	0.245	0.167
		N	29	29	26	26	26	20

*Correlation significant at level 0.05 (two-sided); **Correlation significant at level 0.01 (two-sided).*

DISCUSSION

The primary objective of the current study was to examine whether symptomatic and behavioral changes in young children with ASD were sustained 1 and 2 years after an initial 18 days of intensive FIAS intervention. The 2-year time point corresponded to the end of the FIAS follow-up care for 29 of the 32 children. In an earlier study (10) involving most of the current patient sample, we demonstrated that short-term changes during the initial intervention period could be sensitively captured by means of the Autism Behavior Coding System (ABCS), a video-based instrument for assessing core autism symptoms during therapist–child interactions. The current study focused on longer-term outcomes 1 and 2 years after the initial intervention period, as reflected in different levels of outcome and their potential correspondence.

Baseline ADOS total and severity scores indicated moderate to high autism symptom levels in 18 and 13 children, respectively, while DD-C-GAS scores were suggestive of major deficits in all behavioral subdomains, most clearly in social behavior, as assessed by parents. No relevant age- or sex-related differences were observed for any of the ADOS or DD-C-GAS variables at baseline.

We first analyzed changes over time in core autism symptoms as assessed by experienced ASD clinicians who had not been involved in the intervention. ADOS total and severity scores decreased from baseline to 1-year and 2-year follow-up, the change in ADOS total score from baseline to 2-year follow-up reaching statistical significance, indicating a continuous and relevant overall decrease in core autism symptoms. This finding is of importance, as the ADOS was not primarily designed to be sensitive to intervention-related changes in autism symptoms. For that reason, many other post-intensive intervention long-term follow-up studies did not use the ADOS and did not demonstrate a reduction in core autism symptoms; instead, many concentrated on outcome measures concerning IQ and adaptive behavior (4). Some of the studies that did use the ADOS as an outcome measure also showed symptom reduction following intensive intervention, as reflected in changes in ADOS severity scores (see **Table 7** for an overview).

The decrease in ADOS severity scores reported in previous studies varies from 0.2 (22) to 1.4 points (26). Most of the studies summarized in **Table 7** reported on ADOS severity scores, except for the study by Aldred, Green, and Adams (21) which showed a decrease for ADOS total scores. Interestingly, an evaluation of a 2-year intervention using the Early Start Denver Model (ESDM) revealed no relevant effect on core autism symptoms immediately after treatment (22) but positive findings at a follow-up assessment 2 years later (2). Unfortunately, statistical

TABLE 7 | Early intervention studies reporting post-treatment changes in ADOS scores.

Study	Person implementing	Duration (weeks)	Intervention hours/week	NIG/CG Baseline	NIG/CG Follow-up	Mean Age (years)	IGADOS-SS Pre-/post-intervention	CGADOS-SS Pre-/post intervention
Aldred et al., (21)	P	48	12	14/14	14/14	4.2	*16.1/11.8	*15.6/16.1
Dawson et al. (22)	C/P	96	30	24/24	24/21	4.3	7.2/6.5	6.9/7.3
Estes et al., (2)	C	96	20	24/24	21/18	6	*6.9/5.8	*7.5/7.3
Pickles et al., (23)	C/P	48	12	77/75	59/62	3.6	8/7.3	7.9/7.8
Rogers, et al. (24)	C/P	96	24	55/63	45/36	2	7.2/6.69	7.83/6.19
Kitzerow et al. (25)	C	48	2	20/20	20/18	5.5	7.3/5.95	6.5/6.1
Robain et al. (26)	C	52	1–12 (CG) 18–22 (IG)	22/38	22/38	3.0	8.14/6.73	7.13/7.18

*C, Clinician; P, Parent; IG, Intervention Group; CG, Control group; SS, Severity Score; *, Total score.*

details on the reduction in autism symptoms are not available from this study. A recent publication by Rogers et al. (24) reported no relevant changes nor differences in autism symptom severity between an ESDM intervention and a community treatment group over a 2-year intervention period. Conversely, a study of a 12-month, pre-school, parent-mediated autism communication intervention (Preschool Autism Communication Treatment, PACT) found a significant decrease in autism symptoms (21). The first study to show longer-term autism symptom reduction was that by Pickles et al. (23), who re-evaluated patients from an initial PACT study nearly 6 years after the intervention. At this time point, children who had received PACT still maintained some improvement: their ADOS Severity Score values were down to 7.3 ± 2.0 from 8.0 ± 1.4 points at baseline, whereas those who had been on TAU (treatment as usual) had virtually the same ADOS Severity scores at baseline (7.9 ± 1.4) and at follow-up (7.8 ± 1.8). A very recent publication by Robain et al. (26) revealed positive changes in autism symptom severity as well as of cognitive abilities in an intensive intervention group (following the Early Start Denver Model approach) compared to a control group including different community treatment settings available in the greater Geneva area.

The results from the DD-C-GAS showed highly significant improvements on all subdomains, these changes being numerically more impressive than the results obtained with the ADOS. Overall, DD-C-GAS scores increased by approximately 30 points (within a total range of 100 points), whereas the mean decrease in the ADOS total score was about three points (within a range of 28 points) and around one point in the severity score (within a range of 10 points).

To interpret these findings, one first needs to consider that the four DD-C-GAS subdomains are not independent of one another but are highly intercorrelated. When considering the numerical disparity between the changes in the two scales one should also bear in mind two further aspects. First, the ADOS was administered under narrowly defined conditions, i.e. within approximately 45 min of assessment in a novel environment by a clinician who was initially unknown to the child and was not involved in the treatment. In this regard, the ADOS could be viewed as an objective assessment instrument administered under conditions that were unlikely to lead to an overestimation of the child's capacities. In contrast, the DD-C-GAS ratings were based on information provided by the child's parents, who live and interact daily with the child and who are most likely influenced by their hopes and expectations of positive intervention effects as well as by a generally positive attitude towards their own intervention. This phenomenon of performance bias is ubiquitous although, conversely, caregiver reports are considered to have superior external validity (27). Second, ADOS ratings represent a current, moment-based observation of autism symptoms, whereas the DD-G-GAS includes observations and reports from a longer period, converted into a clinician's rating.

We also investigated whether and how the findings using the ADOS corresponded to the more global behavioral assessments based on the DD-C-GAS. There were mostly non-significant (and as expected, negative) correlations between the two instruments at baseline, yet highly significant negative correlations at 1- as well as 2-year follow-up, i.e. cross-sectionally at three separate time points. In contrast, there were no meaningful correlations between *score changes* observed over time, except for the changes between ADOS total score and the DD-C-GAS subdomain social behavior ($p < 0.01$) at 1-year follow-up. At 2-year follow-up, the changes between these two scores remained relatively high, but did not reach statistical significance. As pointed out before, the two instruments imply different metrics of assessment, different sources of information and assessment conditions, different observation periods and areas of observation, as well as a different potential bias in favor of the intervention. Given these differences, one might assume that the changes seen on the two scales are both clinically relevant but relatively independent of one another. Nevertheless, and importantly, most children's combined outcome scores were located in the upper right quadrant of the scatterplots presented in **Figures 5** and **6**, indicating improvement in autism symptoms *and* level of functioning domains.

Changes on both scales were virtually independent of age and severity of autism symptoms at baseline, suggesting that older and more severely affected children may benefit to a similar extent as younger children do from a FIAS intervention. Although the small sample size in the current study does not permit any general conclusion with regard to the optimal age range for an intensive intervention such as FIAS, our observations are in line with the results of a recent meta-analysis that included 29 early intervention studies (3). These authors found the largest effect sizes for communication outcomes at the age of 3.8 years i.e. almost identical with the median value of the children in our sample (43 months). Estes et al. (2) found long-term effects 2 years after the end of an ESDM intervention which children of less than 30 months of age at baseline, suggesting the effectiveness of early intervention approaches in very young children.

As the parents were instructed by FIAS therapists to continue to provide regular play sessions under their supervision during the 2 years of follow-up, we considered treatment adherence to be of crucial interest in terms of intervention outcome. The findings of a recent meta-analysis (3) suggest that the benefit of early intervention is greatest when it is conducted by clinicians but may also be significant when implemented by parents. The authors observed that both the fidelity of clinicians in teaching parents and the fidelity of parents in ultimately providing the intervention in everyday life were of crucial importance to the overall outcome. In the current study, treatment adherence in the 2 years following the intensive 18-days of in-house FIAS treatment was evaluated by the reference therapist for each family. In support of the conclusions drawn by Fuller & Kaiser (3) we found a close and mostly statistically significant relationship between parents' treatment adherence and the ADOS total and severity scores, indicating that the better parents' treatment adherence was, the lower the children scored on the ADOS at 1- and 2-year follow-up. Interestingly, correlations became even higher at 2-year follow-up. Overall,

treatment adherence was satisfactory in our sample even though a slight decrease over time was observed. Detailed evaluation of treatment adherence at the level of each family revealed a relevant factor of the decrease: as children grew older, the use of external support facilities, such as kindergarten or special education services as well as additional therapies, became more time-consuming. Thus, regular, daily play sessions between parents and their children in time may have become more difficult to accomplish. The relationship between treatment adherence and ADOS scores seems to be more meaningful than the one between treatment adherence and DD-C-GAS subdomain scores. This may be due to the fact that both, treatment adherence and the ADOS, are external measures assessed by independent clinicians, whereas the DD-C-GAS is based on the parents' reports. As stated earlier, the special conditions of the FIAS approach do not allow a matched control group to be included in a study. FIAS demands high motivation and commitment from parents, as well as intensive, active involvement in the intervention both for the initial period of 18 days at the treatment center and for continuing regular play sessions at home. These factors cannot be emulated in a credible control group.

Table 7 provides core findings of seven published controlled intensive intervention trials with young ASD children lasting between 48 and 96 weeks. In three of these studies no relevant positive changes in either ADOS Severity or Total Scores were observed in the control groups, and three studies reported slightly negative changes on TAU; the only paper reporting positive changes of ADOS Severity Scores on TAU was the one by Rogers et al. (24). However, this study differs from the others in at least two relevant respects: The children included were younger (average 2 years) than the ones in the other studies (average between 3.6 and 6 years), and the average improvement observed in the control group was numerically higher than in the group treated according to the Denver model. A very recent paper by Robain et al. (26) reported no positive changes in a TAU control group. This study is of particular interest for a number of reasons: (a) the patient sample is comparable to ours in terms of size and average age of the children in the control TAU group; (b) like ours, the study was performed in Switzerland, and it is reasonable to assume that the families involved in it lived under similar socio-economic circumstances like the ones participating in the FIAS study; (c) availability and use of additional treatments (behavioral, educational) is comparable in Swiss urban and suburban areas such as Geneva (26) and Basel (FIAS study). In summary, there is no evidence from controlled studies that TAU groups show positive changes on a comprehensive clinical scale such as the ADOS. Nevertheless, the changes we observed in favor of an intervention benefit cannot be specifically attributed to the FIAS treatment, as both maturation and influences such as family- and other support-related variables may have affected the children's development. As Robain et al. (26) stated, children in either early intervention as well as in community treatment settings usually receive multiple interventions, yet specifically addressing social communication development may be crucial to improve core autism symptoms. This may explain the advantage of early intensive intervention approaches in improving core autism symptoms compared to nonspecific interventions reflected in control group settings as TAU.

In conclusion, the results of the current study suggest that the FIAS approach, which consists of an initial short and highly intensive 18-day intervention period followed by 2 years of parent-mediated follow-up care, had a positive impact on the core autism symptoms as well as the adaptive functioning of the children analyzed. Changes assessed with the more global clinical scale DD-C-GAS were numerically more impressive, but were also more likely to be biased by parents' expectations, than were the results from the ADOS scale. The reduction in core autism symptoms and the higher level of functioning were found to be independent of age and autism severity at the start of the intervention.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the parents of all children included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or the National Research Committee, as well as with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

AUTHOR CONTRIBUTIONS

EH, MN, and RS designed the study. EH, OL, and EK acquired the data. MN, EH, OL, EK, KS, and RS analyzed and interpreted the data. EH, MN, and RS drafted the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Vorgraft Y, Farbstein I, Spiegel R, Apter A. Retrospective evaluation of an intensive method of treatment for children with pervasive developmental disorder. *Autism* (2007) 11:413–24. doi: 10.1177/1362361307079605
2. Estes A, Munson J, Rogers SJ, Greenson J, Winter J, Dawson G. Long-term outcomes of early intervention in 6-year-old children with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* (2015) 54:580–7. doi: 10.1016/j.jaac.2015.04.005
3. Fuller EA, Kaiser AP. The effects of early intervention on social communication outcomes for children with autism spectrum disorder: a meta-analysis. *J Autism Dev Disord* (2019) 50:1683–700. doi: 10.1007/s10803-019-03927-z
4. Magiati I, Wei Tay X, Howlin P. Early comprehensive behaviourally based interventions for children with autism spectrum disorders: a summary of findings from recent reviews and meta-analyses. *Neuropsychiatry* (2012) 2:543–70. doi: 10.2217/npy.12.59
5. French L, Kennedy EM. Annual research review: Early intervention for infants and young children with, or at risk of, autism spectrum disorder: a systematic review. *J Child Psychol Psychiatry* (2018) 59:444–56. doi: 10.1111/jcpp.12828
6. Vivanti G, Prior M, Williams K, Dissanayake C. Predictors of outcomes in autism early intervention: Why don't we know more? *Front Pediatr* (2014) 2:58. doi: 10.3389/fped.2014.00058
7. Reichow B, Barton EE, Boyd BA, Hume K. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). *Cochrane Database System Rev* (2012) 10:CD009260. doi: 10.1002/14651858.CD009260.pub2
8. Howlin P, Magiati I, Charman T. Systematic review of early intensive behavioural interventions for children with autism. *Am J Intellect Dev Disabil* (2009) 114:23–41. doi: 10.1352/2009.114:23;nd41
9. Fossum KL, Williams L, Garon N, Bryson SE, Smith IM. Pivotal response treatment for preschoolers with autism spectrum disorder: Defining a predictor profile. *Autism Res* (2018) 11:153–65. doi: 10.1002/aur.1859
10. Herbrecht E, Lazari O, Notter M, Schmeck K, Spiegel R. Process research in early intensive intervention in autism spectrum disorder: sensitivity to change of the autism behavior coding system. *Autism Res* (2019) 12:1817–28. doi: 10.1002/aur.2188
11. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop S. *Autism Diagnostic Observation Schedule: ADOS-2*. Los Angeles, CA: Western Psychological Services (2012).
12. Poustka L, Rühl D, Feineis-Matthews S, Bölte S, Poustka F, Hartung M. *ADOS-2, Diagnostische Beobachtungsskala für Autistische Störungen-2*. Bern: Huber (2015).
13. Herbrecht E, Kievit E, Spiegel R, Dima D, Goth K, Schmeck K. Become related: FIAS, an intensive early intervention for young children with autism spectrum disorders. *Psychopathology* (2015) 48:162–72. doi: 10.1159/000375504
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association (1994).
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Association (2013).
16. Rutter M, LeCouteur A, Lord C. *Autism Diagnostic Interview revised (WPS edition manual)*. Los Angeles: Western Psychological Services (2003).
17. Bölte S, Rühl D, Schmötzer G, Poustka F. *Diagnostisches Interview für Autismus–Revidiert (ADI-R)*. Bern: Huber (2006).
18. Dima D, Lazari O, Schmeck K, Spiegel R, Brönnimann A, Goth K, et al. Assessing symptoms during comprehensive interventions for young children with autism spectrum disorder: Development and preliminary analysis of the Autism Behaviour Coding System (ABCS). *Psychiatry Res* (2017) 247:63–7. doi: 10.1016/j.psychres.2016.11.006
19. Wagner A, Lecavalier L, Arnold LE, Aman MG, Scahill L, Stigler KA, et al. Developmental disabilities modification of the Children's Global Assessment Scale. *Biol Psychiatry* (2007) 61:504–11. doi: 10.1016/j.biopsych.2007.01.001
20. Bölte S. *Children's Global Assessment Scale für Entwicklungsstörungen (DD-C-GAS)*. Frankfurt am Main: J.W. Goethe-Universität Frankfurt (2008).
21. Aldred C, Green J, Adams C. A new social communication intervention for children with autism: a pilot randomised controlled treatment study suggesting effectiveness. *J Child Psychol Psychiatry* (2004) 45:1420–30. doi: 10.1111/j.1469-7610.2004.00338.x
22. Dawson G, Rogers S, Munson J, Smith M, Winter J, Greenson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the early start denver model. *Pediatrics* (2010) 125:e17–23. doi: 10.1542/peds.2009-0958
23. Pickles A, Le Couteur A, Leadbitter K, Salomone E, Cole-Fletcher R, Tobin H, et al. Parent-mediated social communication therapy for young children with autism (PACT): long-term follow-up of a randomised controlled trial. *Lancet* (2016) 388:2501–9. doi: 10.1016/S0140-6736(16)31229-6
24. Rogers SJ, Estes A, Lord C, Munson J, Rocha M, Winter J. A multisite randomized controlled two-phase trial of the early start Denver model compared to treatment as usual. *J Am Acad Child Adolesc Psychiatry* (2019) 58:853–65. doi: 10.1016/j.jaac.2019.01.004
25. Kitzerow J, Teufel K, Jensen K, Wilker C, Freitag CM. Case-control study of the low intensive autism-specific early behavioral intervention A-FFIP: Outcome after one year. *Z Kinder Jugendpsychiatr Psychother* (2020) 48:103–12. doi: 10.1024/1422-4917/a000661
26. Robain F, Franchini M, Kojovic N, Wood de Wilde H, Schaer M. Predictors of treatment outcome in preschoolers with autism spectrum disorder: an observational study in the greater Geneva area, Switzerland. *J Autism Dev Disord* (2020). doi: 10.1007/s10803-020-04430-6
27. Fletcher-Watson S, Apicella F, Auyeung B, Beranova S, Bonnet-Brilhault F, Canal-Bedia R, et al. Attitudes of the autism community to early autism research. *Autism* (2017) 21:61–74. doi: 10.1177/1362361315626577

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Cognitive Remediation Interventions in Autism Spectrum Condition: A Systematic Review

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Background: Autism spectrum condition (ASC) is a lifelong neurodevelopmental condition characterized by difficulties in social cognition and heterogeneity of executive function which are suggested to be underpinned by neurobiological, prenatal and genetic factors. Cognitive remediation (CR) interventions are frequently used to address cognitive characteristics and improve cognitive and general functioning. However, the evidence is limited for ASC. This systematic review is the first to provide a narrative synthesis of all studies of CR interventions and ASC. The review aimed to delineate the development of research in this area in both adolescents and adults, with implications for clinical practice and future research.

Method: The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. The literature was reviewed using the PubMed, PsycINFO, Web of Science, Scopus and Embase from inception to 1st April 2020. Out of 1,503 publications, a total of 13 papers were identified as being relevant for the review.

Results: The 13 studies meeting the inclusion criteria were: four randomized control trials (RCTs); two non-randomized control trials, four case series, two feasibility studies and one case study. A narrative synthesis of the data suggested that CR interventions are potentially effective in improving social cognition and cognitive functioning in ASC. RCTs supported the efficacy of CR interventions in improving social cognition and executive functioning. Non-randomized control trials provided evidence for the effectiveness of social cognition remediation interventions in ASC. Case series and a case study have also supported the feasibility of CR interventions, including reflections on their adaptation for ASC populations and the positive feedback from participants.

Conclusions: CR interventions are potentially effective in improving social cognition and cognitive functioning in ASC. However, the generalizability of the included empirical studies was hampered by several methodological limitations. To further strengthen understandings of the effectiveness of CR interventions for ASC, future RCTs are needed with larger sample sizes in exploring the long-term effectiveness of CR

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interventions, using age-appropriate valid and reliable outcome measures. They should also consider the heterogeneity in neuropsychological functioning in ASC and the mediating and moderating mechanisms of the CR intervention for ASC.

Keywords: autism, cognitive remediation, interventions, therapy, cognitive training, social cognition, adolescents, adults

INTRODUCTION

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition characterized by differences in reciprocal social interaction, communication, language, and restricted and repetitive behaviors (1). Although the term ASD is the term used for medical diagnosis, we instead use the term Autistic Spectrum Condition (ASC), which is the preferred term by people with the life experience of this diagnosis (2). In the 1980s, ASC was considered uncommon with a prevalence estimate of around 22 in 10,000 (3). Nonetheless, with increasing recognition the ASC prevalence estimate is now considered to be approximately one in 100 and relatively common (4).

ASC is associated with a spectrum of manifestations and behaviors that affect individuals in different ways. However, these surface differences are theorized to be underpinned by a common cognitive profile: inflexibility of thinking and heightened attention to detail (5, 6). Furthermore, ASC is characterized by difficulties in social cognition and heterogeneity of executive function which are suggested to be underpinned by neurobiological, prenatal and genetic factors (7). A recent systematic review and meta-analysis aimed to systematically map non-social and social cognitive functioning in autistic adults (8). Overall, the findings from 75 included studies comprising of 3,361 autistic people supported the notion that autistic adults show difficulties in non-social and social cognitive domains (theory of mind, verbal learning and memory, emotional processing and perception, and processing speed). This review highlights the significance of identifying remediation interventions that target non-social and social cognition.

The timely identification of ASC can improve quality of life by identifying needs and providing appropriate interventions (9). It has been suggested that cognitive remediation (CR) interventions targeting this underlying cognitive profile may be particularly beneficial for this population (10). CR interventions are an umbrella term for psychological interventions that use cognitive training exercises to remedy difficulties in social cognition and neuropsychological functioning. CR interventions aim to encourage patients to reflect on their thinking styles, planning strategies to enable them to make behavioral changes (11).

The use of cognitive training and later CR remedial interventions were originally developed for use in brain lesions (12, 13) and were then broadened for patients with schizophrenia (14, 15); and adapted further for patients with anorexia nervosa (AN); (11). CR interventions have demonstrated significant improvements in neuropsychological tests of set-shifting (16, 17).

To date, four randomized control trials (RCTs) have been conducted on the use of CR interventions and ASC. The findings from these trials indicate that CR interventions can be effective in improving cognitive flexibility, social cognition and heterogeneity of executive function (10, 18–20). However, the translation of the empirical study findings to further clinical work in this field is hampered by methodological limitations such as heterogeneity in participants clinical presentations, variability in outcome measures used and small sample sizes. Additionally, it is possible that standard CR interventions developed for other populations may benefit from adaptations for ASC populations, an area of research relevant to the successful clinical implementation of these interventions in this field.

Therefore, this systematic review aims to contribute to the field of ASC interventions by presenting a narrative synthesise of all peer-reviewed published studies of CR approaches in this area. To our knowledge, this is the first paper to review the literature specifically for CR interventions and ASC. Hence, the paper aims to add to the field by providing a chronological outline of the current literature and to discuss the implications of these findings for future work in this area.

METHOD

Review and Search Strategy

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (21). The literature was reviewed using the PubMed, PsycINFO, Web of Science, Scopus and Embase from inception to 1st April 2020. The search terms used were autis*—Asperger* and cognit* with remed*—or train*–neuropsychology—cognitive remediation therap*. These terms allowed for multiple spellings, plurals and combinations.

Inclusion Criteria

The pre-determined inclusion criteria were [1] only published, peer-reviewed English language journals; [2] studies of any design (quantitative or qualitative) focusing on CR interventions and ASC [3] empirical studies that include either adolescents or adults [4] studies using any modality of treatment e.g. individual sessions or group sessions.

The definition of CR interventions used for this review was not restricted to cognitive remediation therapy (CRT) but included other CR approaches such as cognitive enhancement therapy, social cognition remediation programs, brain training tasks, flexibility training, or CR interventions that had been adapted for other populations and used for those with ASC. Additionally, the review included studies examining CR approaches in relation to autistic traits, as well as in populations with diagnosed ASC. Furthermore, no limitations were set regarding age or measure of neuropsychological characteristics. This allowed for a wider search.

Exclusion Criteria

Non-English language publications (22) and empirical studies that were not published in peer-reviewed journals were excluded. Secondary systematic or narrative reviews on the wider topic of CR interventions in mental health were also excluded (23–26). However, the first author (YD) and principal author (KT) did hand search the reference list of the reviews for studies relevant to ASC populations to ensure that all empirical studies were included in the final analysis for the review.

Study Selection and Data Extraction

The database searches and study selection were undertaken by five authors. **Figure 1** provides the PRISMA flow diagram (21) of the studies retrieved for the review. The PubMed yielded 478 publications, PsycINFO 619 publications, Web of Science 137 publications, Scopus 239 publications and Embase 30 publications. Together the five searches yielded 1,503 publications. Publication titles and abstracts were screened initially, and eligibility was established by reading the full texts. Duplicates and those that did not meet the inclusion criteria outlined below were removed. A manual reference search by exploring the reference list of the eligible publications was also conducted by the first author (YD) and principal author (KT) to identify additional papers of relevance. A total of 13 papers were then concluded as being relevant.

Data Analysis

Due to the significant heterogeneity between participant characteristics and outcome measures used, it was not feasible to pool the data and undertake a meta-analysis. Therefore, a narrative method of analysis was undertaken.

RESULTS

Study Selection

Table 1 summarizes information about the studies included in the systematic review based on the inclusion criteria. Publications are stratified according to publication type and chronological order, giving insight into how research in this area has developed from case series to RCTs. This paper restricts itself to summarizing the findings narratively. CR interventions and ASC was examined in 13 studies; four RCTs (10, 18–20); two non-randomized control trials (27, 28); four case series (30–32, 34); two feasibility studies (29, 33) and one case study (35). **Table 1** includes a summary of limitations associated with each study that may impact interpretation.

Findings

Interventions

All of the interventions used in these studies were originally developed for use in other populations, rather than specifically designed for autistic people. The majority of the studies (n = 7)

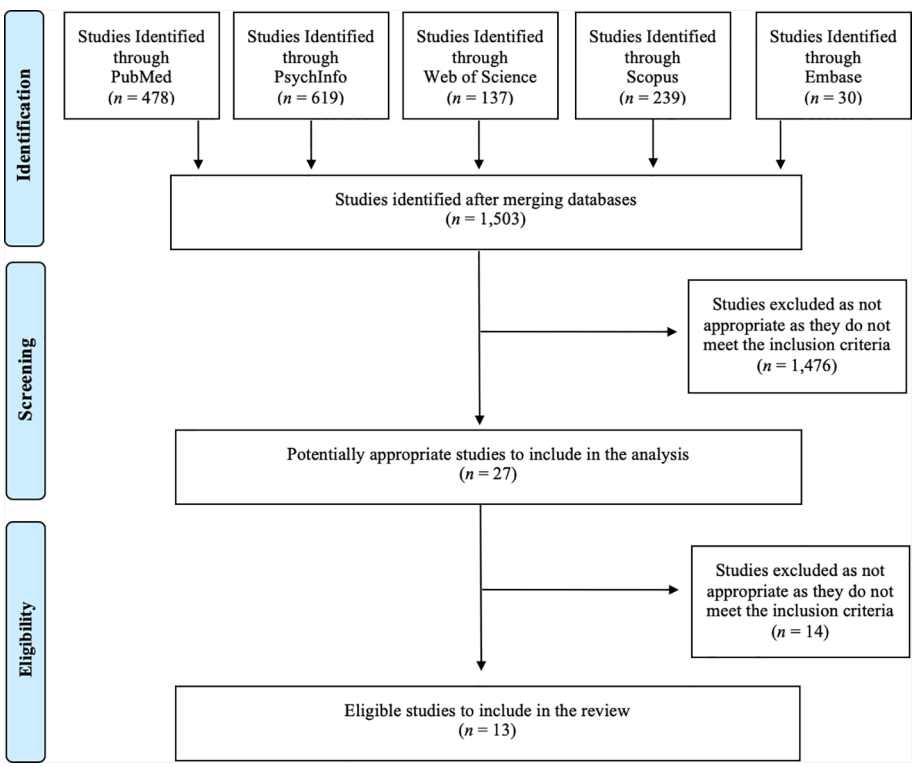

FIGURE 1 | PRISMA flow diagram of the studies retrieved for the review.

TABLE 1 | Characteristics of the included studies.

RANDOMIZED CONTROL TRIALS

Study	Aim of the study	Design	Inclusion Criteria	Sample characteristics	Intervention	Outcome measures	Summary of results	Limitations
Bölte et al. (18)	Preliminary evaluation of the development of a computer-based program (using social cognition remediation) to test and to treat facial affect in autistic people.	RCT	Participants to have a diagnosis of autism or Asperger's*.	*n* = 10 autistic people aged 16–40.	Computer-based program to test using social cognition remediation.	International Affective Picture System* and fMRI-scans.	The results indicated a statistically significant improvement in facial affect in the intervention group post the computer-based program.	Small sample size affected power and limited the generalizability of findings. Gender bias by only including male participants.
De Vries et al. (10)	To investigate the effect of a working memory flexibility-training compared to an active control condition.	RCT	Prior diagnosis of ASC, IQ ≥80* and absence of a seizure disorder.	*n* = 121 children. Diagnosed with ASC.	'Braingame Brian': executive function training. 25 Group sessions.	Corsi-BTT, BRIEF, SSRT, N-Back task, Gender-emotion switch-task*	The trend toward improvement in working memory and cognitive flexibility. Not feasible for autistic children.	High attrition rate. Targeted isolated aspects of cognition with limited functional impact. Does not specify participants gender
Miyajima et al. (20)	To explore the effects of CRT using the frontal/executive program for ASC compared to treatment as usual (normal supportive psychotherapy).	RCT	Outpatients younger than aged 60 & ≥9 years of formal education.	*n* = 14 adult outpatients. Diagnosed with ASC.	CRT using the frontal/executive program—44 individual sessions. (2 sessions a week).	BACS-J, WCST, CPT, ScoRS-J, LASMI*	Intervention group improved in working memory, executive functioning, verbal fluency and planning.	Small sample size. No follow-up investigation to determine the persistence of the effect.
Eack et al. (19)	To examine the efficacy of CET for improving core cognitive (neurocognitive & social-cognitive) and employment outcomes in autistic adults.	RCT	Diagnosis of ASC, IQ ≥80*, adults aged 16-45 and young people aged 16–17.	*n* = 33 adult, 7 adolescent male outpatients. Diagnosed with ASC.	CET—60 h over 18 months. Individual and group sessions.	MCCB, WCST, MSCEIT, PERT, PEDT, PEAT, SCS*	CET significantly increased neurocognitive function & social cognition in comparison to the control group.	Small sample size affected power. Treatment conditions were not matched (hours of treatment).

NON-RANDOMIZED CONTROL TRIAL

Study	Aim of the study	Design	Inclusion criteria	Sample characteristics	Intervention	Outcome measures	Summary of results	Limitations
Golan et al. (27)	To teach autistic adults to recognize complex emotions using interactive multimedia. Using social cognition remediation (SCR) to improve the theory of mind.	Non-randomized controlled	Diagnosis of ASC and not taking part in any other intervention.	*n* = 39 autistic adults (32 males and 7 females). 13 people in each condition.	SCR using the mind reading intervention. Individual and group sessions.	CAM, RME, RMV & RMF*	Significant improvements on measures of face and voice recognition following intervention.	Sample was not randomized. The use of computer-based tasks is different to real life.
Turner-Brown et al. (28)	To evaluate the efficacy of social cognition remediation to improve social-cognitive functioning in high functioning autistic adults.	Non-randomized controlled	Aged 18–55, ASC diagnosis, IQ ≥80.	*n* = 11 high functioning autistic adults	Group based Social Cognition and Interaction Training modified for autism.	FEIT, Hinting Task, SCSQ and SSPA*	Intervention group showed significant improvement in theory of mind & social communication skills.	Small sample size and the quasi-experimental nature of the design where the sample was not randomized.

(Continued)

TABLE 1 | Continued

CASE SERIES

Study	Aim of the study	Design	Inclusion criteria	Sample characteristics	Intervention	Outcome measures	Summary of results	Limitations
Eack et al. (29)	To examine the feasibility and potential efficacy of CET in autistic adults.	Feasibility study	ASC diagnosis, cognitive and social disability, IQ ≥80.	*n* = 14 young autistic adults (12 males 2 females).	CET. 60 hours over 18 months. Individual and group sessions.	CSQ-8, NIMH MATRICS, WCST, CSSCEI, PERT, SCP*	Improvements in cognitive difficulties and social cognition.	Small sample size, limiting generalizability of the results. Gender bias.
Hajri et al. (30)	To investigate whether CRT improves cognitive function in autistic children.	Cross-sectional	ASC diagnosis, cognitive difficulties*, on stable dose/type of medication.	*n* = 16 autistic children, aged 6-21 with regular school curriculum.	Individual CRT 22 sessions (one session per week).	CPM, VSFT, PFT, SF, DST, CARS*	CRT showed significant positive effects on neurocognition.	Small *N*. No follow-up investigation to determine the long-term persistence of the effect. Does not specify participants gender.
Tchanturia et al. (31)	To examine the treatment response of group CRT in anorexia nervosa patients with high or low autistic traits.	Cross-sectional	Adults with a diagnosis of anorexia nervosa.	*n* = 35 adult inpatients with AN diagnosis.	Group CRT 6 once-weekly sessions.	Motivational ruler, DFlex, patient feedback questionnaire*	No improvements following CRT for patients with high autistic traits.	23% of participants were only assessed for ASC with self-report questionnaires.
Hajri et al. (32)	To evaluate CRT's effectiveness for autistic children on executive functions, clinical symptoms & education.	Cross-sectional	ASC diagnosis, cognitive difficulties*, on stable dose/type of medication.	*n* = 16 autistic children and adolescents, aged 6–21 with regular school curriculum.	Individual CRT adapted for young autistic people, once weekly.	CPM, HSCT, ROCF, CARS	Significant improvement in intellectual abilities, executive functions and clinical symptoms following CRT	Small sample size. No control group. Does not specify participants gender.
Okuda et al. (33)	To investigate the effectiveness and feasibility of CRT for ASC individuals.	Single-group pilot study	ASC diagnosis, aged 18–50, IQ ≥80.	*n* =16 female outpatients (4 adolescents and 12 adults).	Individual CRT, 10 sessions (weekly or biweekly).	Brixton, TMT, ST, WCST, ROCF, CFS*	Increase in patient's central coherence following CRT, but not statistically significant.	Small sample size which results in a lack of power to detect statistical differences.
Dandil et al. (34)	To examine the difference in the effects of individual CRT for patients with AN and high autistic features (HAF).	Cross-sectional	Adult females with a diagnosis of AN and completed the AQ-10*.	*n* = 99 adult female inpatients diagnosed AN. (59 with HAF).	Individual CRT, 10 sessions (weekly or biweekly).	ROCF, Brixton SAT, DFlex*	HAF patients showed improvement in cognitive flexibility but not central coherence.	Participants were only assessed using ASC screening tools and not the full ASC diagnostic measures.

SINGLE CASE STUDY

Study	Aim of the study	Design	Inclusion criteria	Sample characteristics	Intervention	Outcome measures	Summary of results	Limitations
Dandil et al. (35)	To investigate the feasibility of individual CRT for a complex single case study of anorexia nervosa (AN) and ASC.	Case study	Diagnosis of ASC and anorexia nervosa.	*n* = 1 inpatient autistic female aged 21 diagnosed with AN.	Individual CRT 13 sessions (twice a week).	DFlex, ROCF, Motivational ruler, Brixton SAT *	CRT indicated improvements in cognitive flexibility and central coherence.	Single case study, therefore, hard to generalise to a larger population.

**Diagnosis of ASC = (1, 36, 37), IQ, Intelligence Quotient (38); Cognitive difficulties, The Cognitive Styles and Social Cognition Eligibility Interview (39); AQ-10, The 10-Item Autism Spectrum Quotient (40); Corsi-BTT, The Corsi block tapping task (41); BRIEF, Behavioral Rating Inventory of Executive Functioning (42); SSRT, The stop-signal reaction time (43); N-back task (44, 45), Gender-emotion switch-task (46). BACS-J, The Brief Assessment of Cognition in Schizophrenia-Japanese version (47); CPT, Continuous Performance Test (48); SCoRS-J, Schizophrenia Cognition Rating Scale-Japanese version (48); LASMI, Life Assessment Scale for the Mentally Ill (49); MCCB, MATRICS Consensus Cognitive Battery (50); MSCEIT, The Mayer–Salovey–Caruso Emotional Intelligence Test (51); CAM, Cambridge Mindreading Face-Voice Battery (52); RME, Reading the Mind in the Eyes (53); RMV, Reading the Mind in the Voice task (54); RMF, Reading the mind in the films (55); FEIT, The Face Emotion Identification Test (56); The Hinting Task (57); SCSQ, Social Communication Skills Questionnaire (58); SSPA, Social Skills Performance Assessment (59); CSQ-8, Client Satisfaction Questionnaire-8 (60); NIMH MATRICS, Consensus Cognitive Battery (50); WCST, Wisconsin Card Sorting Test (61); CSSCEI, Cognitive Style and Social Cognition Eligibility Interview (39); PERT, Penn Emotion Recognition Test-40 (62); PEDT, Penn Emotion Discrimination Task (63); PEAT, Penn Emotional Acuity Test (64); SCS, the Social Cognition Profile (39); CPM, Raven Progressive Matrices (CPM); (65); VSFT, Verbal and Semantic Fluency Tests (66); PFT, phonemic fluency task (67); SF, Semantic Fluency (68); DST, Digit-span task (69); CARS, Childhood autism rating scale (70, 71); HSCT, Hayling Sentence Completion Task (72); TMT, Trail making test (73); ST, Stroop Test (74); CFS, Cognitive Flexibility Scale (75); DFlex, The Detail and Flexibility Questionnaire (76); ROCF, The Rey–Osterrieth Complex Figure (77); Brixton SAT, The Brixton Spatial Anticipation Test (72).*

identified in the systematic review evaluated Cognitive Remediation Therapy (CRT) interventions, originally designed for use in people with schizophrenia (78). Three studies utilized this original program, which included modules targeting cognitive flexibility, memory, and planning (20, 30, 32). More recently CRT has been adapted for use in people with AN, a manualized approach focusing on cognitive flexibility and additions were made to address central coherence—meaning that the adapted manual for eating disorders added cognitive exercises supporting participants in "bigger picture" thinking (11). This intervention was used in four studies (31, 33–35).

Two studies investigated Cognitive Enhancement Therapy (19, 29). CET is a manualized CR approach originally developed for people with schizophrenia that integrates computer-based neurocognitive training with group-based training in social cognition (39). Other interventions focusing on social cognition remediation include the Social Cognition and Interaction Training (SCIT); (79), which is a group intervention that was initially developed for adults with psychotic disorders. One study used SCIT modified for autism (28). SCIT targets various components of social cognition, including theory of mind, emotion recognition, and attributions as well as social interaction skills.

The use of social cognition remediation interventions using computer-based protocols to improve the theory of mind in autistic people was also used in a further two studies (18, 27). This included the Mind Reading intervention (80) which is a computer-based program on emotions and mental states. It is aimed for children and adults to improve their ability to recognize emotions in others. The three main sections in the program include the Emotions Library (allows people to browse through different emotions and emotion groups), the Learning Centre (utilizes lessons and quizzes to teach emotions in a structured and directive way) and the Games Zone (comprises of educational games while studying about emotions). Finally, one study (10) utilized the cognitive flexibility and working memory modules of a computerized executive functioning training program designed for children with Attention Deficit Hyperactivity Disorder (ADHD) known as 'Braingame Brian' (81).

Randomized Control Trials

The first RCT study on the social cognition remediation effects on ASC provided a preliminary evaluation of the use of social cognition remediation, using a computer-based program they designed to test and to teach the recognition of facial affect and improve theory of mind in autistic adults (18). Five of the participants were randomly assigned to receive the computer treatment and five were in the control group ($n = 10$). The results indicated a statistically significant improvement in facial affect ($p < 0.05$, $d = 3.59$) in the intervention group post the computer-based program.

Cognitive remediation effects on ASC were then explored through working memory and cognitive flexibility-training for autistic children using computerized cognitive training (10). The final sample included 121 children who were randomly assigned to an adaptive cognitive flexibility training, an adaptive working memory training or non-adaptive training. 'Braingame Brian' (81) a computerized executive function training with game elements was used. They reported no significant change in neurocognitive and psychosocial outcomes and disorder-related symptoms ($p > .05$) with a small effect size (η_p^2 = 0.01–\0.06). A marginal effect of improvement in working memory, cognitive flexibility, and in disorder-related symptoms was also highlighted.

The following RCT investigated the effects of CRT using the frontal/executive program (FEP) for ASC compared to treatment as usual (normal supportive psychotherapy), (20). The final sample of 14 autistic adults were randomly assigned to one of the groups. Of the initial 15 adults, seven (three males and four females) were assigned to the intervention group, seven (five males and two females) were assigned to the control group and one person dropped out. After completion in the FEP program they reported the intervention group significantly improved in cognitive functioning ($p = 0.018$) working memory ($p = 0.018$), verbal fluency ($p = 0.008$) and planning ($p = 0.012$) with a large effect size ($d = 2.73$).

To date, the final RCT then examined the efficacy of Cognitive enhancement therapy (CET); (39) in an 18-month CR intervention for improving the core cognitive and employment outcomes in 54 autistic adults (19). Participants were randomly allocated to either the CET intervention which incorporates computerized neurocognitive and social-cognitive remediation or an active Enriched Supportive Therapy (EST); (82) comparison focused on psychoeducation and condition management. Participants included 32 adults and seven adolescents. The results indicated that CET significantly ($p < .05$) increased neurocognitive function in comparison to EST ($p = 0.13$) and there was a medium effect size ($d = 0.46$). Although EST was linked to social cognitive improvements, CET demonstrated a larger improvement in social cognition ($p = .020$) with a medium effect size ($d = 0.58$).

Non-Randomized Control Trials

The first non-randomized control trial utilized social cognition remediation interventions, which concentrated on improving the theory of mind in autistic adults (27). This systematic review will focus on experiment two they reported in their study where the outcome focused on social cognition. The authors used the Mind Reading intervention (80) for autistic adults with weekly support of a tutor for the intervention group. This group was then matched to a control group of autistic adults attending social skills training then another general population control group. 13 adults were included in each group ($n = 39$). Improvement of emotion recognition skills was the target outcome measure. Participants were included through two support organizations and two colleges for autistic people. Autistic participants had all been diagnosed using the established criteria (83). Self-reported autistic traits were then assessed using the Autism Quotient (AQ); (84) and the parent version of the AQ (85). The authors found significant improvements on measures of face and voice recognition in the intervention group ($p < 0.001$, $d = 0.14$).

A subsequent non-randomized control trial then aimed to evaluate the efficacy of social cognition remediation to improve social-cognitive functioning in high functioning autistic adults (28). The authors investigated the impact of group-based Social

Cognition and Interaction Training (SCIT); (79) modified for autism to treatment as usual in a pilot study using a non-randomized control trial. The sample included 11 participants. Six adults received SCIT for autism and five received treatment as usual. They reported that participants who received the intervention showed significant improvement in theory of mind skills and trend level improvement in social communication skills (p <0.05). The within-group effect size also indicated a large treatment effect (d = 0.94).

Case Series and Case Study

Two different types of case series were identified: studies focusing on pre and post CR assessments in single or multiple case series and feasibility studies. The first case series in this area was a feasibility study (29), in which authors examined the feasibility of Cognitive enhancement therapy (CET); (82) for autistic adults. Participants included (n = 14) young adults (12 males and two females). They were recruited to participate in an uncontrolled, 18-month trial of CET adapted for autistic adults. The authors reported that CET made a statistically significant (p <0.001) improvement in cognitive performance, social behavior and social cognition and social functioning proved to be the largest domains of improvement within this study with a large effect size (d = 1.40–2.29).

A cross-sectional study then investigated whether a CRT intervention developed for adults with schizophrenia (78) improved cognitive function in autistic children (30). 16 children referred to the children and adolescent Psychiatric Department in Tunisia completed the modified version of CRT adapted for children. The main outcome measures; clinical symptoms, executive function and school performance was calculated at baseline and one week after completing the CRT intervention. CRT showed significant positive effects on clinical symptoms (p = 0.001) and working memory (p = 0.006) for autistic children.

The treatment response of group CRT for people with AN (11) was then examined in patients with AN and high or low autistic traits (31). Participants included 35 adults with a diagnosis of AN by a consultant psychiatrist based on the Diagnostic and statistical manual of mental disorders, fifth edition (DSM-IV); (1) with high or low autistic traits (40) on an inpatient eating disorder unit. All participants completed self-report questionnaires on motivation and thinking styles before CRT and then after CRT. The results indicated that patients with high autistic traits showed no statistically significant (p >.05) improvements and negligible effect sizes in the self-reported outcome measures for CRT (d = 0.10).

In another cross-sectional study, CRT (78) adapted for autistic children and adolescents was used to evaluate the effectiveness on executive functions, clinical symptoms and school performance (32). The final sample included 16 young people. Participants were evaluated pre-CRT intervention and post-CRT intervention. The results supported that after CRT, the young autistic people showed significant improvements in intellectual abilities, phonemic flexibility, working memory, school results and clinical symptoms (p <0.05) with a small effect size (r^2 = 0.95).

Two more recent case series have examined the use of a CRT intervention for people with AN in both autistic people, and people with high autistic traits (11). A small prospective pilot study in Japan (33) then aimed to investigate the effectiveness and feasibility of CRT for anorexia nervosa (11) for ASC individuals. 19 patients diagnosed with ASC were included in the study. Outcome measures were given to participants pre-CRT, post-CRT and at 3-month follow-up. Results demonstrated an increase in the patient's central coherence following CRT. However, these results were not statistically significant (p >.05) although the magnitude of the effect was large (d = 0.80).

Furthermore, a preliminary study aimed to examine the difference in the effects of individual CRT treatment for adult female's diagnosed with anorexia nervosa with either high or low ASC characteristics (34). In total 99 inpatients on an eating disorder unit were initially included in the intervention. Out of the 99 inpatients, 59 patients met the threshold for high autistic traits using the 10-Item Autism Spectrum Quotient (AQ-10); (40). However, there was only complete data for 25 (41%) of the patients that scored with high autistic features. The results indicate that participants with high autistic features showed significant improvements in cognitive flexibility (p <0.001) after CRT with a large effect size (d = 0.77). However, scores did not show a statistically significant improvement in central coherence (p >.05), although there was a larger mean difference of −0.15 (0.38).

The clinical implementation of CRT for AN in ASC populations was investigated in more detail in a single case study (35). To the authors' knowledge, this is the only case study in this area. They investigated the feasibility of individual CRT adapted for AN (11) for a complex single case study of a 21-year-old inpatient female diagnosed with anorexia nervosa and ASC. The paper reflects on possible adaptations to enhance the efficacy of CRT for this population. The results suggested improvements in central coherence and cognitive flexibility following CRT. The authors argue that this study provides preliminary support of the efficacy of individual CRT, before proceeding to more complex psychological work, such as cognitive behavioral therapy.

DISCUSSION

Summary of Main Findings

This systematic review aimed to contribute to the field of ASC by presenting a narrative synthesis of all studies of CR interventions and ASC. Thirteen studies met the pre-determined inclusion criteria. However, several methodological challenges made it difficult to appraise the empirical studies comprehensively. Overall, the results suggest CR interventions are potentially effective in improving social cognition and cognitive functioning in ASC. The review findings are broadly consistent with an earlier review that focused on the current status of CR for psychiatric disorders (26). However, the review only included two RCTs on CR interventions and ASC (10, 20).

The four RCTs presented in this paper, although varying in terms of study design, aims and sample characteristic, depict how CR interventions are currently being implemented in diverse settings for ASC. The first RCT study on the social cognition remediation effects on ASC (18) found an improvement in social functioning and theory of mind in autistic people. Though, limitations of this study included its small sample size, which affected power and limited the generalizability of the findings and its gender bias by only including male participants. Two further studies (10, 20) then supported the efficacy of CR interventions in improving working memory. One of these studies reported that a CRT intervention using the frontal/executive program is effective in improving executive functioning in ASC patients, and in particular to those with impaired frontal lobe function (20). However, the limitations of this RCT included its small sample size. There was also no follow-up investigation to determine the persistence of effect. A following RCT then found that CET increased neurocognition function and improved non-social and social cognition for ASC individuals in comparison to the control group (19). However, the small sample size affected power and the treatment conditions were also not matched in terms of the hours of treatment received.

Despite the limitations of the RCTs, three of the studies (18–20) support the feasibility and potentially effective treatment of CR interventions for core cognitive and social cognition domains in autistic adults. However, one of the RCTs found that the computerized executive training with game elements 'Braingame Brian' (81) at present will not be feasible for autistic children due to the absence of a clear effect and high attrition rate (10).

The two non-randomized control studies included in this review utilized computer-based social cognition remediation to improve the theory of mind in autistic people (27, 28). Both their results showed an improvement in social cognition for autistic people following the interventions. However, it is important to note that while there is an increasing trend in the use of computer-based interventions and approaches, at present there is no research evidence supporting that they are more effective than non-computer-based interventions. Although computer-based interventions can provide controlled and structured assessments, they can be different to real-life. For instance, in one of the studies, participants reported that they found it easier to recognize emotions and mental states on the computer instead of in real-life social situations (27). Hence, the interpretation of findings from computer-based programs to real-life functioning should be interpreted with caution.

Studies identified were predominantly case series and have supported the feasibility and acceptability of individual CR interventions with positive feedback from participants (29, 30, 32–34). However, the case series identified had small sample sizes which resulted in a lack of power to detect statistical differences and limits the generalizability of the findings. The design of these studies also cannot draw causal conclusions about the effect of CR interventions. Additionally, one cross-sectional study examined group CRT for those with high autistic traits and found no improvements following the intervention (31). The intervention used was CRT for anorexia nervosa (11) that may have needed to be adapted further for ASC participants. In particular, the group environment may have presented additional difficulties for participants on the spectrum.

Notwithstanding the findings from the studies included in the review, caution is apt in concluding the current evidence for several other reasons. Some participants in the studies on AN populations did not have a full ASC diagnosis and were only assessed using ASC screening tools and self-report questionnaires (31, 34). However, people with AN on the spectrum are often undiagnosed, and these screening tools are used clinically to inform diagnostic referrals (86).

Furthermore, the studies in this review used various CR programs for a diverse range of age groups, with a variety in intensity, duration, measurement tools and target of the cognitive domain. Thus, this diversity may contribute to inconsistent findings and effect sizes as evident in **Table 1**. In addition, the potential role of other variables is unclear from the present research. For example, the training each facilitator may have had for delivering CR interventions may have also differed, and the results may have been affected by participants learning effect. Finally, ASC research typically focuses on males which are also evident in some of the studies included in this review. Compared to males, females are at elevated risk of their ASC going undiagnosed as their difficulties are frequently mislabeled or missed entirely (87). This may be a result of the "female phenotype" of ASC characteristics, with females showing fewer repetitive and restricted behaviors than males and prone to "camouflage" their social difficulties (6, 88). This review suggests that the field of eating disorders is leading on the inclusion of females with autistic traits in this field of research, with the highest population of female participants self-reporting autistic traits in this review included from this population (31, 34).

It is notable that all of the interventions identified in this systematic review were originally developed for use in other clinical populations (brain injury, schizophrenia, AN, ADHD). Previous research on psychological interventions suggests that they may need to be adapted for ASC populations (89). While larger studies are needed, the single case study presented in this review explored adapting CRT on an individual level, highlighting potential adaptations that can be useful for the ASC population (35). There is a no 'one-size-fits-all' approach as each autistic person is unique, however, possible modifications to CR interventions can include clarifying sensory sensitives, accommodating certain routines and rituals, providing clear examples using a didactic style, reducing the number of skills taught and checking understanding. Other adaptations included the individuals wider social network and using colorful visual materials. One of the case series included in this review also made adaptations to CRT for young autistic people by making the tasks simpler and "funnier" (32). Furthermore, the CET intervention was also adapted, by including psychoeducation about ASC, providing greater support with the interventions, and adapting the computer program to eliminate sounds that might be uncomfortable for participants with sensory difficulties (29).

Although some of the studies were limited, they are informative and have useful implications when considering future

developments in clinical practice and service provision. Early intervention program for ASC are increasingly being held to the matching standards as traditional medical trials. Thus, the practical and collaborative nature of CR interventions can be appealing for the ASC population as an early intervention. The findings also indicate that clinicians delivering CRT interventions for conditions, particularly eating disorders, should be mindful of the possibility of patients presenting with ASC, or high autistic traits, as this may impact outcomes. Collecting information on ASC characteristics such as social and communication difficulties, restricted and repetitive behaviors, and differences in neuropsychological functioning can assist clinicians in making suitable modifications to meet individual needs.

Implications for research include further rigorous studies with large sample sizes such as RCTs that help to better understand the mediating and moderating factors for CR interventions in ASC, as well as the effectiveness and acceptability of CR interventions. Moreover, it is important to increase research into establishing reliable and valid outcome measures through developing measures tailored to the specific needs of individuals with ASC and determining normative thresholds for this population.

Limitations

This systematic review has several limitations that should be noted. First, although we undertook the search using several databases, we excluded non-English language publications. Second, while we searched the published literature systematically, the potential publication bias could not be eliminated, for instance, retrospectively searching trial registers for any potentially unpublished studies. Finally, the various interventions and outcome measures used in the identified studies prevented a meta-analysis, limiting our ability to draw conclusions around efficacy or to assess the risk of bias.

Conclusions

To our knowledge, this is the first paper that presents a narrative synthesis of all studies of CR interventions in ASC, and the first paper delineating its research development from single case studies to RCTs. The review findings indicate that CR interventions are potentially effective in improving social cognition and cognitive functioning in ASC. However, the generalizability of the included empirical studies was hampered by several methodological limitations. To further strengthen our understanding of the effectiveness of CR interventions for ASC, future studies should focus on [1] developing the evidence base about the mediating and moderating mechanisms of CR interventions in ASC, [2] exploring the long-term effects of the treatment, [3] integrating treatment approaches that target both non-social and social cognition difficulties, [4] devising further large scale RCTs exploring the effectiveness of CR interventions in both adolescent and adult populations using age-appropriate valid and reliable outcome measures, and taking into account the heterogeneity in neuropsychological functioning in ASC.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors contributed to the literature search (YD, KS, EK, CT, and KT). KT was the principal investigator and supervisor of the study. YD drafted the manuscript, interpreted the main findings, assembled and analyzed the data, and wrote the first paper. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. In: *American Journal of Psychiatry*, *5th ed*. Washington, DC: American Journal of Psychiatry (2013). doi: 10.1176/appi.books.9780890425596.744053
2. Kenny L, Hattersley C, Molins B, Buckley C, Povey C, Pellicano E. Which terms should be used to describe autism? Perspectives from the UK autism community. *Autism* (2016) 20(4):442–62. doi: 10.1177/1362361315588200
3. Wing L, Gould J. Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. *J Autism Dev Disord* (1979) 9:11–29. doi: 10.1007/BF01531288
4. Happé F, Frith U. Annual Research Review: Looking back to look forward – changes in the concept of autism and implications for future research. *J Child Psychol Psychiatry* (2020) 61(3):218–32. doi: 10.1111/jcpp.13176
5. Geurts HM, De Vries M, Van den Bergh SF. Executive functioning theory and autism. In: *Handbook of Executive Functioning*. New York, NY: Springer (2014). doi: 10.1007/978-1-4614-8106-5_8

6. Westwood H, Mandy W, Tchanturia K. Clinical evaluation of autistic symptoms in women with anorexia nervosa. *Mol Autism* (2017) 8(1):1–9. doi: 10.1186/s13229-017-0128-x
7. Hudepohl MB, Robins DL, King TZ, Henrich CC. The role of emotion perception in adaptive functioning of people with autism spectrum disorders. *Autism* (2015) 19(1):107–12. doi: 10.1177/1362361313512725
8. Velikonja T, Fett AK, Velthorst E. Patterns of Nonsocial and Social Cognitive Functioning in Adults With Autism Spectrum Disorder: A Systematic Review and Meta-analysis. *JAMA Psychiatry* (2019) 76(2):135–51. doi: 10.1001/jamapsychiatry.2018.3645
9. Bargiela S, Steward R, Mandy W. The Experiences of Late-diagnosed Women with Autism Spectrum Conditions: An Investigation of the Female Autism Phenotype. *J Autism Dev Disord* (2016) 46(10):3281–94. doi: 10.1007/s10803-016-2872-8
10. De Vries M, Prins PJM, Schmand BA, Geurts HM. Working memory and f cognitive flexibility-training for children with an autism spectrum disorder: A randomized controlled trial. *J Child Psychol Psychiatry Allied Disciplines* (2015) 56(5):566–76. doi: 10.1111/jcpp.12324
11. Tchanturia K, Davies H, Reeder C, Wykes T. *Cognitive remediation therapy for anorexia nervosa*. London, UK: King's College London, University of London (2010).
12. Luria AR. *Restoration of Functions After Brain Injury*. New York: Macmillan (1963).
13. Das JP. A neo-Lurian approach to assessment and remediation. *Neuropsychol Rev* (1999) 9(2):107–16. doi: 10.1023/A:1025611924842
14. Amado I, Krebs MO, Gaillard R, Olié JP, Lôo H. Principles of cognitive remediation in schizophrenia. *Bull l'Academie Nationale Med* (2011) 195(6), 1319–30. doi: 10.1016/s0001-4079(19)31992-2
15. Wykes T, Reeder C. *Cognitive remediation therapy for schizophrenia: Theory and practice*. Abingdon: Routledge (2006).
16. Tchanturia K, Lounes N, Holttum S. Cognitive remediation in anorexia nervosa and related conditions: A systematic review. *Eur Eating Disord Rev* (2014) 22(6):454–62. doi: 10.1002/erv.2326
17. Tchanturia K, Giombini L, Leppanen J, Kinnaird E. Evidence for cognitive remediation therapy in young people with anorexia nervosa: Systematic review and meta-analysis of the literature. *Eur Eating Disord Rev* (2017) 25 (4):227–36. doi: 10.1002/erv.2522
18. Bölte S, Feineis-Matthews S, Leber S, Dierks T, Hubl D, Poustka F. The development and evaluation of a computer-based program to test and to teach the recognition of facial affect. *Int J Circ Health* (2002) 61:61–8. doi: 10.3402/ijch.v61i0.17503
19. Eack SM, Hogarty SS, Greenwald DP, Litschge MY, Porton SA, Mazefsky CA, et al. Cognitive enhancement therapy for adult autism spectrum disorder: Results of an 18-month randomized clinical trial. *Autism Res* (2018) 11(3):519–30. doi: 10.1002/aur.1913
20. Miyajima M, Omiya H, Yamashita K, Miyata T, Yambe K, Matsui M, et al. The effects of cognitive remediation therapy using the frontal/executive program for autism spectrum disorder. *Int J Psychiatry Med* (2016) 51(3):223–35. doi: 10.1177/0091217416651254
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta- analyses: The PRISMA statement. *PloS Med* (2009) 6(7):e1000097. doi: 10.1371/journal.pmed.1000097
22. Thillay A, Morel-Kohlmeyer S, Roux M, Imbert J, Roul E, Bouillot M, et al. Adaptation of cognitive remediation to adults with ASD: Feasibility and interest from two pilot groups. Presse Medicale. *Presse Medicale* (2019) 48 (10):1019–25. doi: 10.1016/j.lpm.2019.08.010
23. Bishop-Fitzpatrick L, Minshew NJ, Eack SM. A systematic review of psychosocial interventions for adults with autism spectrum disorders. *J Autism Dev Disord* (2013) 43(3):687–94. doi: 10.1007/s10803-012-1615-8
24. Fernández-Sotos P, Torio I, Fernández-Caballero A, Navarro E, González P, Dompablo M, et al. Social cognition remediation interventions: A systematic mapping review. *PloS One* (2019) 14(6):e0218720. doi: 10.1371/journal.pone.0218720
25. Keshavan MS, Vinogradov S, Rumsey J, Sherrill J, Wagner A. Cognitive training in mental disorders: Update and future directions. *Am J Psychiatry* (2014) 171(5):510–22. doi: 10.1176/appi.ajp.2013.13081075
26. Kim EJ, Bahk YC, Oh H, Lee WH, Lee JS, Choi KH. Current status of cognitive remediation for psychiatric disorders: A review. *Front Psychiatry* (2018) 9:461. doi: 10.3389/fpsyt.2018.00461
27. Golan O, Baron-Cohen S. Systemizing empathy: Teaching adults with Asperger syndrome or high-functioning autism to recognize complex emotions using interactive multimedia. *Dev Psychopathol* (2006) 18(2):591–617. doi: 10.1017/S0954579406060305
28. Turner-Brown LM, Perry TD, Dichter GS, Bodfish JW, Penn DL. Brief report: Feasibility of social cognition and interaction training for adults with high functioning autism. *J Autism Dev Disord* (2008) 38(9):1777–84. doi: 10.1007/s10803-008-0545-y
29. Eack SM, Greenwald DP, Hogarty SS, Bahorik AL, Litschge MY, Mazefsky CA, et al. Cognitive enhancement therapy for adults with autism spectrum disorder: Results of an 18-month feasibility study. *J Autism Dev Disord* (2013) 43(12):2866–77. doi: 10.1007/s10803-013-1834-7
30. Hajri M, Abbès Z, Yahia HB, Ouanes S, Halayem S, Bouden A, et al. Effects of Cognitive Remediation Therapy in Children with Autism Spectrum Disorder: Study Protocol. *Int J Sci Res* (2016) 5(7):2007–12. doi: 10.21275/v5i7.art201648
31. Tchanturia K, Larsson E, Adamson J. How anorexia nervosa patients with high and low autistic traits respond to group Cognitive Remediation Therapy. *BMC Psychiatry* (2016) 16(1):334. doi: 10.1186/s12888-016-1044-x
32. Hajri M, Abbes Z, Ben YH, Boudali M, Hamza M, Bouden A, et al. Place of cognitive remedition therapy in the management of autism spectrum disorder. *Int J Psychos Rehabil* (2017) 21(1):55–6. doi: 10.37200/ijpr
33. Okuda T, Asano K, Numata N, Hirano Y, Yamamoto T, Tanaka M, et al. Feasibility of cognitive remediation therapy for adults with autism spectrum disorders: A single-group pilot study. *Neuropsychiatr Dis Treat* (2017) 13:2185–91. doi: 10.2147/NDT.S141555
34. Dandil Y, Smith K, Adamson J, Tchanturia K. Individual cognitive remediation therapy benefits for patients with anorexia nervosa and high autistic features. *Eur Eating Disord Rev* (2020) 28(1):87–91. doi: 10.1002/erv.2707
35. Dandil Y, Baillie C, Tchanturia K. Cognitive Remediation Therapy as a Feasible Treatment for a Young Person With Anorexia Nervosa and Autism Spectrum Disorder Comorbidity: A Case Study. *Clin Case Stud* (2020) 19(2):115–32. doi: 10.1177/1534650119890425
36. Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* (1994) 24:659–85. doi: 10.1007/BF02172145
37. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, Dilavore PC, et al. The Autism Diagnostic Observation Schedule-Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* (2000) 30(3):205–23. doi: 10.1023/A:1005592401947
38. Wechsler D. Manual for the Wechsler abbreviated intelligence scale (WASI). In: *WASI*. San Antonio, TX: The Psychological Corporation (1999). doi: 10.1037/t15170-000
39. Hogarty GE, Greenwald DP. *Cognitive Enhancement Therapy: The Training Manual*. Pittsburgh, Pennsylvania: University of Pittsburgh Medical Center (2006).
40. Allison C, Auyeung B, Baron-Cohen S. Toward brief "red flags" for autism screening: The short Autism Spectrum Quotient and the short Quantitative Checklist in 1,000 cases and 3,000 controls. *J Am Acad Child Adolesc Psychiatry* (2012) 51:202–212.e7. doi: 10.1016/j.jaac.2011.11.003
41. Corsi PM. Human memory and the medial temporal region of the brain. *Dissertation Abstracts Int* (1972) 34(2):819B. doi: 10.1016/B978-0-12-564350-4.50011-7
42. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Test review behaviour rating inventory of executive function. *Child Neuropsychol* (2000) 6:235–8. doi: 10.1076/chin.6.3.235.3152
43. Logan GD, Cowan WB. On the ability to inhibit thought and action: A theory of an act of control. *Psychol Rev* (1984) 91:295–327. doi: 10.1037/0033-295X.91.3.295
44. Casey BJ, Cohen JD, Jezzard P, Turner R, Noll DC, Trainor RJ, et al. Activation of prefrontal cortex in children during a nonspatial working

memory task with functional MRI. *Neuroimage* (1995) 2:221–9. doi: 10.1006/nimg.1995.1029
45. Smith EE, Jonides J. Storage and executive processes in the frontal lobes. *Science* (1999) 283:1657–61. doi: 10.1126/science.283.5408.1657
46. De Vries M, Geurts HM. Cognitive flexibility in ASD; Task switching with emotional faces. *J Child Psychol Psychiatry Allied Disciplines* (2012) 42(12):2558–68. doi: 10.1111/jcpp.12324
47. Kaneda Y, Sumiyoshi T, Keefe R, Ishimoto Y, Numata S, Ohmori T. Brief assessment of cognition in schizophrenia: validation of the Japanese version. *Psychiatry Clin Neurosc* (2007) 61:602–9. doi: 10.1111/j.1440-1819.2007.01725.x
48. Rosvold HE, Mirsky AF, Sarason I, Bransome ED, Beck LH. A continuous performance test of brain damage. *J Consult Psychol* (1956) 20:343. doi: 10.1037/h0043220
49. Keefe RSE, Poe M, Walker TM, Kang JW, Harvey PD. The Schizophrenia Cognition Rating Scale: An Interview-Based Assessment and Its Relationship to Cognition, Real-World Functioning, and Functional Capacity. *Am J Psychiatry* (2006) 163(3):426–32. doi: 10.1176/appi.ajp.163.3.426
50. Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: The NIMH-MATRICS conference to select cognitive domains and test criteria. *Biol Psychiatry* (2004) 56(5):301–7. doi: 10.1016/j.biopsych.2004.06.023
51. Mayer J, Salovey P, Caruso D, Sitarenios G. Measuring Emotional Intelligence With the MSCEIT V2.0. *Emotion* (2003) 3(1):97–105. doi: 10.1037/1528-3542.3.1.97
52. Golan O, Baron-Cohen S, Hill J. The Cambridge Mindreading (CAM) Face-Voice Battery: Testing complex emotion recognition in adults with and without Asperger Syndrome. *J Autism Dev Disord* (2006) 36(2):169–83. doi: 10.1007/s10803-005-0057-y
53. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" Test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry Allied Disciplines* (2001) 42(2):241–51. doi: 10.1017/S0021963001006643
54. Golan O, Baron-Cohen S, Hill JJ, Rutherford MD. The "Reading the Mind in the Voice" test-revised: A study of complex emotion recognition in adults with and without autism spectrum conditions. *J Autism Dev Disord* (2007) 37(6):1096–106. doi: 10.1007/s10803-006-0252-5
55. Golan O, Baron-Cohen S, Hill JJ, Golan Y. The "reading the mind in films" task: complex emotion recognition in adults with and without autism spectrum conditions. *Soc Neurosci* (2006) 1(2):111–23. doi: 10.1080/17470910600980986
56. Kerr SL, Neale JM. Emotion Perception in Schizophrenia: Specific Deficit or Further Evidence of Generalized Poor Performance? *J Abnormal Psychol* (1993) 102(2):312. doi: 10.1037/0021-843X.102.2.312
57. Corcoran R, Mercer G, Frith CD. Schizophrenia, symptomatology and social inference: Investigating "theory of mind" in people with schizophrenia. *Schizophr Res* (1995) 17(1):5–13. doi: 10.1016/0920-9964(95)00024-G
58. Mcgann W, Werven G, Douglas MM. Social competence and head injury: A practical approach. *Brain Injury* (1997) 11(9):621–8. doi: 10.1080/026990597123179
59. Patterson TL, Moscona S, McKibbin CL, Davidson K, Jeste DV. Social skills performance assessment among older patients with schizophrenia. *Schizophr Res* (2001) 48(2–3):351–60. doi: 10.1016/S0920-9964(00)00109-2
60. Larsen DL, Attkisson CC, Hargreaves WA, Nguyen TD. Assessment of client/patient satisfaction: Development of a general scale. *Eval Program Plann* (1979) 2(3):197–207. doi: 10.1016/0149-7189(79)90094-6
61. Heaton RKK, Chelune GJ, Talley JL, Kay GG, Curtiss G, Oreg S, et al. Wisconsin Card Sorting Test Manual: Revised and expanded. *Psychol Res Odessa FL* (1993).
62. Kohler CG, Turner TH, Bilker WB, Brensinger CM, Siegel SJ, Kanes SJ, et al. Facial Emotion Recognition in Schizophrenia: Intensity Effects and Error Pattern. *Am J Psychiatry* (2003) 160(10):1768–74. doi: 10.1176/appi.ajp.160.10.1768
63. Erwin RJ, Gur RC, Gur RE, Skolnick B, Mawhinney-Hee M, Smailis J. Facial emotion discrimination: I. Task construction and behavioral findings in normal subjects. *Psychiatry Res* (1992) 42(3):231–40. doi: 10.1016/0165-1781(92)90115-J
64. Kohler CG, Bilker W, Hagendoorn M, Gur RE, Gur RC. Emotion recognition deficit in schizophrenia: Association with symptomatology and cognition. *Biol Psychiatry* (2000) 48(2):127–36. doi: 10.1016/S0006-3223(00)00847-7
65. Raven JC. Revised manual for Raven's Progressive Matrices and Vocabulary Scale. In: *Revised Manual for Raven's Progressive Matrices and Vocabulary Scale*. Windsor, UK: NFER Nelson (1982).
66. Tallberg IM, Carlsson S, Lieberman M. Children's word fluency strategies. *Scand J Psychol* (2011) 52(1):35–42. doi: 10.1111/j.1467-9450.2010.00842.x
67. Gladsjo JA, Schuman CC, Evans JD, Peavy GM, Miller SW, Heaton RK. Norms for letter and category fluency: Demographic corrections for age, education, and ethnicity. *Assessment* (1999) 6(2):147–78. doi: 10.1177/107319119900600204
68. Bellaj T, Salhi I, Le Gall D, Roy A. Development of executive functioning in school-age Tunisian children. *Child Neuropsychol* (2016) 22(8):919–54. doi: 10.1080/09297049.2015.1058349
69. Shebani MFA, Van De Vijver FJR, Poortinga YH. A strict test of the phonological loop hypothesis with Libyan data. *Memory Cogn* (2005) 33(2):196–202. doi: 10.3758/BF03195308
70. Breidbord J, Croudace TJ. Reliability generalization for childhood autism rating scale. *J Autism Dev Disord* (2013) 43(12):2855–65. doi: 10.1007/s10803-013-1832-9
71. Schopler E, Reichler RJ, DeVellis RF, Daly K. Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). *J Autism Dev Disord* (1980) 9(2):139–52. doi: 10.1007/BF02408436
72. Burgess, Shallice T. (1997). *The Hayling and Brixton tests [Test manual]*. Bury St Edmunds: Thames Valley Test Company Limited (1997). doi: 10.1037/t69253-000
73. Tominaga D. The standardization of the Ryudai's Trail Making Test (RTMT)-from attentional function and working memory's View point. *Bull Faculty Educ Univ Ryukyus* (2005) 67:243–52. doi: 10.1007/springer reference_183035
74. Hirasawa T, Sanada S, Yanagihara M, Miyake K, Tsushima Y, Kado Y, et al. Clinical application of the modified stroop test to children with attention deficit/hyperactivity disorder. *No To Hattatsu* (2010) 42(6):421–6. doi: 10.11251/ojjscn.42.421
75. Martin MM, Rubin RB. A New Measure of Cognitive Flexibility. *psychol Rep* (1995) 76(2):623–6. doi: 10.2466/pr0.1995.76.2.623
76. Roberts ME, Barthel FMS, Lopez C, Tchanturia K, Treasure JL. Development and validation of the Detail and Flexibility Questionnaire (DFlex) in eating disorders. *Eating Behav* (2011) 12:168–74. doi: 10.1016/j.eatbeh.2011.04.001
77. Osterrieth PA. Filetest de copie d'une figure complex: Contribution a l'etude de la perception et de la memoire [The test of copying a complex figure: A contribution to the study of perception and memory]. *Arch Psychol* (1944) 30:286–356. doi: 10.1037/t07717-000
78. Morice R, Delahunty A. Frontal/executive impairments in schizophrenia. *Schizophr Bull* (1996) 22(1):125–37. doi: 10.1093/schbul/22.1.125
79. Penn DL, Roberts DL, Combs D, Sterne A. The development of the social cognition and interaction training program for schizophrenia spectrum disorders. *Psychiatr Serv* (2007) 58(4):449–51. doi: 10.1176/ps.2007.58.4.449
80. Baron-Cohen S, Golan O, Wheelwright S, Hill JJ. *Mind reading: The interactive guide to emotions*. London: Jessica Kingsley Limited (www.jkp.com) (2004).
81. Prins PJM, Brink ET, Dovis S, Ponsioen A, Geurts HM, De Vries M, et al. "Braingame brian": Toward an executive function training program with game elements for children with ADHD and cognitive control problems. *Games Health J* (2013) 2:44–9. doi: 10.1089/g4h.2013.0004
82. Hogarty G. *Personal therapy for schizophrenia and related disorders : A guide to individualized treatment*. New York ; London: Guilford Press (2002).
83. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders. 4th ed.* Washington, DC: American Journal of Psychiatry (1994).
84. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Males and Females, Scientists and Mathematicians. *J Autism Dev Disord* (2001) 31(1):5–17. doi: 10.1023/A:1005653411471
85. Woodbury-Smith MR, Robinson J, Wheelwright S, Baron-Cohen S. Screening adults for Asperger Syndrome using the AQ: A preliminary study of its

diagnostic validity in clinical practice. *J Autism Dev Disord* (2005) 35(3):331–5. doi: 10.1007/s10803-005-3300-7

86. Mandy W, Tchanturia K. Do women with eating disorders who have social and flexibility difficulties really have autism? A case series. *Mol Autism* (2015) 6(1):6. doi: 10.1186/2040-2392-6-6
87. Lai M-C, Baron-Cohen S. Identifying the lost generation of adults with autism spectrum conditions. *Lancet Psychiatry* (2015) 2(11):1013–27. doi: 10.1016/S2215-0366(15)00277-1
88. Hull L, Petrides KV, Mandy W. The Female Autism Phenotype and Camouflaging: a Narrative Review. *Rev J Autism Dev Disord* (2020) 1:1–2. doi: 10.1007/s40489-020-00197-9
89. Walters S, Loads M, Russell A. A Systematic Review of Effective Modifications to Cognitive Behavioural Therapy for Young People with Autism Spectrum Disorders. *Rev J Autism Dev Disord* (2016) 3(2):137–53. doi: 10.1007/s40489-016-0072-2

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Neurocognitive Mechanisms Underlying Social Atypicalities in Autism: Weak Amygdala's Emotional Modulation Hypothesis

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Autism spectrum disorder (ASD) is a neurodevelopmental condition associated with atypicalities in social interaction. Although psychological and neuroimaging studies have revealed divergent impairments in psychological processes (e.g., emotion and perception) and neural activity (e.g., amygdala, superior temporal sulcus, and inferior frontal gyrus) related to the processing of social stimuli, it remains difficult to integrate these findings. In an effort to resolve this issue, we review our psychological and functional magnetic resonance imaging (fMRI) findings and present a hypothetical neurocognitive model. Our psychological study showed that emotional modulation of reflexive joint attention is impaired in individuals with ASD. Our fMRI study showed that modulation from the amygdala to the neocortex during observation of dynamic facial expressions is reduced in the ASD group. Based on these findings and other evidence, we hypothesize that weak modulation from the amygdala to the neocortex—through which emotion rapidly modulates various types of perceptual, cognitive, and motor processing functions—underlies the social atypicalities in individuals with ASD.

Keywords: amygdala, autism spectrum disorder (ASD), emotion, emotional facial expression, functional magnetic resonance imaging (fMRI)

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition associated with atypicalities in reciprocal social interaction (1). Characteristic symptoms of social atypicalities in individuals with ASD include difficulty in perception and recognition of faces and facial expressions (2–4), eye gaze (5–7), action (8–10), and the inner states (11–13) of other individuals.

The neurocognitive mechanisms underlying the social atypicalities of ASD remain elusive. Psychological studies have shown that various types of social cognitive processes are atypical in individuals with ASD compared with those of typically developing (TD) individuals; these atypicalities include emotional, perceptual, cognitive, and motor processing (14). In ASD groups, functional neuroimaging studies also revealed atypical brain activity associated with processing of social stimuli in multiple brain regions, including the amygdala, fusiform gyrus, superior temporal sulcus, and

inferior frontal gyrus (15–17). However, it remains difficult to integrate these divergent psychological and neuroscientific findings to explain the social atypicalities of ASD.

In this article, we briefly review our psychological and neuroscientific findings and present a neurocognitive model seeking to further the understanding of this issue. Our psychological experiment revealed that individuals with ASD exhibit impaired rapid emotional modulation of attentional shift triggered by gaze. Our functional magnetic resonance imaging (fMRI) study demonstrated that individuals with ASD exhibit weak modulatory effects from the amygdala to the neocortical network during the observation of facial expressions. Based on these findings and other evidence, we speculate that weak modulation from the amygdala to the neocortex, *via* which emotion rapidly modulates various types of perceptual, cognitive, and motor processing functions, underlies the social atypicalities of individuals with ASD.

Psychological Study of Emotional Modulation of Reflexive Joint Attention

In the first psychological experiment, we investigated the modulatory effect of emotion on reflexive joint attention (18).

Clinical observations have suggested that one of the most obvious social atypicalities in individuals with ASD is a deficit of joint attention with others (19). However, a number of experimental psychological studies found that individuals with ASD can exhibit intact reflexive joint attention using the cueing paradigm (20, 21). In an effort to resolve this discrepancy, some studies in TD individuals showed that reflexive joint attention can be positively modulated by emotional facial expressions, especially when presented dynamically (22–29), although the effects with static expressions are still debated (30). A developmental study showed that this emotional enhancement of joint attention starts by at least 7 years of age (28). Some studies found that higher autistic traits are associated with weaker emotional enhancement of reflexive joint attention (27, 31). Numerous studies reported that individuals with ASD are impaired in terms of processing emotions in facial expressions (2–4, 32), even at the rapid, unconscious processing stage (33); thus, we hypothesized that individuals with ASD would show impaired joint attention when gaze cues were combined with emotional facial expressions. However, direct evidence of this was lacking. Other studies testing the integration between gaze and emotional expressions in individuals with ASD using different paradigms have reported mixed findings (34–38).

We tested this hypothesis in adolescent/adult individuals with ASD and TD controls using a dynamic fearful gaze as the cue of the cueing paradigm.

Methods

We tested 11 high-functioning individuals with ASD (three women; mean ± SD age, 17.5 ± 6.5 years) and 11 age- and sex-matched TD individuals (three women; mean ± SD age, 19.5 ± 2.2 years). All participants in the ASD group had intelligence quotients (IQs) in the normal range and were diagnosed with Asperger's disorder or pervasive developmental disorder not otherwise specified (PDD-NOS) with milder symptoms of Asperger's disorder.

As cue stimuli, dynamic fearful and neutral facial expressions with changing gaze directions were presented (**Figure 1**); dynamic expressions were created from the photographs of neutral and fearful faces (39) using computer morphing. Stimuli were sequentially presented from neutral to 100% fearful under fearful gaze conditions. Under the neutral gaze condition, only the gaze direction was dynamically changed.

In each trial (**Figure 1**), after point fixation, a dynamic fearful or neutral facial cue with the eyes directed toward either the left or right was presented at the center of the monitor. Subsequently, a target letter "T" appeared in either the left or right visual field Participants were instructed to specify as quickly as possible whether the target appeared by pressing a button; the reaction times (RTs) of button pressing were measured. The participants were instructed that the cues were non-predictive of target appearance.

Results

The RT differences between valid and invalid conditions were used as indices of the gaze cueing effect. One-sample *t*-tests for RT differences (**Figure 1**) showed that the gaze cueing effects were significantly greater than zero in response to both fearful and neutral cues in both the ASD and TD groups. Emotion (fear, neutral) × group (ASD, TD) analysis of variance revealed a

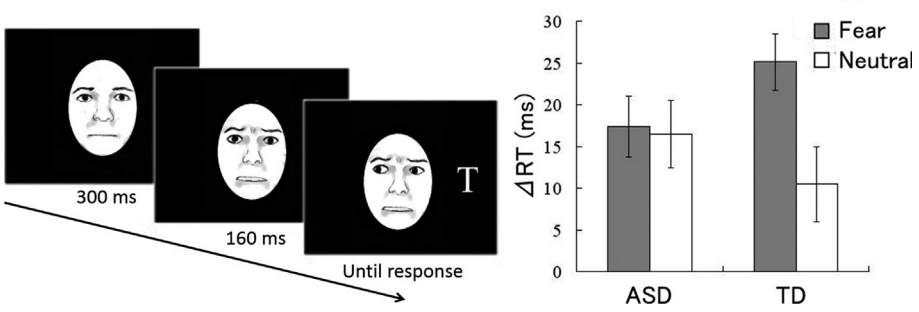

FIGURE 1 | Study by Uono et al. (18). (Left) Illustration of dynamic fearful gaze. (Right) Mean (± standard error) reaction time differences between invalid and valid gaze conditions for autism spectrum disorder (ASD) and typically developing (TD) groups.

significant main effect of emotion and a significant interaction. Follow-up analyses of the interaction demonstrated that the gaze cueing effect was significantly greater in response to fearful cues than to neutral cues in the TD group, but not in the ASD group.

Discussion

Our data under the neutral condition confirmed that gaze cues triggered reflective joint attention in individuals with ASD as observed in previous studies.

More importantly, the gaze cueing effect was greater in response to fearful cues than to neutral cues only in the TD group. The results demonstrate that a dynamic emotional gaze does not facilitate reflexive joint attention in individuals with ASD. Our results may, at least in part, account for the discrepancy between clinical observations and experimental findings in terms of joint attention in individuals with ASD. In naturalistic communication, emotional gaze by other individuals provides important information regarding their evaluation of attended objects (40) and their inner mental state (41). Therefore, although TD individuals evidently show reflective joint attention with the facilitative effect of emotion, individuals with ASD may fail to show such emotional joint attention; this lack of attention may result in difficulty in social learning and social interaction.

Our results indicate that emotional modulation of attentional processing is impaired in individuals with ASD, although their reliability should be further confirmed due to the relatively small sample size and several possible confounding factors (e.g., age). Similar findings have been reported in other studies that used different experimental paradigms. For instance, one previous study using the visual search paradigm showed that the facilitated perception of happy facial expressions in TD individuals was lacking in individuals with ASD (42). When dynamic facial expressions with subtle emotions were presented and participants were instructed to match the image in the response panel to the final image of the stimulus, individuals with ASD were less likely to perceive exaggerated facial expressions than were TD individuals (43). Another study showed that automatic congruent facial responses to emotional facial expressions were reduced in individuals with ASD compared with TD individuals; however, basic facial motor functions were not impaired in individuals with ASD (44). These data suggest that emotional modulation of various types of perceptual, cognitive, and motor processing functions may be atypical in individuals with ASD.

fMRI Study of the Amygdala-Neocortex Network During Facial Expression Processing

In the second fMRI experiment, we explored the functional neural networking patterns underlying atypical processing of dynamic facial expressions (45).

Multiple previous fMRI studies have evaluated the brain activities associated with atypical facial expression processing in individuals with ASD [e.g., (46)]. Although the results varied somewhat, most studies reported that observation of emotional facial expressions induced less activation in the ASD group than the TD group, in both subcortical regions (e.g., the amygdala) and neocortical regions (e.g., the fusiform gyrus, superior temporal sulcus, and inferior frontal gyrus). A considerable body of neuropsychological and neuroimaging evidence from TD individuals implies that these brain regions are related to specific social information processing, such as emotional evaluation in the amygdala (47), visual decoding of faces in the fusiform gyrus and superior temporal sulcus (48), and action-observation matching in the inferior frontal gyrus (49). These data suggest that reduced activity in these subcortical and neocortical regions may underlie atypical facial expression processing in individuals with ASD. Among these regions, the amygdala has long received much attention in ASD research based on divergent lines of evidence; for example, the amygdala works as a hub for brain regions associated with social perception and social affiliation (50), which are affected in individuals with ASD; amygdala-damaged monkeys show abnormal behavioral symptoms similar to ASD (51, 52); and the amygdala in individuals with ASD show structural regional abnormalities, both microscopic (53, 54) and macroscopic (55, 56), and connectivity abnormalities (57).

However, the coupling patterns between the subcortical and neocortical regions during observation of emotional facial expressions in individuals with ASD remain unclear. A previous study (58) investigated this issue in TD individuals by analyzing fMRI data while the participants observed dynamic facial expressions using dynamic causal modeling (DCM); this allows inferences to be drawn about the causal and directional effects among brain regions (59). The models compared included those considering a modulatory effect of dynamic expressions from the amygdala to the neocortical network, from the neocortical network to the amygdala, and a joint effect. The optimal model was that featuring a modulatory effect from the amygdala to the neocortical network. This result is compatible with anatomical findings in monkeys; specifically, the amygdala receives inputs *via* subcortical visual pathways that bypass the neocortical visual pathways (60), and it sends projections to many neocortical regions, including the visual and motor cortices (61). Based on these data and the above-described psychological findings on reduced emotional modulation of facial expression processing in individuals with ASD, we hypothesized that modulation of the neocortical network by the amygdala during observation of dynamic facial expressions may be reduced in individuals with ASD.

We tested this hypothesis in an fMRI experiment with ASD and TD groups. The participants passively observed dynamic facial expressions of anger and happiness and dynamic randomized mosaic images (control stimuli). Following analysis of group differences in regional brain activity, we performed DCM and compared models featuring modulation of dynamic expressions from the amygdala to the neocortical network, from the neocortical network to the amygdala, and a joint effect. We predicted that the first model would optimally explain the between-group differences.

Methods

We tested 31 high-functioning individuals with ASD (nine women; mean ± SD age, 27.2 ± 8.5 years) and 31 age- and sex-matched TD individuals (nine women; mean ± SD age, 24.2 ± 1.0 years). All participants in the ASD group had IQs in the normal range and were diagnosed with Asperger's disorder or PDD-NOS with milder symptoms of Asperger's disorder.

The dynamic expression stimuli used were video clips of Japanese models that progressed from neutral to angry or from neutral to happy in terms of facial expression (**Figure 2**). Dynamic randomized mosaic images were created using the same materials. All dynamic expression frames were divided into very small squares and randomly re-ordered to yield dynamic information lacking facial features. Corresponding to the original dynamic expressions, the mosaic image stimuli were serially presented as a moving clip.

During each stimulus trial, after point fixation, the dynamic face or dynamic mosaic stimulus was presented. During each dummy-target trial, a red cross was presented instead of the stimulus and participants were instructed to press a button when the cross appeared.

Image scanning was performed with the aid of a 3-T scanning system at ATR Brain Activity Imaging Center. Image analyses (**Supplementary Figure 1**) featured standard preprocessing procedures and statistical tests at the group level (62). For data analyses, first region of interest (ROI) analyses were conducted using multivariate analyses of covariance and follow-up univariate *t*-tests. Then, DCM was performed in a standard manner (63–65). To investigate the direction of functional interaction between the amygdala and neocortex, seven brain regions (the pulvinar, amygdala, primary visual cortex, fifth visual area, fusiform gyrus, superior temporal sulcus, and inferior frontal gyrus) of the right hemisphere were selected (**Figure 2**). The coordinates of each ROI were derived from the results of a previous study (58). We assumed that the neocortical, social signal processing, network was in play based on previous evidence (66, 67). We also assumed that the subcortical visual pathway to the amygdala processed emotional facial expressions based on previous evidence (68, 69). Three models were constructed in terms of the direction of the modulatory effects (i.e., change in the connectivity between regions caused by experimental manipulation) of dynamic facial expressions: from the amygdala to the neocortex, from the neocortex to the amygdala, and bidirectional (**Figure 2**). We compared these models and selected that which optimally explained the data (70). Between-group

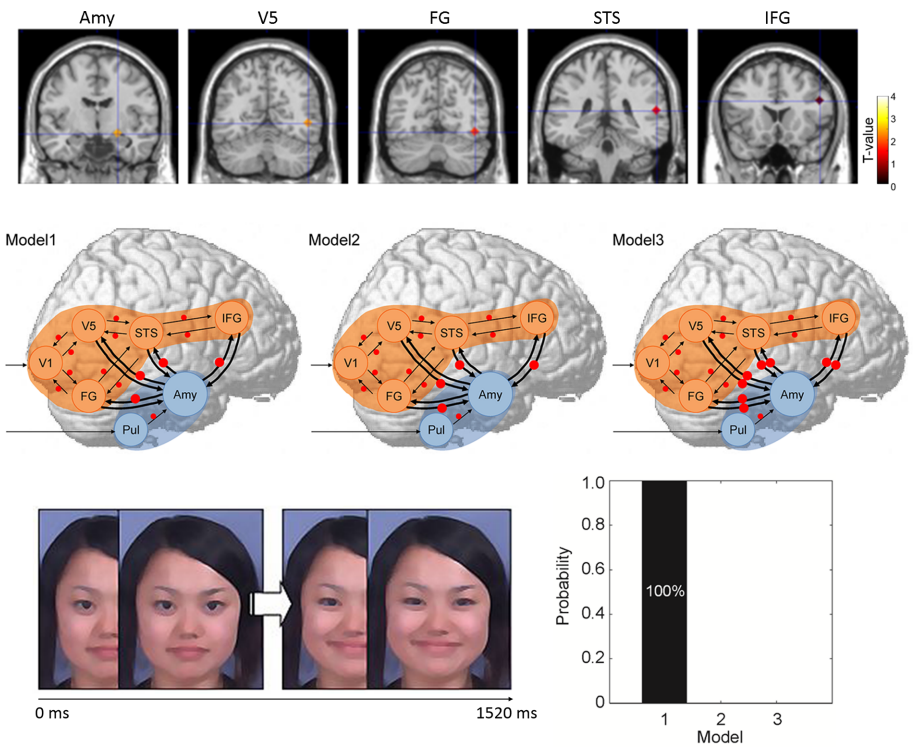

FIGURE 2 | Study by Sato et al. (45). (Upper) Regions of interest in terms of regional brain activity and dynamic causal modeling analysis rendered on the spatially normalized brain of a representative participant. The degree of activation (a stronger response to dynamic facial expressions vs. dynamic mosaics in typically developing (TD) vs. autism spectrum disorder (ASD) groups) is overlaid using a red-yellow color scale. (Middle) Models for differences between ASD and TD groups in terms of the modulatory effect of dynamic expression in dynamic causal modeling. Arrows indicate intrinsic connections between brain regions. Red circles indicate modulation of dynamic expression. (Lower left) Illustration of dynamic facial expression. (Lower right) Results of model comparison for group differences. Amy, amygdala; FG, fusiform gyrus; IFG, inferior frontal gyrus; STS, superior temporal sulcus; V5, fifth visual area/middle temporal area.

differences in the modulatory effects of dynamic expressions were also evaluated (71).

Results

ROI analyses revealed that activities in the predefined brain regions during observing dynamic facial expressions (compared with dynamic mosaics) were significantly lower in the ASD than the TD group.

We used DCM to compare three models of the modulatory influences of dynamic facial expressions between the amygdala and neocortical network (**Figure 2**). This revealed that modulation of dynamic facial expressions from the amygdala to the neocortical network best explained the differences between the ASD and TD groups (**Figure 2**). The profile of modulatory effects demonstrated that modulation of dynamic expressions was reduced in all connections from the amygdala to the neocortical regions in the ASD group.

Discussion

The overall activities of the subcortical and neocortical regions involved in specific aspects of facial expression processing (e.g., the amygdala) were reduced in the ASD group during observation of dynamic facial expressions. These results are largely consistent with previous findings (46, 72).

Furthermore, DCM demonstrated that the model featuring modulation of dynamic facial expression from the amygdala to the neocortical network optimally explained the differences between the ASD and TD groups. The ASD group exhibited reduced modulation. The atypical functional networking patterns in individuals with ASD are in line with the previous description of weak modulation of dynamic expression within neocortical regions (72) and weak resting-state connectivity between the amygdala and neocortical regions (73) in ASD groups. However, this is the first evidence that modulation from the amygdala to the neocortex is weak in individuals with ASD during dynamic facial expression processing.

Neurocognitive Model of Weak Amygdala's Modulation in Autism

In summary, our psychological data demonstrate that individuals with ASD exhibit impaired rapid emotional modulation of attentional shift triggered by gaze. Our fMRI study demonstrated that individuals with ASD exhibit weak modulation from the amygdala to the neocortex during facial expression processing.

Although there is minimal direct evidence in individuals with ASD related to these topics, findings and theories in TD individuals have provided suggestions to further understand these psychological and neural phenomena. From a psychological perspective, considerable evidence and influential theories suggest that emotional processing can be rapidly implemented, even before subjective stimulus perception (74). Abundant evidence and theories suggest that emotional processing can modulate various types of other cognitive and motor processes (75, 76). Furthermore, psychological theories of emotion suggest that emotional processing is conducted for each external stimulus regardless of clear subjective experience (77). These data suggest that rapid emotional modulation of other processes is important in social interaction.

From a neural perspective, previous functional neuroimaging studies in TD participants have revealed that the amygdala implements emotional processing of external stimuli, even before conscious perception of the stimuli, *via* subcortical visual pathways (68, 78). Electrophysiological studies directly recording electric amygdala activity demonstrated that emotion-related activity occurs in the amygdala within 100 ms (79). Earlier DCM of electrophysiological data from TD participants suggested that modulation of dynamic facial expressions from the amygdala to the neocortical network commences before 200 ms (58). Other electrophysiological studies with TD individuals also showed that the emotional modulation of the neocortex during facial expression processing begins at approximately 200 ms (80, 81). Collectively, these data suggest that the amygdala rapidly modulates activity in the neocortex *via* the subcortical visual pathway, in accordance with the emotional significance of stimuli.

Based on our results, together with these data, we formulate a hypothesis regarding the neurocognitive mechanisms underlying social atypicalities of ASD (**Figure 3**). From a psychological perspective, individuals with ASD have weak implementation of [1] rapid emotional processing and [2] emotional modulation of diverse processing of social stimuli. From a neural perspective, individuals with ASD have reductions in [1] rapid emotion-related amygdala activity *via* the subcortical visual pathway at approximately 100 ms and [2] emotion-related modulation from the amygdala to the widespread neocortical network at approximately 200 ms, which are associated with modulated perceptual, cognitive, and motor processing of social stimuli. This hypothesis can integrate previous psychological and neuroscientific findings of atypicalities in divergent psychological and neural processing in individuals with ASD, as described in the Introduction.

We also hypothesize that the neurocognitive mechanisms of weak amygdala modulation may be important during early development in individuals with ASD. Researchers have proposed that subcortical regions functioning from early infancy, such as the amygdala, show a bias to face- and eye-like stimuli; these regions develop cortical specialization for face and gaze processing through modulation of cortical activity (82). An anatomical study with large samples identified the smaller volume of subcortical regions (e.g., the amygdala) throughout development in individuals with ASD compared with TD individuals (56). However, it is unclear whether infants later diagnosed with autism initially exhibit a lack of bias to face and direct gaze (83). Investigation of the response to emotional facial expressions might be a promising approach to more effectively differentiate typical infants from infants with high risk of autism, because emotional facial expression triggers a robust activation of the amygdala (84); moreover, emotional sharing during joint attention facilitates the development of social functions (85). There have been few studies regarding this perspective in early infancy, although a recent study demonstrated a comparable

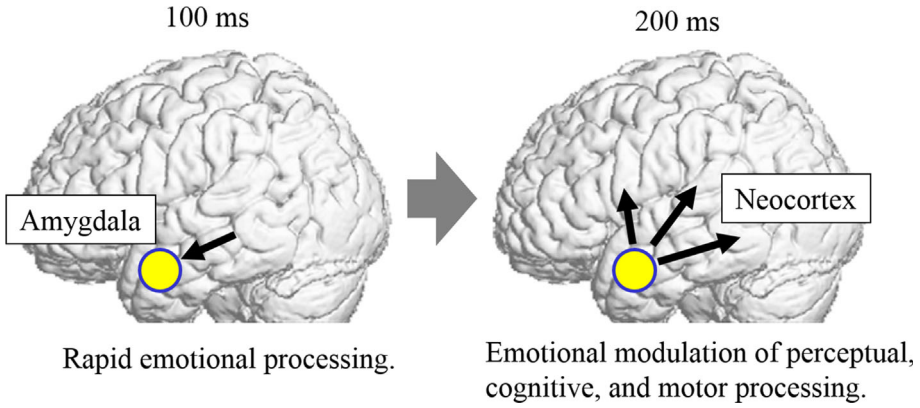

FIGURE 3 | Hypothetical neurocognitive mechanisms underlying social atypicalities of autism spectrum disorder (ASD). In this model, individuals with ASD exhibit weak emotion-related activation in the amygdala *via* the subcortical visual pathway at approximately 100 ms (left). They also exhibit weak modulation from the amygdala to the widespread neocortical network, which is associated with modulated perceptual, cognitive, and motor processing functions of social stimuli, at approximately 200 ms (right).

attentional bias to fearful facial expressions in infants at low and high risks of ASD (86). To confirm the hypothesis of weak amygdala modulation in response to social stimuli, future studies should explore the processing of emotional facial expressions and the underlying neural correlates in individuals with ASD from infancy to adulthood.

Our hypothesis positing weak amygdala's modulation of the widespread neocortical regions may have practical implications, suggesting that improved amygdala activity might exert several positive effects on perceptual, cognitive, or motor processing of social stimuli. Consistent with this notion, a previous study has shown that electrical stimulation of the amygdala in individuals with ASD modified their autistic symptoms and face-to-face interaction behaviors (87). The influence of oxytocin may also be relevant. Some previous psychological studies have shown that intranasal administration of oxytocin to individuals with ASD facilitated their perceptual and cognitive processing of emotional facial expressions (88, 89). An fMRI study demonstrated that improved emotion recognition based on facial expressions due to intranasal administration of oxytocin was associated with increased amygdala reactivity in response to facial stimuli in ASD and TD participants (90). Modulation from the amygdala to the neocortical regions may thus explain the behavioral influences of oxytocin in individuals with ASD, although the effect of oxytocin on social atypicalities in ASD remains controversial (91). In sum, electrical or pharmacological intervention to modulate the activity of the amygdala may usefully improve social functioning in individuals with ASD.

However, it must be noted that several issues remain, and future extension of this work is needed. First, because the hypothetical model was proposed based on relatively few findings, more evidence is needed, especially neuroscientific evidence. Because psychological studies have demonstrated atypical emotional modulation of social stimuli in individuals with ASD using various types of psychological tasks (e.g., the cueing paradigm), neuroimaging investigation using such tasks could provide direct tests of the neurocognitive model we proposed. Testing different stimuli (e.g., movies and live interactions) would be valuable, as previous fMRI studies have reported different activation patterns with different stimuli; for example, static social stimuli evoked different patterns of neural activity compared to dynamic stimuli in individuals with ASD (46, 72).

Second, because findings regarding ASD could be subject to multiple confounding factors, such as trait anxiety (92) and alexithymia (93), which could be associated atypical amygdala function (94, 95), further investigations would be needed to separate the effects of core ASD symptoms from the effects of these factors on psychological and neural activity in the proposed model.

Third, the neurocognitive model we propose in this article may not be specific to ASD but common across several neurodevelopmental and neuropsychiatric disorders. Some studies have reported behavioral problems having to do with emotional modulation and neurological abnormalities in amygdala activity and connectivity in other clinical groups. For example, previous studies have reported that individuals with attention-deficit hyperactivity disorder were impaired in emotion recognition from facial expressions (96) and showed atypical amygdala activity (97). Both the sensitivity and specificity of the model in describing the social atypicalities of ASD should be tested.

CONCLUSIONS

Based on our psychological and neuroimaging data and other related evidence, we presented our hypothetical neurocognitive model that weak modulation from the amygdala to neocortical regions—through which emotion rapidly modulates various types of perceptual, cognitive, and motor processing functions—underlies social atypicalities in individuals with ASD. Our model may enable integration of divergent psychological and neuroscientific findings showing atypical psychological and neural processes in individuals with ASD. However, the model

lacks sufficient evidence. We hope that our hypothesis will stimulate empirical research regarding social atypicalities in individuals with ASD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors designed the research and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00864/full#supplementary-material

SUPPLEMENTARY FIGURE 1 | Flowchart of functional magnetic resonance imaging (fMRI) data analysis. The fMRI data for each subject were first preprocessed (realigned using the first scan as a reference to correct for head motion, corrected for slice timing, coregistered to the anatomical image, normalized to the Montreal Neurological Institute space, and smoothed with an isotopic Gaussian kernel). Next, a general linear model was estimated for each subject. For regional brain activity analyses, multivariate analyses of covariance were conducted on the beta estimates (i.e., task-related increments of each subject's blood oxygen level-dependent signal) for regions of interest. For effective or directional connectivity analysis, dynamic causal modeling (DCM) was performed on three network models dealing with the amygdala-neocortex interaction using time series data extracted from the regions of interest of individual subjects. Group level DCMs were estimated using a second-level parametric empirical Bayesian DCM engine. Bayesian model comparisons and parameter inferences derived *via* Bayesian averaging were accomplished to evaluate group differences.

REFERENCES

1. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders. 5th ed*. Arlington (VA): American Psychiatric Publishing (2013).
2. Hobson RP. *Autism and the development of mind*. Lawrence Erlbaum Associates: Hove (UK) (1993).
3. Uljarevic M, Hamilton A. Recognition of emotions in autism: a formal metaanalysis. *J Autism Dev Disord* (2013) 43(7):1517–26. doi: 10.1007/s10803-012-1695-5
4. Tang J, Falkmer M, Horlin C, Tan T, Vaz S, Falkmer T. Face recognition and visual search strategies in autism spectrum disorders: Amending and extending a recent review by Weigelt et al. *PloS One* (2015) 10:e0134439. doi: 10.1371/journal.pone.0134439
5. Mundy P, Sigman M, Kasari C. Understanding other minds: Perspectives from autism. In: . *The theory of mind and joint-attention deficits in autism*. New York (NY): Oxford University Press (1994). p. 181–203.
6. Canigueral R, Hamilton AFC. The role of eye gaze during natural social interactions in typical and autistic. *People Front Psychol* (2019) 10:560. doi: 10.3389/fpsyg.2019.00560
7. Tanaka JW, Sung A. The "eye avoidance" hypothesis of autism face processing. *J Autism Dev Disord* (2016) 46(5):1538–52. doi: 10.1007/s10803-013-1976-7
8. Williams JH, Whiten A, Singh T. A systematic review of action imitation in autistic spectrum disorder. *J Autism Dev Disord* (2004) 34:285–99. doi: 10.1023/B:JADD.0000029551.56735.3a
9. Federici A, Parma V, Vicovaro M, Radassao L, Casartelli L, Ronconi L. Anomalous perception of biological motion in autism: A conceptual review and meta-analysis. *Sci Rep* (2020) 10:4576. doi: 10.1038/s41598-020-61252-3
10. Nadel J. perception-action coupling and imitation in autism spectrum disorder. *Dev Med Child Neurol* (2015) 57:55–8. doi: 10.1111/dmcn.12689
11. Baron-Cohen S. *Mindblindness: An essay on autism and theory of mind*. Cambridge (MA): MIT Press (1995).
12. Brewer N, Young RL, Barnett E. Measuring theory of mind in adults with autism spectrum disorder. *J Autism Dev Disord* (2017) 47:1927–41. doi: 10.1007/s10803-017-3080-x
13. Livingston LA, Carr B, Shah P. Recent advances and new directions in measuring theory of mind in autistic adults. *J Autism Dev Disord* (2019) 49:1738–44. doi: 10.1007/s10803-018-3823-3
14. Amaral DG, Dawson G, Geschwind DH. *Autism spectrum disorders*. New York (NY): Oxford University Press (2011).
15. Sato W, Uono S. The atypical social brain network in autism: advances in structural and functional MRI studies. *Curr Opin Neurol* (2019) 32(4):617–21. doi: 10.1097/WCO.0000000000000713
16. Bernhardt BC, Di Martino A, Valk SL, Wallace GL. Neuroimaging-based phenotyping of the autism spectrum. *Curr Top Behav Neurosci* (2017) 30:341–55. doi: 10.1007/7854_2016_438
17. Müler RA, Fishman I. Brain connectivity and neuroimaging of social networks in autism. *Trends Cognit Sci* (2018) 22:1103–16. doi: 10.1016/j.tics.2018.09.008
18. Uono S, Sato W, Toichi M. Dynamic fearful gaze does not enhance attention orienting in individuals with Asperger's disorder. *Brain Cogn* (2009) 71(3):229–33. doi: 10.1016/j.bandc.2009.08.015
19. Mundy P, Sigman M, Ungerer J, Sherman T. Defining the social deficits of autism: The contribution of nonverbal communication measures. *J Child Psychol Psychiatry* (1986) 27(5):657–69. doi: 10.1111/j.1469-7610.1986.tb00190.x
20. Posner MI. Orienting of attention. *Q J Exp Psychol* (1980) 32(1):3–25. doi: 10.1080/00335558008248231
21. Okada T, Sato W, Murai T, Kubota Y, Toichi M. Eye gaze triggers visuospatial attentional shift in individuals with autism. *Psychologia* (2003) 46(4):246–54. doi: 10.2117/psysoc.2003.246
22. Graham R, Friesen CK, Fichtenholz HM, LaBar KS. Modulation of reflexive orienting to gaze direction by facial expressions. *Vis Cogn* (2010) 18:331–68. doi: 10.1080/13506280802689281
23. Lassalle A, Itier RJ. Fearful, surprised, happy, and angry facial expressions modulate gaze-oriented attention: Behavioral and ERP evidence. *Soc Neurosci* (2013) 8:583–600. doi: 10.1080/17470919.2013.835750
24. Lassalle A, Itier RJ. Emotional modulation of attention orienting by gaze varies with dynamic cue sequence. *Vis Cogn* (2015) 23:720–35. doi: 10.1080/13506285.2015.1083067
25. Liu J, Shi Y, Whitaker L, Tian Y, Hu Z. Facial expressions modulate the gaze orienting effect on sound localization judgement. *Vis Cogn* (2019) 27:109–19. doi: 10.1080/13506285.2019.1606128
26. McCrackin SD, Itier RJ. Both fearful and happy expressions interact with gaze direction by 200 ms SOA to speed attention orienting. *Vis Cogn* (2018) 26:231–52. doi: 10.1080/13506285.2017.1420118

27. McCrackin SD, Itier RJ. Individual differences in the emotional modulation of gaze-cuing. *Cognit Emot* (2019) 33:768–800. doi: 10.1080/02699931.2018.1495618
28. Neath K, Nilsen ES, Gittsovich K, Itier RJ. Attention orienting by gaze and facial expressions across development. *Emotion* (2013) 13:397–408. doi: 10.1037/a0030463
29. Uono S, Sato W, Toichi M. Dynamic fearful expressions enhance gaze-triggered attention orienting in high and low anxiety individuals. *Soc Behav Pers* (2009) 37:1313–26. doi: 10.2224/sbp.2009.37.10.1313
30. Dalmaso M, Castelli L, Galfano G. Social modulators of gaze-mediated orienting of attention: a review. *Psychon Bull Rev* (in press). doi: 10.3758/s13423-020-01730-x
31. Lassalle A, Itier RJ. Autistic traits influence gaze-oriented attention to happy but not fearful faces. *Soc Neurosci* (2015) 10:70–88. doi: 10.1080/17470919.2014.958616
32. Uono S, Sato W, Toichi M. The specific impairment of fearful expression recognition and its atypical development in pervasive developmental disorder. *Soc Neurosci* (2011) 6(5–6):452–63. doi: 10.1080/17470919.2011.605593
33. Hall GB, West CD, Szatmari P. Backward masking: Evidence of reduced subcortical amygdala engagement in autism. *Brain Cogn* (2007) 65(1):100–6. doi: 10.1016/j.bandc.2007.01.010
34. Akechi H, Senju A, Kikuchi Y, Tojo Y, Osanai H, Hasegawa T. Does gaze direction modulate facial expression processing in children with autism spectrum disorder? *Child Dev* (2009) 80(4):1134–46. doi: 10.1111/j.1467-8624.2009.01321.x
35. Akechi H, Senju A, Kikuchi Y, Tojo Y, Osanai H, Hasegawa T. The effect of gaze direction on the processing of facial expressions in children with autism spectrum disorder: An ERP study. *Neuropsychologia* (2010) 48(10):2841–51. doi: 10.1016/j.neuropsychologia.2010.05.026
36. Ioannou C. Shared mechanism for emotion processing in adolescents with and without autism. *Sci Rep* (2017) 7:42696. doi: 10.1038/srep42696
37. Tell D, Davidson D, Camras LA. Recognition of emotion from facial expressions with direct or averted eye gaze and varying expression intensities in children with autism disorder and typically developing children. *Autism Res Treat* (2014) 2014:816137. doi: 10.1155/2014/816137
38. Vida MD, Maurer D, Calder AJ, Rhodes G, Walsh JA, Pachai MV, et al. The influences of face inversion and facial expression on sensitivity to eye contact in high-functioning adults with autism spectrum disorders. *Autism Dev Disord* (2013) 43:2536–48. doi: 10.1007/s10803-013-1802-2
39. Ekman P, Friesen WV. *Pictures of Facial Affect*. Palo Alto (CA): Consulting Psychologist (1976).
40. Bayliss AP, Frischen A, Fenske MJ, Tipper SP. Affective evaluations of objects are influenced by observed gaze direction and emotional expression. *Cognition* (2007) 104(3):644–53. doi: 10.1016/j.cognition.2006.07.012
41. Shamay-Tsoory SG, Tibi-Elhanany Y, Aharon-Peretz J. The green-eyed monster and malicious joy: the neuroanatomical bases of envy and gloating (schadenfreude). *Brain* (2007) 130(6):1663–78. doi: 10.1093/brain/awm093
42. Sato W, Sawada R, Uono S, Yoshimura S, Kochiyama T, Kubota Y, et al. Impaired detection of happy facial expressions in autism. *Sci Rep* (2017) 7 (1):13340. doi: 10.1038/s41598-017-11900-y
43. Uono S, Sato W, Toichi M. Reduced representational momentum for subtle dynamic facial expressions in individuals with autism spectrum disorders. *Res Autism Spectr Disord* (2014) 8(9):1090–9. doi: 10.1016/j.rasd.2014.05.018
44. Yoshimura S, Sato W, Uono S, Toichi M. Impaired overt facial mimicry in response to dynamic facial expressions in high-functioning autism spectrum disorders. *J Autism Dev Disord* (2015) 45(5):1318–28. doi: 10.1007/s10803-014-2291-7
45. Sato W, Kochiyama T, Uono S, Yoshimura S, Kubota Y, Sawada R, et al. Atypical amygdala–Neocortex interaction during dynamic facial expression processing in autism spectrum disorder. *Front Hum Neurosci* (2019) 13:351. doi: 10.3389/fnhum.2019.00351
46. Pelphrey KA, Morris JP, McCarthy G, Labar KS. Perception of dynamic changes in facial affect and identity in autism. *Soc Cognit Affect Neurosci* (2007) 2(2):140–9. doi: 10.1093/scan/nsm010
47. Calder AJ, Lawrence AD, Young AW. Neuropsychology of fear and loathing. *Nat Rev Neurosci* (2001) 2(5):352–63. doi: 10.1038/35072584
48. Haxby JV, Hoffman EA, Gobbini MI. The distributed human neural system for face perception. *Trends Cognit Sci* (2000) 4(6):223–33. doi: 10.1016/S1364-6613(00)01482-0
49. Rizzolatti G, Fogassi L, Gallese V. Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat Rev Neurosci* (2001) 2(9):661–70. doi: 10.1038/35090060
50. Bickart KC, Dickerson BC, Barrett LF. The amygdala as a hub in brain networks that support social life. *Neuropsychologia* (2014) 63:235–48. doi: 10.1016/j.neuropsychologia.2014.08.013
51. Bachevailer J. The amygdala, social behaviour, and autism. In: Aggleton JP, editor. *The Amygdala: A Functional Analysis*. New York, NY: Oxford University Press (2000). p. 509–44.
52. Amaral DG, Bauman MD, Schumann CM. The amygdala and autism: implications from non-human primate studies. *Genes Brain Behav* (2003) 2 (5):295–302. doi: 10.1034/j.1601-183X.2003.00043.x
53. Kemper TL, Bauman ML. The contribution of neuropathologic studies to the understanding of autism. *Neurol Clinics* (1993) 11:175–87. doi: 10.1016/S0733-8619(18)30176-2
54. Schumann CM, Amaral DG. Stereological analysis of amygdala neuron number in autism. *J Neurosci* (2006) 26:7674–9. doi: 10.1523/JNEUROSCI.1285-06.2006
55. Aylward EH, Minshew NJ, Goldstein G, Honeycutt NA, Augustine AM, Yates KO, et al. MRI volumes of amygdala and hippocampus in non–mentally retarded autistic adolescents and adults. *Neurology* (1999) 53:2145–50. doi: 10.1212/WNL.53.9.2145
56. van Rooij D, Anagnostou E, Arango C, Auzias G, Behrmann M, Busatto GF, et al. Cortical and subcortical brain morphometry differences between patients with autism spectrum disorders (ASD) and healthy individuals across the lifespan: results from the ENIGMA-ASD working group. *Am J Psychiatry* (2018) 175(4):359–69. doi: 10.1176/appi.ajp.2017.17010100
57. Gibbard CR, Ren J, Skuse DH, Clayden JD, Clark CA. Structural connectivity of the amygdala in young adults with autism spectrum disorder. *Hum Brain Mapp* (2018) 39:1270–82. doi: 10.1002/hbm.23915
58. Sato W, Kochiyama T, Uono S, Yoshikawa S, Toichi M. Direction of amygdala–neocortex interaction during dynamic facial expression processing. *Cereb Cortex* (2017) 27(3):1878–90. doi: 10.1093/cercor/bhw036
59. Friston KJ, Harrison L, Penny W. Dynamic causal modelling. *Neuroimage* (2003) 19(4):1273–302. doi: 10.1016/S1053-8119(03)00202-7
60. Day-Brown JD, Wei H, Chomsung RD, Petry HM, Bickford ME. Pulvinar projections to the striatum and amygdala in the tree shrew. *Front Neuroanat* (2010) 4:143. doi: 10.3389/fnana.2010.00143
61. Amaral DG, Price JL, Pitkanen A, Pitkanen A, Carmichael ST. The amygdala: Neurobiological aspects of emotion, memory, and mental dysfunction. In: . *Anatomical organization of the primate amygdaloid complex*. New York (NY): Oxford University Press (1992). p. 1–66.
62. Holmes AP, Friston KJ. Generalisability, random effects and population inference. *Neuroimage* (1998) 7:S754. doi: 10.1016/S1053-8119(18)31587-8
63. Friston KJ, Litvak V, Oswal A, Razi A, Stephan KE, van Wijk BCM, et al. Bayesian model reduction and empirical Bayes for group (DCM) studies. *Neuroimage* (2016) 128:413–31. doi: 10.1016/j.neuroimage.2015.11.015
64. Zeidman P, Jafarian A, Seghier ML, Litvak V, Cagnan H, Price CJ, et al. A guide to group effective connectivity analysis, part 2: second level analysis with PEB. *Neuroimage* (2019) 200:12–25. doi: 10.1016/j.neuroimage.2019.06.032
65. Zeidman P, Jafarian A, Corbin N, Seghier ML, Razi A, Price CJ, et al. A guide to group effective connectivity analysis, part 1: first level analysis with DCM for fMRI. *Neuroimage* (2019) 200:174–90. doi: 10.1016/j.neuroimage.2019.06.031
66. Oram MW, Perrett DI. Integration of form and motion in the anterior superior temporal polysensory area (STPa) of the macaque monkey. *J Neurophysiol* (1996) 76(1):109–29. doi: 10.1152/jn.1996.76.1.109
67. Hamilton AF. Emulation and mimicry for social interaction: A theoretical approach to imitation in autism. *Q J Exp Psychol* (2008) 61(1):101–15. doi: 10.1080/17470210701508798
68. Vuilleumier P. How brains beware: Neural mechanisms of emotional attention. *Trends Cognit Sci* (2005) 9(12):585–94. doi: 10.1016/j.tics.2005.10.011
69. Morris JS, Ohman A, Dolan RJ. A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc Natl Acad Sci U S A* (1999) 96(4):1680–5. doi: 10.1073/pnas.96.4.1680
70. Stephan KE, Penny WD, Daunizeau J, Moran RJ, Friston KJ. Bayesian model selection for group studies. *Neuroimage* (2009) 46(4):1004–17. doi: 10.1016/j.neuroimage.2009.03.025

71. Penny WD, Stephan KE, Daunizeau J, Rosa MJ, Friston KJ, Schofield TM, et al. Comparing families of dynamic causal models. *PloS Comput Biol* (2010) 6:e1000709. doi: 10.1371/journal.pcbi.1000709
72. Sato W, Toichi M, Uono S, Kochiyama T. Impaired social brain network for processing dynamic facial expressions in autism spectrum disorders. *BMC Neurosci* (2012) 13:99. doi: 10.1186/1471-2202-13-99
73. Rausch A, Zhang W, Haak KV, Mennes M, Hermans EJ, van Oort E, et al. Altered functional connectivity of the amygdaloid input nuclei in adolescents and young adults with autism spectrum disorder: a resting state fMRI study. *Mol Autism* (2016) 7:13. doi: 10.1186/s13229-015-0060-x
74. Zajonc RB. On the primacy of affect. *Am Psychol* (1984) 39(2):117–23. doi: 10.1037/0003-066X.39.2.117
75. Levenson RW. The intrapersonal functions of emotion. *Cognit Emot* (1999) 13:481–504. doi: 10.1080/026999399379159
76. Oatley K, Johnson-Laird PN. Striving and feeling: Interactions among goals, affect, and self-regulation. In: *The communicative theory of emotions: Empirical tests, mental models, and implications for social interaction*. Hillsdale (NJ): Lawrence Erlbaum Associates (1996). p. 363–93.
77. Wundt W. *An introduction to psychology*. London: G. Allen (1912). p. 1–198.
78. Sato W, Kochiyama T, Minemoto K, Sawada R, Fushiki T. Amygdala activation during unconscious visual processing of food. *Sci Rep* (2019) 9 (1):7277. doi: 10.1038/s41598-019-43733-2
79. Sato W, Kochiyama T, Uono S, Matsuda K, Usui K, Inoue Y, et al. Rapid amygdala gamma oscillations in response to fearful facial expressions. *Neuropsychologia* (2011) 49(4):612–7. doi: 10.1016/j.neuropsychologia.2010.12.025
80. Balconi M, Pozzoli U. Face-selective processing and the effect of pleasant and unpleasant emotional expressions on ERP correlates. *Int J Psychophysiol* (2003) 49(1):67–74. doi: 10.1016/S0167-8760(03)00081-3
81. Sato W, Kochiyama T, Yoshikawa S, Matsumura M. Emotional expression boosts early visual processing of the face: ERP recording and its decomposition by independent component analysis. *Neuroreport* (2001) 12 (4):709–14. doi: 10.1097/00001756-200103260-00019
82. Johnson MH, Senju A, Tomalski P. The two-process theory of face processing: modifications based on two decades of data from infants and adults. *Neurosci Biobehav Rev* (2015) 50:169–79. doi: 10.1016/j.neubiorev.2014.10.009
83. Guillon Q, Hadjikhani N, Baduel S, Rogé B. Visual social attention in autism spectrum disorder: insights from eye tracking studies. *Neurosci Biobehav Rev* (2014) 42:279–97. doi: 10.1016/j.neubiorev.2014.03.013
84. Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, et al. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *J Psychiatry Neurosci* (2009) 34(6):418–32.
85. Mundy P, Sigman M. The theoretical implications of joint-attention deficits in autism. *Dev Psychopath* (1989) 1(3):173–83. doi: 10.1017/S0954579400000365
86. Wagner JB, Keehn B, Tager-Flusberg H, Nelson CA. Attentional bias to fearful faces in infants at high risk for autism spectrum disorder. *Emotion* (in press). doi: 10.1037/emo0000628
87. Sturm V, Fricke O, Bührle CP, Lenartz D, Maarouf M, Treuer H, et al. DBS in the basolateral amygdala improves symptoms of autism and related self-injurious behavior: A case report and hypothesis on the pathogenesis of the disorder. *Front Hum Neurosci* (2013) 6:341. doi: 10.3389/fnhum.2012.00341
88. Domes G, Normann C, Heinrichs M. The effect of oxytocin on attention to angry and happy faces in chronic depression. *BMC Psychiatry* (2016) 16:92. doi: 10.1186/s12888-016-0794-9
89. Xu L, Ma X, Zhao W, Luo L, Yao S, Kendrick KM. Oxytocin enhances attentional bias for neutral and positive expression faces in individuals with higher autistic traits. *Psychoneuroendocrinology* (2015) 62:352–8. doi: 10.1016/j.psyneuen.2015.09.002
90. Domes G, Kumbier E, Heinrichs M, Herpertz SC. Oxytocin promotes facial emotion recognition and amygdala reactivity in adults with asperger syndrome. *Neuropsychopharmacology* (2014) 39:698–706. doi: 10.1038/npp.2013.254
91. Keech B, Crowe S, Hocking DR. Intranasal oxytocin, social cognition and neurodevelopmental disorders: A meta-analysis. *Psychoneuroendocrinology* (2018) 87:9–19. doi: 10.1016/j.psyneuen.2017.09.022
92. White SW, Bray BC, Ollendick TH. Examining shared and unique aspects of social anxiety disorder and autism spectrum disorder using factor analysis. *J Autism Dev Disord* (2012) 42:874–84. doi: 10.1007/s10803-011-1325-7
93. Berthoz S, Hill EL. The validity of using self-reports to assess emotion regulation abilities in adults with autism spectrum disorder. *Europ Psychiatry* (2005) 20:291–8. doi: 10.1016/j.eurpsy.2004.06.013
94. Reker M, Ohrmann P, Rauch AV, Kugel H, Bauer J, Dannlowski U, et al. Individual differences in alexithymia and brain response to masked emotion faces. *Cortex* (2010) 46(5):658–67. doi: 10.1016/j.cortex.2009.05.008
95. Thomas KM, Drevets WC, Dahl RE, Ryan ND, Birmaher B, Eccard CH, et al. Amygdala response to fearful faces in anxious and depressed children. *Arch Gen Psychiatry* (2001) 58(11):1057–63. doi: 10.1001/archpsyc.58.11.1057
96. Borhani K, Nejati V. Emotional face recognition in individuals withattention-deficit/hyperactivity disorder: A review article. *Dev Neuropsychol* (2018) 43 (3):256–77. doi: 10.1080/87565641.2018.1440295
97. Brotman MA, Rich BA, Guyer AE, Lunsford JR, Horsey SE, Reising MM, et al. Amygdala Activation During Emotion Processing of Neutral Faces in Children With Severe Mood Dysregulation Versus ADHD or Bipolar Disorder. *Am J Psychiatry* (2010) 167(1):61–9. doi: 10.1176/appi.ajp.2009.09010043

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Social Visual Perception Under the Eye of Bayesian Theories in Autism Spectrum Disorder Using Advanced Modeling of Spatial and Temporal Parameters

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Social interaction in individuals with Autism Spectrum Disorder (ASD) is characterized by qualitative impairments that highly impact quality of life. Bayesian theories in ASD frame an understanding of underlying mechanisms suggesting atypicalities in the evaluation of probabilistic links within the perceptual environment of the affected individual. To address these theories, the present study explores the applicability of an innovative Bayesian framework on social visual perception in ASD and demonstrates the use of gaze transitions between different parts of social scenes. We applied advanced analyses with Bayesian Hidden Markov Modeling (BHMM) to track gaze movements while presenting real-life scenes to typically developing (TD) children and adolescents (N = 25) and participants with ASD and Attention-Deficit/Hyperactivity Disorder (ASD+ADHD, N = 15) and ASD without comorbidity (ASD, N = 12). Regions of interest (ROIs) were generated by BHMM based both on spatial and temporal gaze behavior. Social visual perception was compared between groups using transition and fixation variables for social (faces, bodies) and non-social ROIs. Transition variables between faces, namely gaze transitions between faces and likelihood of linking faces, were reduced in the ASD+ADHD compared to TD participants. Fixation count to faces was also reduced in this group. The ASD group showed similar performance to TD in the studied variables. There was no difference between groups for non-social ROIs. Our study provides an innovative, interpretable example of applying Bayesian theories of social visual perception in ASD.

BHMM analyses and gaze transitions have the potential to reveal fundamental social perception components in ASD, contributing thus to amelioration of social-skill interventions.

Keywords: Bayesian theories, social perception, eye movements (EM), hidden Markov models (HMM), advanced analysis, autism spectrum disorder (ASD)

INTRODUCTION

Autism Spectrum Disorder is a heterogeneous disorder, with qualitative impairments in social interaction being one of the cardinal symptoms (1). Considering the challenges these symptoms evoke in everyday life of affected people and the need for effective interventions, many theories in autism spectrum disorder have laid their focus upon social cognition (2–4). Some of the most recent and promising theories are the Bayesian theories of autism spectrum disorder, which also unify a wide range of its clinical characteristics. In this Bayesian framework, it is suggested that perception in autism spectrum disorder is atypically resistant to prior acquired information, thus the affected individual engages with an "almost always new" input in probabilistic terms when experiencing an event (5). This implicit divergence in predictive coding is also referred to as «Hypothesis of Predictive Impairment in Autism» (6). Regarding social perception, these theories can explain manifestations of autism spectrum disorder such as atypicalities in apprehending social stimuli, inferring social causalities, predicting social intention or developing a regulating system for social processes (7).

Social interactions can be more demanding, complicated and unpredictable than one tends to believe (8). A basic source of social perception is visual and thus the orientation of gaze is crucial for the observer in order to comprehend social signals (9). Therefore, recording of gaze movements with the eye-tracking technique represents an objective measure in studying social perception (10). Common practices include measurements of fixation direction and duration at different parts of social scenes. Usually, stimuli are differentiated in social (e.g. faces, bodies) and non-social elements (e.g. objects) (11). Such paradigms have been widely investigated and particularly eye tracking provides insights about the underlying mechanisms of the social understanding in autism spectrum disorder (12, 13). On the one hand some studies report that participants with autism spectrum disorder prefer looking to non-social in comparison to social stimuli (14) and less to faces compared to non-face parts of a social scene (15). Moreover, regarding atypicalities in following the gazes of others, deficits in joint attention have been shown in participants with autism spectrum disorder (16). On the other hand, there are studies reporting no difference regarding social attention between participants with autism spectrum disorder and their typically developed peers (17). Also, it has been reported that deficits of joint attention are specifically found in its initiation part and not in the response to joint attention (18). Albeit such inconsistencies, studies suggest that participants with autism spectrum disorder focus less on social elements than typically developing controls (19).

However, with the established methods of gaze analysis, the actual process of social perception is limited to a quantification of attention isolated to specific areas. Particularly, they mostly refer to fixation variables, in terms of time spent in predefined, manually drawn, regions of the scene (20). This quantification of social focus neglects the importance of actively combining different aspects of the stimuli, for example the gaze connection between two interacting people in a social scene. Nevertheless, the linking between informational areas has been reported to reflect the actual gaze patterns of individuals (21). In gaze movement terms, the linking of visual inputs is defined as transitions and refers to the saccadic paths between Regions of interest (ROIs), namely a cluster of fixations gathered in an informative area, e.g. a face or a body. Moreover, in order to perceive social information, there is a tendency to orient the gaze to the face, particularly the eyes of the presented person (22). Therefore, when looking at a scene of people interacting, it is likely to orient the gaze from one face to another, as part of social content exploration (23). Consequently, linkage of socially relevant areas is neither completely random nor completely deterministic and is thus related to a certain degree of probability (24).

Leaning on Bayesian theories of autism, social understanding in autism spectrum disorder can also be atypical at the level of engaging with the aforementioned probabilistic associations, namely gaze transitions. Prior inputs and the inference of further outputs are regulated by the strength of these associations (25) which in visual perception can be manifested in the interdependence of successive fixations. In other words, the current point of gaze is influenced by the previous one and further the current step affects the next gaze shift (26). Moreover, the actual attentional processing of the individual looking at a scene remains "hidden" in the sense that it cannot be observed directly but can be inferred through the gaze movements. Under this perspective, the underlying mechanisms of the atypical social perception in individuals with autism spectrum disorder are still unclear and require analyses that treat social visual perception as a process that unfolds in space and time and accounts for its probabilistic components.

Our study applies Bayesian Hidden Markov Modeling (BHMM) (21, 27, 28) to capture both dynamics and structure of visual exploration of social scenes in autism spectrum disorder and typical developed (TD) children and adolescents. A BHMM represents the moment-to-moment evolution of a random variable whose values are observable (the observable stochastic process) and generated conditionally on the temporal evolution

of a hidden random variable (the hidden or latent process). The hidden variable can take values over a finite number of states and the state at the current timepoint only depends on the state at the previous timepoint, representing a Markovian process. In the example of eye tracking, gaze data can be addressed as time-series of a stochastic Markovian process (29). Both the model selection (number of ROIs) and the learning of the BHMM parameters are completely data driven. Further, the specific kind of BHMM we are exploiting here (30) also allows for the hierarchical representation and inference of group gaze behavior and attention dynamics (see also Methods section 2.4.1). We surmise that prior distributions on individual and group parameters of gaze behavior inferred at the data analysis stage can be usefully integrated with Bayesian models of sensory input in order to provide a broader sensorimotor account of atypical behavior in ASD.

Finally, the recent DSM-V diagnostical guidelines (1) recognize the comorbidity of autism spectrum disorder with other conditions and enable for the first time their simultaneous diagnoses. Particularly it is reported that around 70% of individuals with autism spectrum disorder might also fulfill the criteria for another co-morbid mental disorder and approximately 40% can have two or more co-morbid mental disorders (1). Common comorbid conditions include anxiety disorders, epilepsy, depression, gastrointestinal symptoms, challenging behavior, sleep problems, toileting, and feeding issues (31–36), as well as Attention-Deficit/Hyperactivity Disorder (ADHD) (37). Interestingly, even before DSM-V, studies have reported ADHD traits in populations with autism spectrum disorder in the areas of attention and social cognition (38). Moreover, symptoms of ADHD in autism spectrum disorders have been also associated with impairments in executive function (39). In our study, considering the feasibility of a dual diagnosis of ASD and ADHD, we included autism spectrum disorder participants both with comorbid ADHD (from now on referred to as ASD+ADHD) and without (from now on referred to as ASD). Thus, we consider current diagnostic recommendations and the emerging research in the comorbid group, highlighting its clinical significance and manifestation (40, 41).

Thus, our study aims to demonstrate a novel approach in psychiatric research applying BHMM to gaze data of ASD, ASD +ADHD participants and TD controls with stimuli depicting real-life social scenes. Apart from considering the comorbid group as a separate entity, other novelties of our approach from a methodological standpoint include: i) the feasibility of applying advanced analytical methods to clinical populations, ii) the investigation of both fixation and interpretable transition variables and, more subtle, iii) the integration of both i) and ii) in the principled framework of Bayesian inference. Beyond the technical novelties that to the best of our knowledge have not been exploited in this research field, this latter aspect paves the way to bridge advanced methods for data analysis with Bayesian theories of autism spectrum disorder. In particular, approaches focusing on active inference (42) suggest that the core aspects of autism relate fundamentally to how individuals sample the world. Indeed, the very idea of sampling is at the heart of the BHMM: giving the current state, sampling the next ROI and, in turn, sampling the new gaze position. We hypothesize that compared to the control group, the autism spectrum disorder groups will show less dynamical links, in terms of gaze transitions, between the socially relevant ROIs and also fixate less the presented social elements.

METHODS

Participants

Inclusion criteria were normal or corrected-to-normal vision, native-speaker level in the local language, age between 10 and 14 years and intelligence quotient (IQ) within two standard deviations at the lower end (≥70) (43). Exclusion criteria were strabismus, diagnoses of Tourette syndrome, specific reading disorder, epilepsy or other neurologic disorders, severe psychiatric disorders like schizophrenia, acute depressive episode, suicidal ideation and any known ASD- or ADHD-related specific genetic syndrome. Initially, 59 participants were examined (26 TD, 18 ASD+ADHD and 15 ASD). Recordings of seven participants not fulfilling eye-tracking quality criteria (see below in *Apparatus*) were excluded (1 TD, 3 ASD+ADHD and 3 ASD). Finally, data of N = 52 participants were available for analysis, namely N = 25 TD (average age: ± one standard deviation 12.1 ± 1.5 years; 52% male; IQ: 110 ± 17), N = 15 participants with ASD and co-morbid ADHD (ASD+ADHD; age: 12.0 ± 1.0 years; 93% male; IQ: 96 ± 15) and N= 12 participants without comorbidity (ASD; age: 12.3 ± 1.1 years; 83% male; IQ: 103 ± 21). Diagnoses were made by a group of clinical psychologists and child and adolescent psychiatrists based on International Classification of Diseases (ICD-10) criteria. Details on diagnostic tests and screenings applied are described in the **Supplementary Data**. Other comorbidities included for the ASD group: diurnal/nocturnal enuresis (N = 2), specific insect phobia (N = 1), developmental dyspraxia (N = 1), mixed receptive-expressive language disorder (N = 1), chronic tic disorder (N = 1), obsessive compulsive disorder (N = 1); and for the ASD+ADHD group: diurnal/nocturnal enuresis (N = 1), adjustment disorder (N = 1), vocal tic disorder (N = 1), expressive language disorder (N = 1). The study was approved by the institutional ethics committee. All participants and their parents gave their written informed consent before participation.

Apparatus

Participants were seated in a sound attenuated cabin, with a distance of 70 cm from a 24"-screen (1920 × 1080 pixels, 60 Hz). Stimuli were presented with Presentation® software (version 17.2, Neurobehavioral Systems, Inc., Berkley, CA). Binocularly gaze recordings were accomplished with the iView RED250 system (Senso-Motoric Instruments GmbH, SMI, Teltow, Germany; sampling rate: 120 Hz). Based on 5-point calibration an accuracy of <0.05° was achieved for every participant. Data were preprocessed and exported with SMI-BeGaze version 3.7, using its default fixation classification, where fixations are defined as events of minimum 60 milliseconds and with a

maximum dispersion of 2 degrees. Blinks and off-screen fixations were excluded. To ensure adequate gaze data quality only data sets with a tracking ratio >75% and a total fixation time above 50% of the stimulus duration had been included.

Stimuli and Procedure

The participants completed a battery of eye-tracking tasks, totaling 90 minutes with breaks, while for the free-viewing stimuli, two pairs of stimuli with real-world pictures were presented – two depicting one actor and two depicting four actors. Total task duration, including instruction and calibration, was less than 10 minutes and eye movements were recorded for 120 seconds per stimulus. Beforehand, questioning about the pictures was announced to ascertain the attention of the participant. An experimenter sat with the participant in the cabin and care was taken to adapt task progression to each participant's demands.

Data Analysis

Markov Modeling

In the present study, we use a Bayesian Hidden Markov Model (BHMM) as previously described (27, 28). The BHMM relies on a finite number of hidden states (in this study, Regions of Interest, ROIs) and contains a vector of prior values, which indicates the probability of a time-series beginning with each state; a transition matrix, which parameterizes the transition probabilities between any two hidden states; and a Gaussian emission for each state, which represents the probabilistic association between recorded eye fixation locations and a hidden state. Different from a classic, frequentistic Hidden Markov Model (HMM), a Bayesian HMM treats the HMM parameters (e.g., the transition matrix) as random variables and assigns Gaussian emissions on such parameters. At the learning stage, a Bayesian variant of the parameter estimation algorithm automatically penalizes model complexity *via* the distributions on the model parameters. A variational Bayesian expectation maximization (VBEM) algorithm is being used starting from the priors and learning the model parameters in a data-driven way. Further, it provides the option for learning shared fixation patterns and producing representative ROIs, by clustering individual BHMMs using a variational hierarchical expectation maximization (VHEM) algorithm (30).

The *scanpath modeling and classification with hidden Markov models* toolbox (27, 28) was applied in MATLAB (R2018b, The MathWorks, Natick, MA, United States) for the analysis following, separately for the picture with four depicted actors (stimulus A) and one depicted actor (stimulus B). Default hyperparameters were used.

In this study each participant was summarized by an individual HMM, the observable process being the gaze positions that the participant generates while sequentially deploying attention to a finite number of ROIs. The process analysis was composed of the following steps:

Step 1) Scan-paths of all participants from every group are clustered by BHMMs with the goal of generating representative ROIs (see **Figure 1**).

Step 2) Scan-paths of each participant are modeled by individual BHMMs, which are initiated from the representative ROIs found in step 1.

Two features describe the data-driven generation of attentional states for both steps. Firstly, the ROIs are assumed to be the hidden attentional states. While the participant is dwelling on a specific ROI, a number of actual gaze positions is generated by sampling from an emission probability distribution, with a decreasing probability from center to periphery. Thus, a single fixation receives a posterior probability of belonging to a ROI and is assigned to the ROI where it exhibits the highest probability. Secondly, during the process of ROI generation the above modeling additionally considers a temporal third dimension, namely the duration of every single fixation. Thus, the term "regions" of interest in this study, although potentially misleading at the first glance, does not refer to a spatial entity alone, but also incorporates the temporal component of each fixation duration as well as its displacement in the x and y axis. Importantly, this temporal component considers the processing speed in terms of fixation duration of every single fixation (44). Moreover, the temporal dimension incorporated in the BHMM accounts for the processing of visual attention as it unfolds in time (27).

Definition of Gaze Variables

The ROIs were categorized in *social* and *non-social*, former consisting of depicted faces and bodies and latter included ROIs containing objects and background. For the purpose of this study we define transition and fixation variables as follows.

Transition variables investigate the dynamical links between any combination of ROI pairs and can be expressed as *transition count* and *transition probabilities*. Transition count is the actual amount of unidirectional transitions between two given ROIs. The Bayesian transition probability is an essential part of the BHMM and expresses for each individual the probability of a unidirectional transition taking place between two given ROIs during the experiment. For our analysis, we considered social-to-social and non-social to non-social ROI pairs (hereinafter referred as social and non-social transitions). The social transitions were composed of the following transition pairs: face to face, body to body, face to body and body to face.

Additionally, established fixation variables were calculated based on the three BHMM ROI types (faces, bodies and non-social ROIs). *Fixation* and *visit count* were defined as the number of fixations or visits in a specific ROI category, respectively. A visit describes the event, beginning from the entrance of the gaze into a ROI and ending at its exit. Thus, a visit can contain one or more fixations (45).

Finally, *total fixation duration*, defined as the total amount of time spent on a stimulus, regardless of ROI, and *total transition count* representing the total number of transitions performed in one stimulus were calculated.

Statistical Analysis

Linear mixed effects models were applied separately for each gaze variable and each ROI category similar to (46) using the statistical software R (R Core Team, v 3.6.1) and the lme4 library (v 1.1-19). In general, the patient group was the main effect term of interest. The number of depicted actors and the interaction term of the two main effects served as additional fixed effects, although not of primary interest. Before introducing total

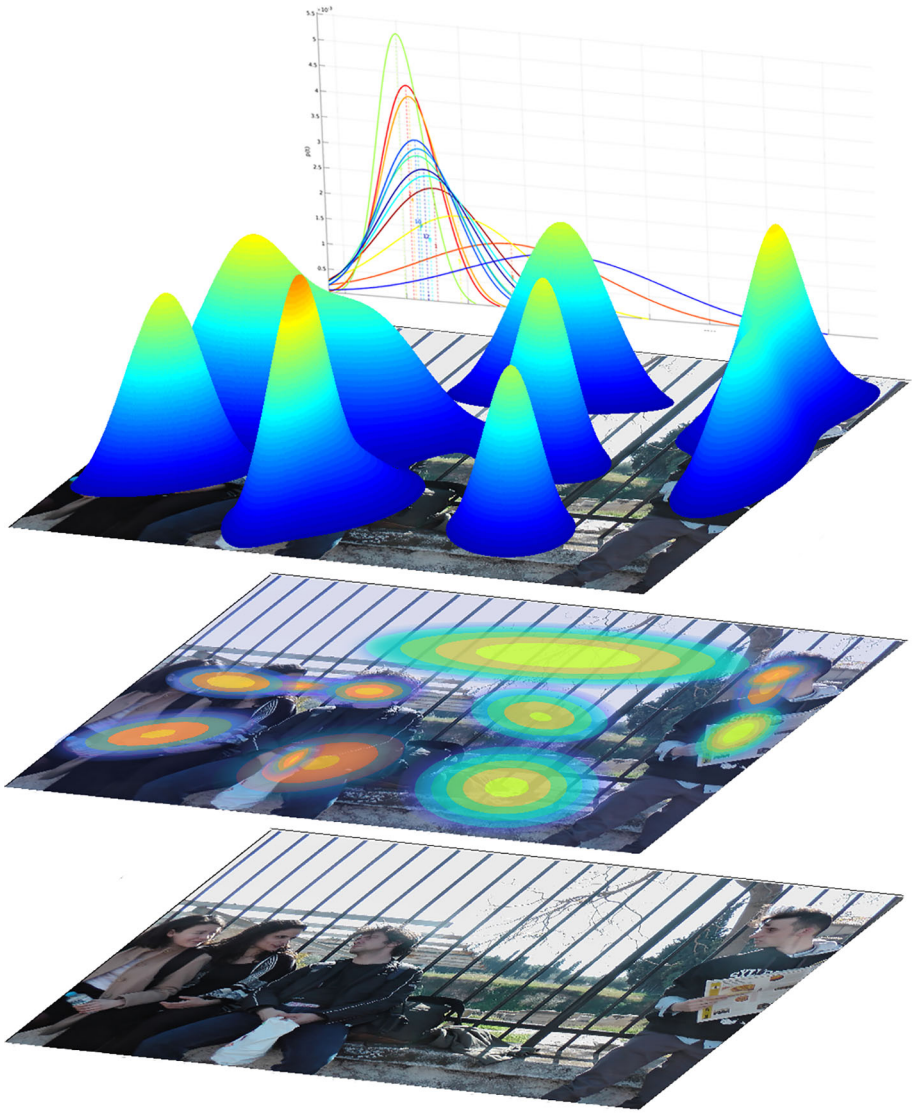

FIGURE 1 | Illustration of the composition of Regions of Interest (ROI) and the process of their generation. The ROIs depicted here were formed from gaze data of all participants, including the fixation durations. i) lower layer: the input stimulus A. ii) middle layer: the stimulus with separate modeled ROIs, depicted as flattened two-dimensional Gaussian distributions, where the concentric ellipses depict the probability of a fixation belonging to that ROI, decreasing from center to periphery. iii) upper level: an alternate illustration of the same Gaussian distributions, here in three-dimensional representation. In the background the Gaussian distributions of the fixation duration are depicted, which for each ROI were also based on the data of all participants.

fixation duration or total transition count as covariates in the model, the effect of patient group on these variables was examined (47). P-value <0.05 was used for statistical significance.

For the transition variables the model was structured as follows:

$$\textit{transition variable} \sim 1 + \textit{group} + \textit{actors} + \textit{group} : \textit{actors} + \textit{total transitions} + (1 \mid \textit{participant})$$

where participant group (TD, ASD+ADHD, ASD) and number of depicted actors (one or four) were the fixed effects with an interaction term. The covariate total transitions per stimulus was centered at its mean. The analysis was performed for the five available ROI combinations and analogous model structures were used for the variable of transition probabilities. Due to the nature of the later variable no covariate term was applied in this case.

For the basic fixation variables (fixation and visit count) the model was structured with the same fixed effect terms as above and with individual mean-centered total fixation duration (in seconds) per stimulus as a covariate, separately for the three ROI types:

$$fixation\ variable \sim 1 + group + actors + group : actors + total\ fixation\ duration + (1 \mid participant)$$

RESULTS

Generated ROIs

The process of ROI generation by the BHMM is visualized in **Figure 1**, exemplary for stimulus A. The ROIs represent Gaussian distributions of probabilities at x-y coordinates, which can be best understood as 3D Gaussian bells with the highest probability in the center and decreasing probability to the periphery. In order to semantically separate the elements of the scenes, the optimal number of ROIs was found to be $N = 10$ for stimulus A and $N = 13$ for stimulus B. Additionally, the temporal dimension of each single fixation duration is integrated. Thus, the gaze variables investigated here, based on the BHMM and the respective ROIs, represent the processing of visual attention evolving in time and consider the temporal aspect of attention processing. Considering the categorization into social and non-social ROIs, one BHMM state of each stimulus representing sparse fixations with the longest durations and no regional pattern was not included, resulting in 12 ROIs for stimulus A and 9 ROIs for stimulus B. For stimulus A 8 ROIs were categorized as social (5 for faces and 3 for bodies), while for stimulus B there were 2 social ROIs (1 face and 1 body) (see also **Figure 2** and **Supplementary Figure S1**).

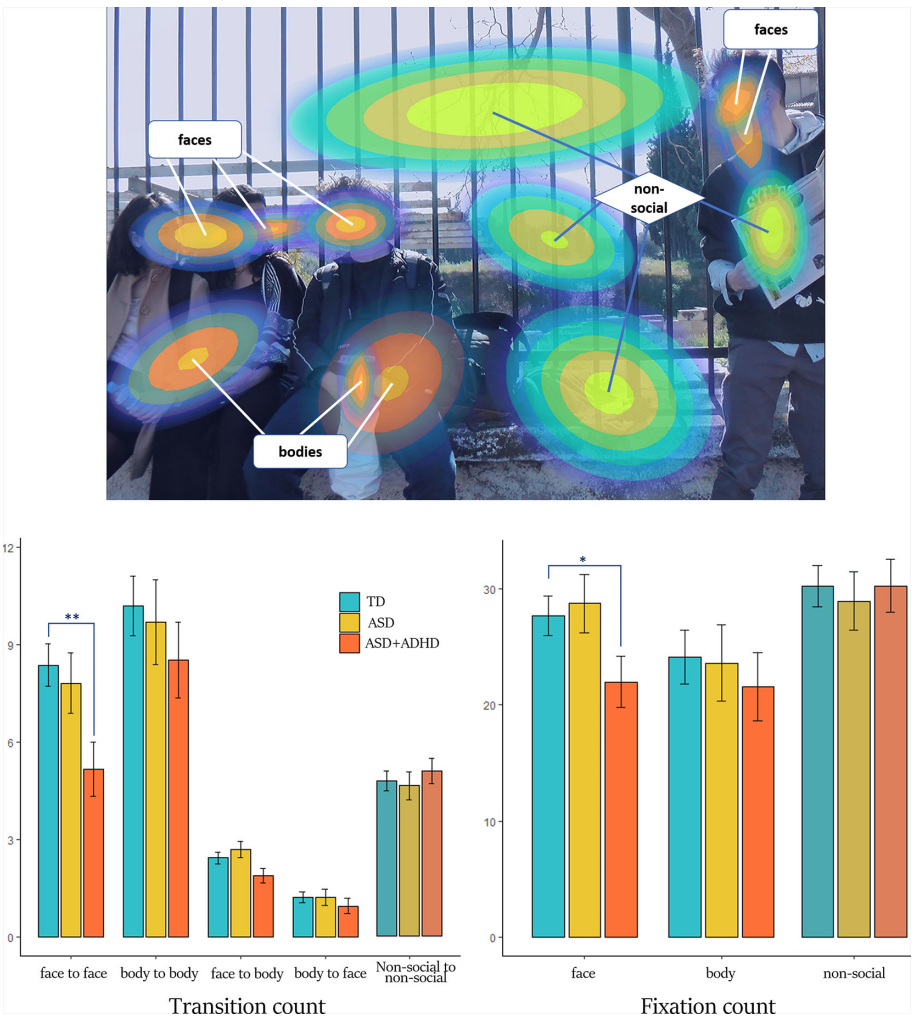

FIGURE 2 | Generated ROIs and results for transition and fixation count. Upper: The ROIs of stimulus A formed from the gaze data of all participants are shown as Gaussian distributions, categorized in "social" (composed by faces and bodies) and "non-social". The probability of a fixation belonging to a ROI is decreasing from center to periphery. Here, the outer borders of the ROIs represent the 95% of the Gaussian distribution. Lower left: transition count for the different types of transition and groups. Lower right: fixation count for the different ROI categories and groups. Bar charts are composed of mean estimates and standard error. Color-matching to groups is explained in the figure legend. Note the statistic significant lower the transition and fixation count for the ASD+ADHD group compared to the TD for the ROI of faces (* denotes p-value < 0.05, ** denotes p-value < 0.01).

Transitions

The total count of transitions for stimulus A was on average ± one standard deviation 304 ± 56, 290 ± 57, and 302 ± 66 for groups TD, ASD+ADHD and ASD, respectively. For stimulus B it was 298 ± 52, 293 ± 49, and 300 ± 32, respectively. The total transition count did not differ statistically neither between groups nor stimuli ($p = 0.808$ and 0.843, respectively, see **supplementary Table S1**). It was nevertheless added as a covariate to the subsequent analysis, for reasons of completeness (47) (see **Supplementary Table S1**).

Social Transitions

The total count of social transitions was on average 96 ± 26 for the TD group, 83 ± 23 for the ASD+ADHD group and 96 ± 21 for the ASD group (see also **Supplementary Table S2**). Mixed-effects analysis revealed a significant effect of clinical group, regarding transitions between faces. Compared to the TD group, transition count between faces was overall lower for the ASD+ADHD group (mean estimates ± standard error 5.2 ± 0.8 vs 8.4 ± 0.6, $p = 0.002$, see **Table 1**), while the ASD group did not differ (7.8 ± 0.9). **Figure 3** illustrates gaze trajectory recordings for one exemplary participant out of each group. Noticeably, the participant of the comorbid group avoided transitions between faces, whereas the ASD participant showed a rigid pattern in comparison to the TD participant.

The other social transitions were lower in the ASD+ADHD compared to the TD group, nevertheless did not differ statistically. Particularly, the transition count from body to body and 8.5 ± 1.2 vs 10.2 ± 0.9 ($p = 0.267$), face to body: 1.9 ± 0.2 vs 2.4 ± 0.2 ($p = 0.057$) and body to face: 1.0 ± 0.2 vs 1.2 ± 0.2 ($p = 0.357$). The ASD group did not show any statistically significant different transition values to the TD group for any of the four social categories (see **Table 1**).

Similar results were shown for transition probabilities, where transition between faces was significantly different, with lower values for the ASD+ADHD group (mean estimates ± standard error, 22 ± 2%) compared to the TD group (30 ± 2%, $p = 0.012$), while there was no difference for the other transition categories or for the ASD group. The complete results are summarized in **Supplementary Tables S3, S4**.

Non-Social Transitions

The total count of non-social transitions was on average ± one standard deviation 146 ± 41 for the TD group, 150 ± 44 for the ASD+ADHD group and 148 ± 40 for the ASD group. The

TABLE 1 | Results of mixed effects analyses on transition counts and probabilities for social and non-social ROIs.

	F-value	Estimated means			p-value	
	Group Effect	*TD*	*ASD*	*ASD + ADHD*	*TD vs. ASD*	*TD vs. ASD+ADHD*
A. Transition count						
face to face	4.86	8.4 ± 0.6	7.8 ± 0.9	5.2 ± 0.8	0.622	0.002**
body to body	0.62	10.2 ± 0.9	9.7 ± 1.3	8.5 ± 1.2	0.757	0.267
face to body	3.1	2.4 ± 0.2	2.7 ± 0.3	1.9 ± 0.2	0.406	0.057
body to face	0.5	1.2 ± 0.2	1.2 ± 0.3	1.0 ± 0.2	0.972	0.357
non-social ROIs	0.3	4.8 ± 0.3	4.6 ± 0.4	5.1 ± 0.4	0.757	0.549
B. Transition probability						
face to face	3.2	30 ± 2	26 ± 3	22 ± 2	0.251	0.012*
body to body	0.4	38 ± 2	39 ± 3	36 ± 3	0.721	0.540
face to body	1.4	11 ± 1	11 ± 1	13 ± 1	0.730	0.098
body to face	0.1	9 ± 1	8 ± 1	8 ± 1	0.915	0.618
non-social ROIs	0.4	24 ± 1	23 ± 1	24 ± 1	0.439	0.980

*F-value for the fixed effect of clinical group and post-hoc tests for groups (with p-value) are listed. Estimated mean values are mean ± standard error. Mean estimate values for transition probabilities are in %. * denotes p-value < 0.05,*

*** denotes p-value < 0.01.*

ASD, Autism Spectrum Disorder; ADHD, Attention Deficit and Hyperactivity Disorder; ROIs, Regions of interest.

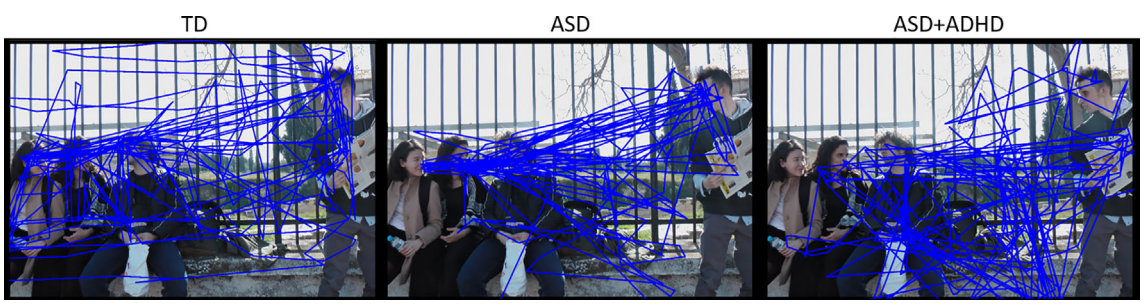

FIGURE 3 | Gaze trajectory recordings of three different exemplary participants (from left to right: TD, ASD and ASD+ADHD). Note the differences in exploration, transitions between faces and non-social ROIs.

ASD+ADHD group showed higher, yet not-significantly different, transition counts in non-social ROIs (average ± standard error: for TD 4.8 ± 0.3, for ASD+ADHD 4.6 ± 0.4, for ASD 5.1 ± 0.4) and similar transition probabilities (average± standard error: for TD 0.24 ± 0.01, for ASD+ADHD 0.24 ± 0.01, for ASD 0.23 ± 0.01, non-significant, see **Supplementary Materials S3, S4**).

Fixation Variables

The variable of total fixation duration, used as a covariate for the subsequent analyses, did not differ statistically between groups or between stimuli (*p-value=0.158 and 0.549*, respectively, **Supplementary Table S1**). Compared to the TD group, the number of fixations on faces was lower in the ASD+ADHD group (average ± standard error: 22 ± 2.2 vs 27.7±1.7, $p = 0.046$), while there were no significant differences to the ASD group (28.7 ± 2.5) (see **Figure 2** and **Supplementary Table 5**). The number of visits to faces did not significantly differ between groups (average ± standard error: for TD 16.1 ± 1.0, for ASD+ADHD 14.8 ± 1.3, for ASD 17.3 ± 1.5, non-significant). For the body ROIs and for the non-social ROIs there were no significant group differences for the two fixation variables (see **Supplementary Table 6**).

DISCUSSION

We set out to investigate social perception in autism spectrum disorder groups under the framework of the current Bayesian autism spectrum disorder theories and using, to our knowledge for the first time in this field, dynamic gaze modeling with Bayesian Hidden Markov Models (BHMM) on real-life scenes. We found that gaze transitions between faces were significantly less in the ASD+ADHD group compared to TD. Interestingly, transitions between faces were also less likely, in terms of probabilities, to occur in the ASD+ADHD group. Regarding established gaze variables, fixation count to faces was reduced in ASD+ADHD, whereas visit count to faces did not differ across groups. Moreover, the ASD group showed similar social visual perception to TD in the studied variables. Finally, there were no differences between groups in the non-social transitions and fixation variables. Therefore, the hypothesis of reduced social perception in participants with autism spectrum disorder was confirmed particularly for the comorbid group and only for the face regions.

Transition variables, reflecting a more dynamical aspect of gaze, were sensitive to group differences and seem to reflect atypicalities of social visual perception. According to our results, the reduced amount and likelihood of social transitions did not come with an overall reduced visit count in the ROIs, indicating that differences found in transition variables are a consequence of reduced gaze linkages between the stimulus elements. Besides, it is important to note that the regression analysis controlled for total transition count. Our results confirm recent suggestions in the eye tracking literature, that not only the fixations per se, but also the dynamical linkage of fixation clusters contribute to individual differences in gazing behavior (21). Surprisingly, there is a gap in autism spectrum disorder literature exploring transitions between social elements in social scenes. A possible reason for this lack of studies investigating social transition may be the fact that the importance of presenting social interaction has been highlighted only recently (48). Therefore, the majority of studies until then have been focusing on a quantification of attention in isolated social elements of the presented stimuli. Thus, our study supports the measurement of social transitions as an objective variable for investigating social perception in autism spectrum disorder.

The present study has a special bearing for current influential theories of autism spectrum disorder (7). Specifically, the hypothesis of "Predictive Impairment in Autism" (6) is associated with Markov models and the hypothesized impaired capability of individuals with autism spectrum disorder to evaluate the probabilistic links within their environment. In our example, the social elements of each scene represent the hidden states of a Markov process and the probabilistic links between them are reflected by the respective transition probabilities. Hence, if it is more likely to visually link two faces that interact with each other and this behavior is considered typical for social understanding, then in case this linkage is less likely, the social understanding might be atypical. This atypical, or even impaired, understanding could presumably lead to more frequent "surprises" – or prediction errors –, an outcome of social interactions that is usually undesired (7). Thus, the approach introduced here composes an illustrative example of the appropriateness of a Bayesian framework on social visual perception in autism spectrum disorder research.

Here, we incorporate not only conceptual but also methodological advantages. Social perception is regarded and analyzed as a dynamical process that unfolds in space and time, thus being more representative of the evolving gaze trajectories (49). To deal with this complexity in the analysis of eye-tracking data, few dynamical approaches have been previously proposed. Based on the calculation of transition and entropy measures, children with autism spectrum disorder were shown to utilize immature exploration strategies for faces (50). Another study, applied networking analyses on transition data showing that autism spectrum disorder participants differ from controls in the aspect of centrality when exploring faces (51). Expanding on these viewpoints, our study shows following strengths. *Firstly*, participants were presented full-featured real-life social scenes and not isolated faces, following recommendations regarding the importance of naturalistic assessments for quantifying atypicalities in social attention in autism spectrum disorder (52). *Secondly*, with the adopted methodology, generation of ROIs additionally included the temporal dimension of each single fixation duration, enabling a more detailed analysis of gaze movements (27). *Thirdly*, the representative model of ROIs considered all participants' individual gaze trajectories and thus accounts for the heterogeneity of the studied clinical populations and the importance of individual differences in scene viewing (53, 54). Hence, the demonstrated analysis extends the potentials of dynamical approaches in this field.

Furthermore, in accordance with recent studies suggesting that social impairments are more pronounced in comorbid cases

compared to individuals without this comorbidity (55–57), here only the ASD+ADHD comorbid group manifested reduced social perception both in transition and fixation variables. However, it is important to consider that until the release of the new diagnostic guidelines (1), few eye tracking studies in social cognition distinguished between these groups (19, 58). Therefore, it is unclear if previous studies recruited participants with comorbid ASD+ADHD in their ASD groups and if the overall performance of the reported ASD group was influenced from the comorbid participants. This might also explain why some studies find similar performance of ASD and TD (17). Our results, regarding the ASD group agree with these studies suggesting a similar social perception to the TD group. Another explanation for these results might be the fact that our study included only participants with high-functioning autism spectrum disorder which reportedly have milder symptoms (59) and thus did not show differences in these variables with TD. On the contrary, it has been suggested that ASD+ADHD individuals have greater treatment demand (60). Therefore, we contribute to the understanding of social perception in the comorbid group which needs to be further investigated.

This study has several caveats. The implemented method has been utilized for studying healthy adults and has not been previously applied to clinical groups or children. It thus might ignore potential assumptions made during conceptualization. Further, the limited sample size of this exploratory analysis did not allow replication of the results. Concerning the clinical groups, potential factors influencing visual processing, such as IQ, education, age or visual processing deficits, were not considered in the statistical analysis, again due to the limited sample size. Moreover, the real-life scenes presented in this study explicitly did not include any extreme facial emotion expressions in order to avoid further bias of attentional gaze. Yet, difficulties in recognizing subtle or complex emotions have been reported for participants with autism spectrum disorder (61). Thus, a possible influence of emotion expression to the gaze behavior of our participants cannot be ruled out and therefore future studies could investigate effects of emotions in further detail and in real-life scenes. Furthermore, the presence of the experimenter in the cabin, although assuring engagement and safety of participants, should be also considered as a limitation of the study as it could have an impact on social anxiety and task performance. Particularly it is shown that fear or anxiety of negative evaluation have an effect on gaze (62) and therefore the impact of anxiety which is also a common comorbid condition in ASD should be also controlled for (63). Finally, this analysis distinguishes between social and non-social transitions and compares each of these categories between groups, while the transitions between social and non-social ROIs are not addressed and thus, the range of the gaze behavior is not fully covered.

Implications, for the design of future studies arise not only *via* the inclusion of measurements such as transition variables, but also from the entire analysis approach. The interpretable measurements presented in combination with a promising theoretical background, could for example aid in a step by step visual training of social perception, thus objectifying treatment outcomes and contributing to the development of risk assessments (48, 64). Given the flexibility of the social scene presentation paradigm and the practicality of eye tracking technique, such trainings could be developed specifically for children, customized for different developmental ages and levels of difficulties (65). This can eventually facilitate the realization of longitudinal studies and monitoring of long-time interventions (66, 67). Moreover, our method can be extended by combining other sensory inputs, neurophysiological measurements or other functions such as decision making (68–70). Finally, multimodal analysis of social interactions and real-life settings will be of great importance and could represent the everyday challenges of the autism spectrum disorder population in a better way (71, 72).

In conclusion, we show that Bayesian theories provide a reliable approach to study social perception deficits of autism spectrum disorder and we contribute to social cognition in autism spectrum disorder research in various aspects: *theoretically*, current Bayesian theories are here demonstrated in an interpretable example of social visual perception (to our knowledge for the first time); *methodologically*, an innovative Bayesian Modeling is applied, contributing to the further development of advanced dynamical gaze analysis; and *clinically*, practical measurements are presented with the scope of developing more accurate interventions for social skills in children and adults with autism spectrum disorder.

DATA AVAILABILITY STATEMENT

The stimuli supporting the conclusions of this article will be made available by the authors upon request, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethik-Kommission der Albert-Ludwigs-Universität Freiburg, University Freiburg, Freiburg, Germany. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CI—data collection, conceptualization, data analysis, statistical analyses, original draft writing. DS—study design, data collection. M-ES—statistical analyses, manuscript writing. MB—study design, manuscript writing. LT—manuscript writing, review, and editing. CF—funding Acquisition, manuscript editing. GB—statistical analyses, data analysis, manuscript writing, review, and editing CK—study design, contributed data, manuscript editing.

All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.585149/full#supplementary-material

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Arlington, VA: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596
2. Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a "theory of mind" ? *Cognition* (1985) 21:37–46. doi: 10.1016/0010-0277(85)90022-8
3. Frith U. Autism and theory of mind in everyday life. *Soc Dev* (1994) 3:108–24. doi: 10.1111/j.1467-9507.1994.tb00031.x
4. Chevallier C, Kohls G, Troiani V, Brodkin ES, Schultz RT. The social motivation theory of autism. *Trends Cognit Sci* (2012) 16:231–9. doi: 10.1016/j.tics.2012.02.007
5. Pellicano E, Burr D. When the world becomes 'too real': a Bayesian explanation of autistic perception. *Trends Cognit Sci* (2012) 16:504–10. doi: 10.1016/j.tics.2012.08.009
6. Sinha P, Kjelgaard MM, Gandhi TK, Tsourides K, Cardinaux AL, Pantazis D, et al. Autism as a disorder of prediction. *Proc Natl Acad Sci* (2014) 111:15220–5. doi: 10.1073/pnas.1416797111
7. Haker H, Schneebeli M, Stephan KE. Can Bayesian Theories of Autism Spectrum Disorder Help Improve Clinical Practice? *Front Psychiatry* (2016) 7:107. doi: 10.3389/fpsyt.2016.00107
8. Pauker K, Rule NO, Ambady N. *Ambiguity and social perception*. Balcetis E, Lassiter GD, editors. New York: Psychology Press (2010). doi: 10.4324/9780203848043
9. Nummenmaa L, Calder AJ. Neural mechanisms of social attention. *Trends Cognit Sci* (2009) 13:135–43. doi: 10.1016/j.tics.2008.12.006
10. Birmingham E, Kingstone A. Human social attention. *Prog Brain Res* (2009) 176:309–20. doi: 10.1016/S0079-6123(09)17618-5
11. Holmqvist K, Nyström M, Andersson R, Dewhurst R, Jarodzka H, van de Weijer J. *Eye Tracking A Comprehensive Guide to Methods and Measures*. Oxford: Oxford University Press (2017).
12. Nelson CA. Facing Autism: Eye Tracking Paves the Way to Underlying Mechanisms. *J Am Acad Child Adolesc Psychiatry* (2012) 51:233–4. doi: 10.1016/j.jaac.2011.12.015
13. Boraston Z, Blakemore S-J. The application of eye-tracking technology in the study of autism. *J Physiol* (2007) 581:893–8. doi: 10.1113/jphysiol.2007.133587
14. Pierce K, Marinero S, Hazin R, McKenna B, Barnes CC, Malige A. Eye Tracking Reveals Abnormal Visual Preference for Geometric Images as an Early Biomarker of an Autism Spectrum Disorder Subtype Associated With Increased Symptom Severity. *Biol Psychiatry* (2016) 79:657–66. doi: 10.1016/j.biopsych.2015.03.032
15. Sumner E, Leonard HC, Hill EL. Comparing Attention to Socially-Relevant Stimuli in Autism Spectrum Disorder and Developmental Coordination Disorder. *J Abnorm Child Psychol* (2018) 46:1717–29. doi: 10.1007/s10802-017-0393-3
16. Falck-Ytter T, Von Hofsten C. How special is social looking in ASD: A review. In: Braddick O, Atkinson J, Innocenti GM, editors *Progress in brain research: Gene expression to neurobiology and behavior: Human brain development and developmental disorders*. Amsterdam: Elsevier (2011) vol. 188, pp. 209–22. doi: 10.1016/B978-0-444-53884-0.00026-9
17. van der Geest JN, Kemner C, Verbaten MN, van Engeland H. Gaze behavior of children with pervasive developmental disorder toward human faces: a fixation time study. *J Child Psychol Psychiatry* (2002) 43:669–78. doi: 10.1111/1469-7610.00055
18. Billeci L, Narzisi A, Campatelli G, Crifaci G, Calderoni S, Gagliano A, et al. Disentangling the initiation from the response in joint attention: An eye-tracking study in toddlers with autism spectrum disorders. *Transl Psychiatry* (2016) 6:e808. doi: 10.1038/tp.2016.75
19. Guillon Q, Hadjikhani N, Baduel S, Rogé B. Visual social attention in autism spectrum disorder: Insights from eye tracking studies. *Neurosci Biobehav Rev* (2014) 42:279–97. doi: 10.1016/j.neubiorev.2014.03.013
20. Hessels RS, Kemner C, van den Boomen C, Hooge ITC. The area-of-interest problem in eyetracking research: A noise-robust solution for face and sparse stimuli. *Behav Res Methods* (2016) 48:1694–712. doi: 10.3758/s13428-015-0676-y
21. Chuk T, Chan AB, Hsiao JH. Understanding eye movements in face recognition using hidden Markov models. *J Vis* (2014) 14:8. doi: 10.1167/14.11.8
22. Birmingham E, Bischof WF, Kingstone A. Gaze selection in complex social scenes. *Vis Cognit* (2008) 16:341–55. doi: 10.1080/13506280701434532
23. Brooks JA, Freeman JB. Neuroimaging of person perception: A social-visual interface. *Neurosci Lett* (2019) 693:40–3. doi: 10.1016/j.neulet.2017.12.046
24. Canosa RL. Real-world vision. *ACM Trans Appl Percept* (2009) 6:1–34. doi: 10.1145/1498700.1498705
25. Otten M, Seth AK, Pinto Y. A social Bayesian brain: How social knowledge can shape visual perception. *Brain Cognit* (2017) 112:69–77. doi: 10.1016/j.bandc.2016.05.002
26. Boccignone G. Advanced Statistical Methods for Eye Movement Analysis and Modelling: A Gentle Introduction. In: Klein C, Ettinger U, editors. *Eye Movement Research: An Introduction to its Scientific Foundations and Applications*. Berlin: Springer Publishers (2020). p. 309–405. doi: 10.1007/978-3-030-20085-5_9
27. Chuk T, Chan AB, Hsiao JH. Is having similar eye movement patterns during face learning and recognition beneficial for recognition performance?

Evidence from hidden Markov modeling. *Vision Res* (2017) 141:204–16. doi: 10.1016/j.visres.2017.03.010
28. Coutrot A, Hsiao JH, Chan AB. Scanpath modeling and classification with hidden Markov models. *Behav Res Methods* (2018) 50:362–79. doi: 10.3758/s13428-017-0876-8
29. Boccignone G. *A probabilistic tour of visual attention and gaze shift computational models. arXiv. preprint arXiv:1607.01232* (2016).
30. Coviello E, Chan AB, Lanckriet GRG. Clustering hidden Markov models with variational HEM. *J Mach Learn Res* (2014) 15:697–747.
31. Mannion A, Leader G. Comorbidity in autism spectrum disorder: A literature review. *Res Autism Spectr Disord* (2013) 7:1595–616. doi: 10.1016/j.rasd.2013.09.006
32. Kirsch AC, Huebner ARS, Mehta SQ, Howie FR, Weaver AL, Myers SM, et al. Association of Comorbid Mood and Anxiety Disorders With Autism Spectrum Disorder. *JAMA Pediatr* (2020) 174:63. doi: 10.1001/jamapediatrics.2019.4368
33. Tye C, Runicles AK, Whitehouse AJO, Alvares GA. Characterizing the Interplay Between Autism Spectrum Disorder and Comorbid Medical Conditions: An Integrative Review. *Front Psychiatry* (2019) 9:1–21. doi: 10.3389/fpsyt.2018.00751
34. Penzol MJ, Salazar de Pablo G, Llorente C, Moreno C, Hernández P, Dorado ML, et al. Functional Gastrointestinal Disease in Autism Spectrum Disorder: A Retrospective Descriptive Study in a Clinical Sample. *Front Psychiatry* (2019) 10:179. doi: 10.3389/fpsyt.2019.00179
35. Guerrera S, Menghini D, Napoli E, Di Vara S, Valeri G, Vicari S. Assessment of Psychopathological Comorbidities in Children and Adolescents With Autism Spectrum Disorder Using the Child Behavior Checklist. *Front Psychiatry* (2019) 10:535. doi: 10.3389/fpsyt.2019.00535
36. Mannion A, Leader G, Healy O. An investigation of comorbid psychological disorders, sleep problems, gastrointestinal symptoms and epilepsy in children and adolescents with Autism Spectrum Disorder. *Res Autism Spectr Disord* (2013) 7:35–42. doi: 10.1016/j.rasd.2012.05.002
37. Stevens T, Peng L, Barnard-Brak L. The comorbidity of ADHD in children diagnosed with autism spectrum disorder. *Res Autism Spectr Disord* (2016) 31:11–8. doi: 10.1016/j.rasd.2016.07.003
38. Taurines R, Schwenck C, Westerwald E, Sachse M, Siniatchkin M, Freitag C. ADHD and autism: differential diagnosis or overlapping traits? A selective review. *ADHD Atten Deficit Hyperact Disord* (2012) 4:115–39. doi: 10.1007/s12402-012-0086-2
39. Lukito S, Jones CRG, Pickles A, Baird G, Happé F, Charman T, et al. Specificity of executive function and theory of mind performance in relation to attention-deficit/hyperactivity symptoms in autism spectrum disorders. *Mol Autism* (2017) 8:60. doi: 10.1186/s13229-017-0177-1
40. Doernberg E, Hollander E. Neurodevelopmental Disorders (ASD and ADHD): DSM-5, ICD-10, and ICD-11. *CNS Spectr* (2016) 21:295–9. doi: 10.1017/S1092852916000262
41. Carta A, Fucà E, Guerrera S, Napoli E, Valeri G, Vicari S. Characterization of Clinical Manifestations in the Co-occurring Phenotype of Attention Deficit/Hyperactivity Disorder and Autism Spectrum Disorder. *Front Psychol* (2020) 11:861. doi: 10.3389/fpsyg.2020.00861
42. Palmer CJ, Lawson RP, Hohwy J. Bayesian approaches to autism: Towards volatility, action, and behavior. *Psychol Bull* (2017) 143:521–42 doi: 10.1037/bul0000097
43. Weiß R. *Grundintelligenztest Skala 2—Revision (CFT 20-R) [Culture FairIntelligence Test 20-R—Scale 2]*. Göttingen: Hogrefe (2006).
44. Mayes SD, Calhoun SL. Learning, Attention, Writing, and Processing Speed in Typical Children and Children with ADHD, Autism, Anxiety, Depression, and Oppositional-Defiant Disorder. *Child Neuropsychol* (2007) 13:469–93. doi: 10.1080/09297040601112773
45. SensoMotoric Instruments. *BeGaze Manual version 3.1 SensoMotoric Instruments*. Teltow (2012).
46. Muszkat M, de Mello CB, Muñoz P de OL, Lucci TK, David VF, Siqueira J de O, et al. Face Scanning in Autism Spectrum Disorder and Attention Deficit/Hyperactivity Disorder: Human Versus Dog Face Scanning. *Front Psychiatry* (2015) 6:150. doi: 10.3389/fpsyt.2015.00150
47. Parish-Morris J, Pallathra AA, Ferguson E, Maddox BB, Pomykacz A, Perez LS, et al. Adaptation to different communicative contexts: an eye tracking study of autistic adults. *J Neurodev Disord* (2019) 11:5. doi: 10.1186/s11689-019-9265-1
48. Frazier TW, Strauss M, Klingemier EW, Zetzer EE, Hardan AY, Eng C, et al. A Meta-Analysis of Gaze Differences to Social and Nonsocial Information Between Individuals With and Without Autism. *J Am Acad Child Adolesc Psychiatry* (2017) 56:546–55. doi: 10.1016/j.jaac.2017.05.005
49. Bertenthal BI, Puce A. A Look Toward the Future of Social Attention Research. In: *The Many Faces of Social Attention*. Cham: Springer International Publishing (2015). p. 221–45. doi: 10.1007/978-3-319-21368-2_8
50. Shic F, Chawarska K, Bradshaw J, Scassellati B. Autism, eye-tracking, entropy. In: *2008 7th IEEE International Conference on Development and Learning*. Monterey, CA: IEEE (2008). pp. 73–8. doi: 10.1109/DEVLRN.2008.4640808
51. Guillon Q, Afzali MH, Rogé B, Baduel S, Kruck J, Hadjikhani N. The Importance of Networking in Autism Gaze Analysis. *PloS One* (2015) 10:e0141191. doi: 10.1371/journal.pone.0141191
52. McPartland JC, Webb SJ, Keehn B, Dawson G. Patterns of Visual Attention to Faces and Objects in Autism Spectrum Disorder. *J Autism Dev Disord* (2011) 41:148–57. doi: 10.1007/s10803-010-1033-8
53. Mottron L, Bzdok D. Autism spectrum heterogeneity: fact or artifact? *Mol Psychiatry* (2020) 1–8 doi: 10.1038/s41380-020-0748-y
54. Hayes TR, Henderson JM. Scan patterns during scene viewing predict individual differences in clinical traits in a normative sample. *PloS One* (2018) 13:e0196654. doi: 10.1371/journal.pone.0196654
55. Margari L, Craig F, Margari F, Legrottaglie A, Palumbi R. De Giambattista C. A review of executive function deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder. *Neuropsychiatr Dis Treat* (2016) 12:1191. doi: 10.2147/NDT.S104620
56. Rao PA, Landa RJ. Association between severity of behavioral phenotype and comorbid attention deficit hyperactivity disorder symptoms in children with autism spectrum disorders. *Autism* (2014) 18:272–80. doi: 10.1177/1362361312470494
57. Reiersen AM, Todd RD. Co-occurrence of ADHD and autism spectrum disorders: phenomenology and treatment. *Expert Rev Neurother* (2008) 8:657–69. doi: 10.1586/14737175.8.4.657
58. Carrascosa-Romero MC, De La Vega CDC. The Comorbidity of ADHD and Autism Spectrum Disorders (ASDs) in Community Preschoolers. In: Norvilitis JM, editor. *ADHD - New Directions in Diagnosis and Treatment*. InTech (2015). doi: 10.5772/61400
59. Scheeren AM, de Rosnay M, Koot HM, Begeer S. Rethinking theory of mind in high-functioning autism spectrum disorder. *J Child Psychol Psychiatry* (2013) 54:628–35. doi: 10.1111/jcpp.12007
60. Scandurra V, Emberti Gialloreti L, Barbanera F, Scordo MR, Pierini A, Canitano R. Neurodevelopmental Disorders and Adaptive Functions: A Study of Children With Autism Spectrum Disorders (ASD) and/or Attention Deficit and Hyperactivity Disorder (ADHD). *Front Psychiatry* (2019) 10:673. doi: 10.3389/fpsyt.2019.00673
61. Wingenbach TSH, Ashwin C, Brosnan M. Diminished sensitivity and specificity at recognising facial emotional expressions of varying intensity underlie emotion-specific recognition deficits in autism spectrum disorders. *Res Autism Spectr Disord* (2017) 34:52–61. doi: 10.1016/j.rasd.2016.11.003
62. Black MH, Chen NTM, Iyer KK, Lipp OV, Bölte S, Falkmer M, et al. Mechanisms of facial emotion recognition in autism spectrum disorders: Insights from eye tracking and electroencephalography. *Neurosci Biobehav Rev* (2017) 80:488–515. doi: 10.1016/j.neubiorev.2017.06.016
63. Avni E, Ben-Itzchak E, Zachor DA. The Presence of Comorbid ADHD and Anxiety Symptoms in Autism Spectrum Disorder: Clinical Presentation and Predictors. *Front Psychiatry* (2018) 9:717. doi: 10.3389/fpsyt.2018.00717
64. Kasari C, Patterson S. Interventions Addressing Social Impairment in Autism. *Curr Psychiatry Rep* (2012) 14:713–25. doi: 10.1007/s11920-012-0317-4
65. Fujioka T, Tsuchiya KJ, Saito M, Hirano Y, Matsuo M, Kikuchi M, et al. Developmental changes in attention to social information from childhood to adolescence in autism spectrum disorders: a comparative study. *Mol Autism* (2020) 11:24. doi: 10.1186/s13229-020-00321-w
66. Moessnang C, Baumeister S, Tillmann J, Goyard D, Charman T, Ambrosino S, et al. Social brain activation during mentalizing in a large autism cohort: the Longitudinal European Autism Project. *Mol Autism* (2020) 11:17. doi: 10.1186/s13229-020-0317-x

67. Hotton M, Coles S. The Effectiveness of Social Skills Training Groups for Individuals with Autism Spectrum Disorder. *Rev J Autism Dev Disord* (2016) 3:68–81. doi: 10.1007/s40489-015-0066-5
68. Dijkhuis R, Gurbuz E, Ziermans T, Staal W, Swaab H. Social Attention and Emotional Responsiveness in Young Adults With Autism. *Front Psychiatry* (2019) 10:426. doi: 10.3389/fpsyt.2019.00426
69. Sevgi M, Diaconescu AO, Tittgemeyer M, Schilbach L. Social Bayes: Using Bayesian Modeling to Study Autistic Trait–Related Differences in Social Cognition. *Biol Psychiatry* (2016) 80:112–9. doi: 10.1016/j.biopsych.2015.11.025
70. Nikolaev AR, Meghanathan RN, van Leeuwen C. Combining EEG and eye movement recording in free viewing: Pitfalls and possibilities. *Brain Cognit* (2016) 107:55–83. doi: 10.1016/j.bandc.2016.06.004
71. Falck-Ytter T. Gaze performance during face-to-face communication: A live eye tracking study of typical children and children with autism. *Res Autism Spectr Disord* (2015) 17:78–85. doi: 10.1016/j.rasd.2015.06.007
72. Pan Y, Cheng X. Two-Person Approaches to Studying Social Interaction in Psychiatry: Uses and Clinical Relevance. *Front Psychiatry* (2020) 11:301. doi: 10.3389/fpsyt.2020.00301

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Comorbidity Matters: Social Visual Attention in a Comparative Study of Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder and Their Comorbidity

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Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) represent two common neurodevelopmental disorders with considerable co-occurrence. Their comorbidity (ASD + ADHD) has been included in the latest diagnostic guidelines (DSM-V, 2013). The present study focuses on social visual attention that i) is a main aspect of social attention reflecting social cognition and ii) its atypicalities have been suggested as a potential biomarker for ASD. Considering the possible shared background of both disorders and their comorbidity, it is important to compare such traits directly. Here, 73 children and adolescents paired for age and IQ diagnosed with ASD (N = 12), ADHD (N = 21), comorbid ASD + ADHD (N = 15), and "typically developing" (TD) controls (N = 25), were shown static real-life social scenes while their gaze movements were recorded with eye-tracking. Scenes with two levels of social complexity were presented: low complexity (one person depicted) and high (four interacting individuals). Gaze fixation variables were investigated. Fixation duration on faces was significantly reduced only in ASD + ADHD which also required longer time to fixate all faces at least once. Fixation duration on faces in ASD was reduced, compared to TD, only when looking at scenes with high versus low social complexity. ADHD individuals did not differ from TD. Concluding, the observed alterations of social visual attention support the existence of possible dysfunctional particularities differentiating ASD, ADHD, and ASD + ADHD, which can be revealed with the new method of eye-tracking technique. The objective gaze measurements provided contribute to the development of biomarkers enabling early diagnosis, amelioration of care and further interventions specified for each group.

Keywords: autism spectrum disorder, attention-deficit/hyperactivity disorder, comorbidity, neurodevelopmental disorders, eye tracking, social cognition

INTRODUCTION

Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) are two of the most studied Neurodevelopmental Disorders (1). The main diagnostic criteria of autism include qualitative impairments in social communication and interaction, restricted repetitive patterns of behavior and hyper- or hyporeactivity to sensory aspects of the environment, while those of ADHD consist mainly of inattention, impulsivity and hyperactivity (2). The prevalence of both disorders has risen both in industrial and in low-income countries to a globally estimated 1% or higher for ASD and 2%–7% for ADHD (3–5). Interestingly, ASD and ADHD are frequently co-occurring with an estimated 30%–80% of ADHD in the autistic population and 20%–50% of ASD in the ADHD population (6). Importantly, the latest diagnostic criteria of DSM-V have allowed their simultaneous diagnosis (2).

This co-occurrence has been under discussion both for clinicians and researchers even before DSM-V implemented the changes, in relation to symptom manifestation, both of autistic traits in ADHD individuals (7) and vice versa (8), as well as comparisons of the two disorders concerning their social deficits (9, 10), their neurophysiological similarities and the potential aetiological and biological overlap (11, 12). However, for the most part, research studies of the ASD samples have not controlled for comorbidity with ADHD. This ambiguity in sample definitions might have resulted in misinterpretations of ASD or ADHD traits and in reduced awareness of the specific characteristics of the comorbid population (from now on referred to as ASD + ADHD). Particularly, social cognition traits that highly affect the quality of life of both ASD and ADHD (13, 14) are thought to be more severely impaired in comorbid ASD + ADHD cases (15). Also, comorbid individuals seem to respond differently to existing interventions as they cause challenges in medical treatment (16) and may benefit less from social skills trainings (17). Finally, comorbid cases have been proposed to present a more complex phenotype with more severe deficits in the clinical and cognitive domains, including social deficits (18). Taken together, there is a need for valid biomarkers characterizing and differentiating ASD, ADHD, and ASD + ADHD groups (19).

Social cognition traits represent a main domain of shared and unique characteristics in ASD and ADHD (12). The two disorders share similar social cognitive deficits (9, 10), but their comorbidity may also reflect representative social features of each disorder (20). Interestingly, the link between social ineptness and inattention has been suggested as a pathway which could explain the co-occurrence of ASD and ADHD (21). Under this perspective, the functions combining these elements, such as attention to social information, are worth investigating. Concretely, as defined in a recent conceptual review, visual social attention composes together with social motivation and social behavior, the three core aspects of social attention (22) and can be examined with the eye tracking technique (23). Due to its non-invasiveness and suitability for testing young and/or intellectually impaired individuals, this technique has been applied in neurophysiologic and psychiatric research (24–26). The Free Viewing Task is one of the basic eye-tracking paradigms in social cognition, where the participant is viewing social scenes without specific instructions while his/her gaze is recorded.

In ASD research, various eye-tracking studies including participants from infancy until adulthood exist (27–30). Particularly, in children or adolescents, some studies report that ASD participants look less to the faces of social scenes compared to Typically Developing (TD) peers (31, 32), whereas other studies report similar performance of TD and ASD (33, 34). In some such cases, the ASD participants, however, needed longer to fixate on faces (35). These inconsistencies are addressed by seminal review articles, concluding that social attention in ASD participants is most impacted when stimuli have a high social content, namely, when stimuli show more than one person (33, 34) and human interactions (36). Importantly, this criterium is proposed as a discriminating factor differentiating ASD from TD and is referred to as social complexity (37). The level of social complexity of the depicted scenes is thus defined as the number of people in the scene and the degree of social interaction between them. Accordingly, higher social complexity of a scene should reveal atypical visual attention in ASD participants in terms of reduced attention at social elements.

Compared to the ASD literature, a limited number of studies have emerged regarding ADHD and social visual attention (38). The few existing studies focus mainly on isolated face pictures and report deficits in facial emotion recognition (39) or reduced looking preferences for the eye region (40). Moreover, in non-eye tracking studies, ADHD shows deficits in theory of mind, prosody perception, and empathy (41) and it is reported that deficits in social cognition may impact their symptomatology altogether (42). However, others suggest that children with ADHD are not as impaired as children with ASD on theory of mind tasks (43). Thus, there is not enough evidence that social attention deficits occur when looking at real-life social scenes.

Even less is known about participants with comorbid ASD and ADHD and to the best of our knowledge, there have been no eye-tracking studies about the visual exploration of social scenes in this group. However, it has been reported that ASD + ADHD participants showed deficits in attentional orienting as measured with Event-Related Potentials of face and gaze processing (44). Moreover, a behavioral social cognition study without eye-tracking suggested that children with comorbid ASD + ADHD are at highest risk for emotion recognition problems in comparison with TD, ASD, and ASD-unaffected siblings (45). Interestingly, the scope of this approach was to investigate whether emotion recognition may represent an endophenotypic candidate for ASD while evaluating the impact of comorbid ADHD (45).

Eye tracking measurements represent accurate, reproduceable measures that might serve as potential objective indications of medical states in order to predict the incidence and early diagnosis of a disorder as well as monitor outcomes of interventions (46). Regarding ASD, visual attention to social relevant stimuli has been recently suggested as a promising early behavioral biomarker (47). In addition, considering the high comorbidity of the ASD and ADHD and their suggested

aetiological and biological overlap (48), comparisons between all respective clinical groups are necessary for the development of such valid biomarkers.

The present study sets out to fill the described gap by directly comparing the ASD, ADHD, and comorbid ASD + ADHD groups in social visual attention to real-life scenes with different levels of social complexity. The study design enables us to differentiate the following scenarios: whether altered social visual attention measures are (a) specific to ASD and thus absent in those with ADHD symptoms; (b) present in ASD and more pronounced in comorbid cases; (c) a shared feature of these neurodevelopmental disorders. Additionally, interactions with the level of social complexity, early gazing behavior, and latencies until first facial fixations are explored.

MATERIAL AND METHODS

Participants

Children and adolescents were recruited from four predefined groups: TD, ADHD, ASD, and ASD + ADHD. Inclusion criteria were normal or corrected-to-normal vision, intelligence quotient (IQ) ≥70, native-speaker level in the local language and age between 10 and 14 years. The minimum required age was chosen, since participants had to read for one of the overall study's tasks, while the age span was kept relatively short in order to reduce the developmental bias. Subjects with strabismus, clinical diagnoses of Tourette syndrome, specific reading disorder, epilepsy, schizophrenia, depression or any known specific genetic syndrome associated with ASD or ADHD were explicitly excluded. Finally, 73 out of the 89 recruited children and adolescents aged 10–14 years were included (TD: N = 26; ADHD: N = 26; ASD: N = 16; and ASD + ADHD: N = 21; see *Results*), paired for age and IQ [for power calculations see (49)].

TD participants were recruited from local schools, sports groups and the institutional database including children or adolescents that had participated in previous unrelated neuropsychological studies and had expressed interest in participating in further studies. Participants for the clinical groups were recruited from the department database. The diagnoses were made prior to the study by three experienced child- and adolescent psychiatrists (with 22, 16, and 14 years of experience) and three clinical psychologists (with 19, 12, and 10 years of experience) based on the ICD-10 criteria (in our study F84.0, childhood autism; F84.1, atypical autism; F84.5, Asperger's syndrome; F90.0, predominantly inattentive type ADHD; F90.1, predominantly hyperactive type ADHD). Diagnoses were verified before recruitment.

ASD was diagnosed based on the gold standard for autism diagnosis, namely, the self-rated Autism Diagnostic Observation Schedule [ADOS (50)] and the parent-rated semi-structured Autism Diagnostic Interview [ADI-R (51)]. These measures, especially in combination, are suggested to have the largest sensitivity and specificity (52). Status of previously accomplished social competence training, consisting of 12 hourly modules, was extracted from the database of our department for the ASD and ASD + ADHD groups (53). Particularly, the social competence training used, the so-called "Theory-of-Mind-Training in Autism Spectrum" [TOMTASS (54)], is an established method based on behavioral therapy and specified autistic intervention, namely, the program "Treatment and Education of Autistic and Related Communication Handicaped Children" [TEACCH, (55)]. In our study, it was applied in local language, in a time period of five months, in small groups of three participants. The diagnosis of ADHD was based on: i) the Conner's parent and teacher rating scales (56); ii) comprehensive interviews and history with the child's adult caregivers; iii) comprehensive interviews and behavioral observation of the child. This diagnostical procedure is in alignment with recommendations for reliability of diagnosis (57).

For the purpose of this study, assessments of general and specific symptomatology in native language were applied additionally, characterizing the semiology of each group. Assessment of general emotional and behavioral problems was realized for all participants with the parent-rated Child Behavior Checklist (CBCL/6-18) (58), which has been proved valid in screening of ADHD (59). Specific assessment of autistic semiology was performed across all participants using the school-age Social Responsiveness Scale (SRS), a quantitative measure of autistic traits applicable in both clinical settings and large-scale research studies of ASD conditions (60). For assessment of ADHD semiology, the established parent-rated external assessment questionnaire (EAQ) and the self-assessment questionnaire (SAQ) questionnaires based on the ICD-10 and the DSM-IV were used in native language (61). All participants were asked to be medication-free from psycho-stimulants for at least 24 h before testing (62). Medication intake of the clinical groups is listed in **Table 1**.

The local institutional ethics committee approved the study protocol, which was conducted in accordance with the Declaration of Helsinki (63). All participants and their parents/legal guardians were comprehensively informed about the purpose and the procedures of the study and gave their written consent before participating.

Procedure

The experimental procedure was composed of two sessions, for the majority of the participants in following order: in the first session (60 min, including breaks) an IQ test was performed [Culture Fair Intelligence Test 20, CFT 20-R; (64)] and previously distributed questionnaires were collected. The second session (a battery of six eye-tracking tasks totalling 90 min, including breaks) was conducted in a sound-attenuated Faraday cage, while an experimenter provided instructions and observed the participants from a lateral-rear position. A second experimenter monitored the gaze attention and eye trackability of the participant throughout the whole experiment. Participant-screen distance was 70 cm. Participants were instructed to avoid unnecessary head movements or speaking during the task and a comfortable position was ensured without chin-/forehead rest. The various tasks of the experiment, including the Free Viewing task, were presented in counterbalanced order across participants of each group. After successful calibration, as described below, participants were presented with static stimuli of different social

TABLE 1 | Demographics, assessment and diagnostic scoring of the distinct groups.

Variable	TD	ADHD	ASD	ASD + ADHD	Statistical inference	
					Hypothesis testing	contrasts
Number of participants	25	21	12	15	–	–
Males (in %)	52	76	83	93	$\chi^2 = 9.4$ p = 0.02	–
Age in years	12.1 ± 1.5 (10.6–13.6)	12.6 ± 0.9 (11.9–13.1)	12.3 ± 1.1 (11.7–13.0)	12 ± 1.0 (11.4-12.8)	p = 0.48	–
IQ	110 ± 17 (96–122)	102 ± 13 (92–111)	103 ± 21 (88–114)	96 ± 15 (84–109)	p = 0.07	–
Education level 1, 2a, 2b, 2c (in %)[#]	8, 0, 40, 52	0, 10, 76, 14	8, 25,42,25	20, 7, 7, 66		
Social training (in %)	–	–	50	40	$\chi^2 = 0.02$ p = 0.89	
CBCL-total problems	50 ± 6.6 (46–55)	64.9 ± 7.9 (59–72)	68.1 ± 8.3 (64–74)	64.7 ± 8.5 (62–70)	p <.001	TD < ADHD, ASD, ASD + ADHD
SRS-total	44.2 ± 8.7 (40–48)	66.6 ± 10 (62.5–71)	76.6± 13.4 (67–83)	77.0 ± 8.4 (72–78)	p <.001	TD < ADHD < ASD, ASD + ADHD
ADHD symptomatology						
EAQ-total	–	7.1 ± 1.1 (6.5–7)	6.6 ± 1.1 (6.8–7)	7.2 ± 0.9 (6.9–7.1)	p = 0.28	–
EAQ-Competence*	–	3.4 ± 1.2 (3–4)	4.8 ± 1.6 (4–5.5)	4.1 ± 1.4 (3.3–5)	p = 0.02	ADHD < ASD
SAQ-total	–	6.3 ± 1.8 (5–8)	5.5 ± 1.6 (4–7)	6.8 ± 1.3 (6–8)	p = 0.13	–
SAQ-Competence*	–	4.9 ± 1.8 (4.3–6)	5.8 ± 1.1 (5.8–6.3)	5.3 ± 1.7 (5–6)	p = 0.29	–
ADOS total score	–	–	12.6 ± 4.9 (10–17)	10.2 ± 4.3 (7–13)		
ADI-R interaction	–	–	12.6 ± 4.9 (10–17)	12.6 ± 4.9 (10–17)		
ADI-R communication	–	–	13.8 ± 5.1 (11–14)	15.6 ± 7.6 (10–22)		
ADI-R restricted and repetitive behavior	–	–	5.2 ± 2.9 (8–13)	4.8 ± 3.1 (3–6)		
Permanent medication (count)	–	MPH 12[†]	AAP 1	AAP 2, MPH 6[†]		

*Values correspond to group mean ± 1 standard deviation, while 25th percentile and 75th percentile are inside parentheses, if not stated otherwise. All scores for CBCL and SRS are T-scores, while all scores for EAQ and SAQ are Stanine scores. [#]Education level is categorical (1: primary school, 2a–c: secondary level, lowest to highest sublevels). *Higher competence scores are associated with normal functioning. [†]Medication had been discontinued at the day of the experiment. Abbreviations: TD, Typically Developing; ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; ASD + ADHD, comorbid group with ASD and ADHD; χ^2, chi-squared; p, p-value; "<" and ">" symbols indicate statistically significant contrasts; CBCL, Child Behavior Checklist; SRS, Social Responsiveness Scale; EAQ and SAQ, External- and Self-assessment Questionnaires for ADHD, respectively, based on ICD-10, DSM-V (39); ADOS, Autism Diagnostic Observation Schedule; ADI-R, Autism Diagnostic Interview-Revised; MPH, methylphenydate; AAP, atypical antipsychotics.*

complexities in fixed order with a run duration of 2 min. These consisted of four original pictures of real-life scenes, two with one person and two with four people interacting, representing low versus high social complexity stimuli, respectively (see **Figure 1**). Their content and scenery was developed based on existing literature and the International affective picture System (IAPS) (65) with participation of professional actors. For both levels of social complexity, the scenes take place both indoors and outdoors. All scenes represent everyday situations: i) the social interactions of four individuals show people sitting and discussing, and ii) the single-person scenes show an individual from a frontal or side view. Details regarding selection criteria and scene content are listed in Supplementary Materials S1. In order to minimize the effects of workload and fatigue, participants were mostly tested on weekends or during school holidays and had adequate breaks between tasks, if needed.

Eye tracking stimuli were presented on a 24"-TV Monitor (screen resolution of 1,920 × 1,080 pixels and screen refresh rate of 60 Hz) with the Presentation® software (Version17.2, Neurobehavioral Systems, Inc., Berkley, CA). For data recording the iView RED250 remote eye tracker (SensoMotoric Instruments GmbH, SMI) was used with a sampling frequency of 120 Hz and a visual angle of 20° and binocular tracking mode. Preceding each task, a standard five-point calibration and four-point validation was conducted, as suggested by the software's manufacturer, which was considered as successful if the deviance was lower than 0.5° (66). Event classification in fixations, saccades or blinks and data export was accomplished with the SMI software *BeGaze 3.7*, excluding off-screen fixations and/or blinks. The default software thresholds for identification of fixations, defined as a gaze event of minimum 60 ms and a maximum dispersion of 2°, were applied (67).

In addition to the above-mentioned selection criteria, data were examined separately in real time speed and only data fulling following thresholds were included: tracking ratio >75% (percentage of non-zero gaze positions divided by sampling frequency multiplied by run duration) and/or a total fixation duration ratio >50% (percentage of total fixation duration divided by run duration), as previously described (68, 69).

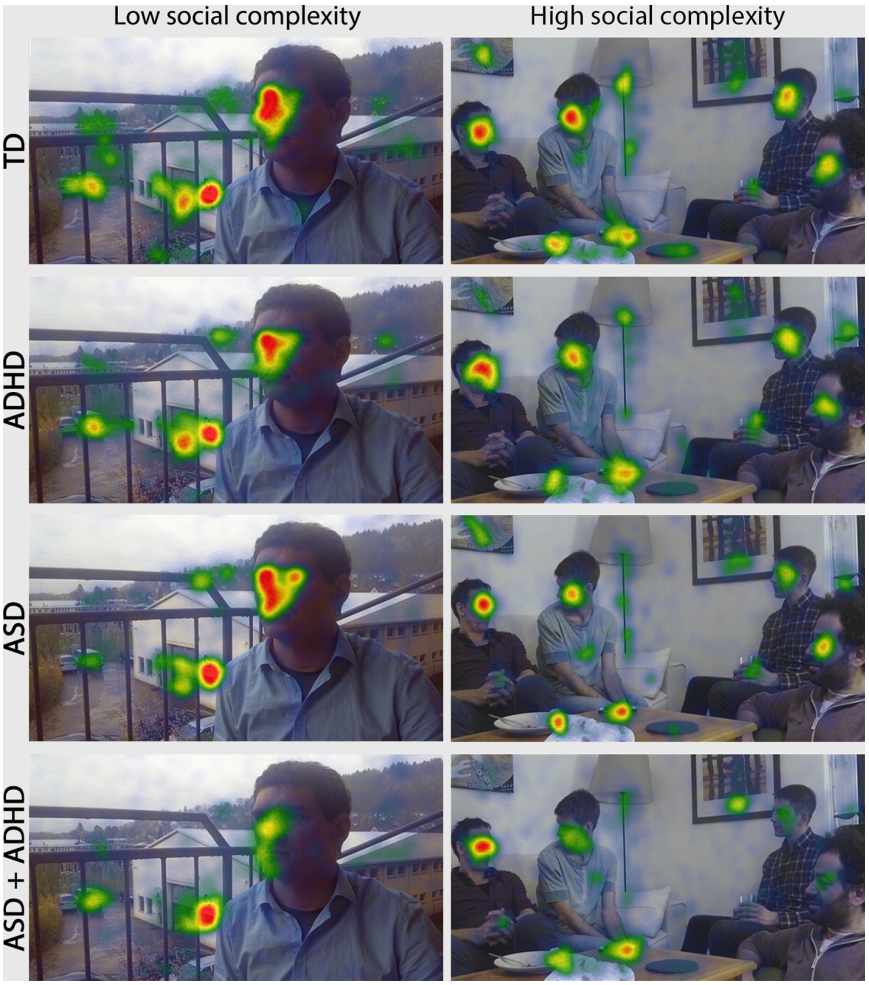

FIGURE 1 | Heatmaps representing the amount of fixation duration for each group and stimuli of high and low social complexity. The warmer the color of the superimposed heatmap, the higher the fixation duration, while the scale is common for all subfigures. The ASD + ADHD group looks on average less at faces in both levels of social complexity, while ASD participants look less at faces when looking at the social complex picture with four interacting people rather than in the picture of low social complexity with one face only. The ADHD participants look at faces similar to TD. Abbreviations: TD, Typically Developing; ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; ASD + ADHD, Autism Spectrum Disorder with comorbid Attention-Deficit/Hyperactivity Disorder.

Data Analysis

Areas of Interest (AOIs) were delineated for every picture annotating the whole image and differentiating the following categories: face, body and non-social, the latter including all non-social elements of the stimulus (i.e., objects). This categorization on naturalistic scenes, including images of people during an interaction, has been used in previous studies (70). Eye tracking measurements were exported for each subject and AOI from the SMI Software and heatmaps of fixation duration were generated for quality control. Fixation data were further processed with MATLAB (R2018b, The MathWorks, Natick, MA, USA) for the calculations described below.

Fixation Durations

Two basic types of fixation duration variables were calculated (in seconds, s) for each participant: i) total fixation duration representing the sum of fixation durations over one stimulus, irrespective of AOI and ii) fixation durations for each AOI category, defined as the sum of fixation durations for each stimulus and representing the total fixation duration spent respectively in the three AOI categories. For the face AOIs, the analysis was additionally conducted for the first 5 and 10 seconds, representing the early gazing behavior of the visual exploration (33).

Latencies to Face Fixations

Additionally, two latency variables were investigated for the face AOIs (in seconds) (70). Firstly, the "latency to first face fixation", defined as the time required until the first fixation to a face AOI. Secondly, only for the stimuli of high social complexity, the "latency to completion of face fixations" was defined as the time period required until all four interacting faces were fixated for the first time. Former variable has been used before (70), while latter was introduced here in order to capture the time required for visually exploring all faces and not only one of them.

Statistical Analysis

Statistical analysis was conducted with the statistical software R (R Core Team, v3.6.1). Linear mixed effects models were implemented for the analysis of the interaction between fixation duration and clinical groups with the "lme4" library (v1.1-19) (71), while p-values were obtained by the "lmertest" library with a significance threshold defined as p-value < 0.05. In general, small sample sizes are tolerated with linear mixed effects models, as this type of linear regression accounts both for by-item and by-subject variation in a single model (fixed and random effects, respectively), the latter also being an important advantage when applying to psychiatric populations. Based on the described benefits, linear mixed effects analyses are strongly recommended and their application is rapidly increasing (72), while they have been recently introduced in eye-tracking data analysis (40) and neurophysiological studies (73).

Firstly, total fixation duration was examined and following fixed effects were entered into the model: i) group of participants (TD, ADHD, ASD, ASD + ADHD), ii) level of social complexity (high, low), iii) interaction term between group of participants and level of social complexity, and iv) status of previous social training (yes, no). A random intercept was used for each subject. Secondly, the fixation duration of each of the three AOI-categories (face, body, and non-social elements) was examined with separate linear mixed effects models, structured accordingly. Here, the same explanatory variables as above were introduced as fixed effects, while individual total fixation duration for the respective stimulus was added as a covariate, in order to limit the effect of inter-individual differences in total fixation duration. Finally, similarly to the analysis of the whole run duration, the fixations to the faces were analysed separately for the first 5 and 10 s with total duration of fixations in the respective timespan as a covariate.

For the latency variables two-way analysis of variance (ANOVA) was implemented, with the group of participants as the between-subject factor and stimuli as the within-subject factor. As only one value is available per stimulus, mixed effects models cannot be applied. For the statistical analysis of demographics, an ANOVA was used for continuous variables and a chi-square (χ^2) with Yates' continuity correction for categorical variables.

RESULTS

From the recruited participants three did not complete all sessions (1 ADHD, 2 ASD + ADHD), three did not fulfil the IQ criterion (1 ADHD, 1 ASD, and 1 ASD + ADHD) and one ADHD patient had not discontinued medication, leading to their exclusion from the analysis. Datasets of further nine participants with subthreshold values of tracking ratio and/or total fixation duration ratio (1 TD, 2 ADHD, 3 ASD, 3 ASD + ADHD) were excluded. Finally, datasets from n = 73 participants were included in this present study. Groups did not differ in age and IQ (mean ± standard deviation for age: 12.1 ± 1.5, 12.6 ± 0.9, 12.3 ± 1.1, 12 ± 1.0, p-value 0.48; and for IQ: 110 ± 17, 102 ± 13, 103 ± 21, 96 ± 15, p-value 0.07 for TD, ADHD, ASD, ASD + ADHD, respectively). There was a male predominance in the clinical groups (sex-ratio 52%, 76%, 83%, 93%, respectively). Previously accomplished social training in the ASD groups was equally balanced (50% and 40% for ASD and ASD + ADHD, respectively). In the ADHD group both main types were represented (N = 13 with F90.0 and 8 with F90.1). In the ASD group childhood autism and Asperger's syndrome were the main diagnoses (N = 3 with ICD-10 F84.0 and N = 8 with F84.5, respectively), while 1 subject was diagnosed with atypical autism (F84.1). In the ASD + ADHD group the distribution was similar (N = 4 with F84.0, N = 9 with F84.5 and N = 2 with F84.1) and regarding comorbidity, either it was diagnosed as such, or the criteria for both ASD and ADHD were fulfilled (for those diagnosed before the introduction of DSM-V). Confirmed diagnoses, as well as ADOS and ADI-R, are listed at the bottom of **Table 1**. Reported comorbidities of included participants are listed in the **Supplementary Table 1**.

Descriptive statistics of diagnostic tests, questionnaire scoring results and results of statistical inference, as well as sociodemographic variables are shown in **Table 1**. TD participants showed T-scores inside the reference range (values below 60 are categorized as normal) in the CBCL-total problems (50 ± 6.6) and the SRS-total score (44.2 ± 8.7). Clinical groups showed average T-scores above the cut-off in the CBCL-total and SRS-total scoring (values above are categorized as borderline or clinical see **Table 1**). Specifically, concerning the scoring of autistic symptomatology, the ASD and ASD + ADHD groups did not differ significantly but showed a statistically significant higher SRS-total score (76.6 ± 13.4 and 77.0 ± 8.4, respectively, values above 75 indicate severe social impairment) compared to the TD and ADHD group (44.2 ± 8.7, p-value < 0.001 and 66.6 ± 10, p-value < 0.05, respectively). Finally, in the scoring of ADHD symptomatology, the ADHD and ASD + ADHD groups did not differ statistically in the Stanine-scores (7.1 ± 1.1 and 7.2 ± 0.9, respectively), which were above average (meaning a Stanine > 7) in the EAQ total score and showed lower values in the competence scores compared to the ASD (3.4 ± 1.2 vs. 4.8 ± 1.6, p-value < 0.02).

Total Fixation Duration

For the stimuli with low social complexity, the control group showed a total fixation duration of 109 ± 7.1 s (mean ± standard deviation, SD), while the clinical groups showed lower total fixation durations: the ADHD group 104 ± 11.6 s, the ASD group 103 ± 12 s and the ASD + ADHD group 103 ± 10.6 s. For the two stimuli with high social complexity, the control group showed a mean total fixation duration of 104 ± 9.8 s, while the ADHD group spent 103 ± 7.6 s fixating, the ASD 100 ± 12.3 and the ASD + ADHD 98 ± 13.1 s. Boxplots did not show any extreme outliers.

In the respective mixed effects analysis, the total fixation duration was significantly longer by 3.6 s for all groups at the stimuli with low socially complexity (F-value = 15.5, p-value of *post-hoc* test < 0.001). For the ASD + ADHD group and both levels of social complexity, total fixation duration was significantly lower by 6.2 s (F-value = 1.7, p-value of *post-hoc* test = 0.038, see **Supplementary Table 2**). There was no significant interactive effect between social complexity of stimuli and group of participants or effect of previous training of social competence on total fixation duration. Inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality.

Fixation Duration on Faces

Across all groups the average of total fixation duration on faces was 21 ± 9.9 s for low social-complexity stimuli and 7.1 ± 4.7 s for high social-complexity stimuli, as in the latter stimuli the fixation duration was distributed among the four depicted face AOIs. **Figure 1** shows fixation distribution representations (heatmaps) for participants of all groups in two levels of social complexity.

In the mixed effects analysis, only the comorbid group showed significantly lower fixation durations on faces irrespective of social-complexity, with 2.3 s less (F-value = 4.65, p-value of *post-hoc* test = 0.032), while the two other groups did not differ compared to TD (see **Table 2**). For the ASD group there was a significant interaction with social-complexity, with 4.9 s shorter fixation durations to faces in stimuli with high social-complexity (F-value = 4.75, p-value of *post-hoc* test = 0.001, see **Table 2**). Previous training of social competence did not affect fixation duration on the face AOIs. Fixation estimates are visualized in **Figure 2**.

For the first 5 and 10 s, analogous mixed effects analysis of fixations on faces was implemented. For the first 5 s, no group difference was evident. At 10 s, the total fixation duration on face AOIs across all groups was on average 2.6 ± 1.3 s for low versus 0.9 ± 0.7 s for high social-complexity stimuli. In the ASD + ADHD, the fixation duration on faces was significantly lower for both social-complexities by 0.3 s compared to the TD group (F-value = 4.1, p-value of *post-hoc* test = 0.015). Consistent with the results for the total run duration, the other clinical groups did not show any significant differences. The interaction observed between social-complexity and the ASD group for the total run duration, was at trend level at early gazing (F-value = 2.1, p-value of *post-hoc* test = 0.051). Tabular results of fixed effects parameter estimates for 5 and 10 s can be found in **Supplementary Tables 3** and **4**.

Fixation Duration on Bodies and on Non-Social Elements

No significant group effects and no interactive effects were observed for the AOIs of bodies. Similar to the face AOI the fixation duration on high social complexity stimuli was distributed among the bodies of the four depicted persons (F-value = 173.9, p-value of *post-hoc* test < 0.001). The mixed effects analysis with the non-social elements AOI category did not show any group differences or any interactions of group with social complexity. There was a significant effect of social complexity, with participants fixating more on non-social elements in low social complexity stimuli (F-value = 118.3, p-value of *post-hoc* test < 0.001). Detailed fixed effects parameter estimates can be found in **Supplementary Tables 5** and **6**.

Latency to First Face Fixation and Completion of Face Fixations

All four groups showed similar latencies to first face fixation (Group $F_{(3,283)} = 1.0$, p = 0.392; all contrasts versus TD: p-values non-significant) and no interactive effects with social complexity. By contrast, the latency to completion of face fixations was 5.7 s higher in the ASD + ADHD compared to the TD group (Group $F_{(3,141)} = 3.49$, p = 0.017, p-value of contrast 0.003). The other two clinical groups did not show prolonged latencies compared to the TD group.

DISCUSSION

The present study set out to investigate social visual attention in the neurodevelopmental disorders ASD, ADHD, and their comorbidity ASD + ADHD applying objective gaze measurements which are proposed to contribute to the development of valid biomarkers. To our knowledge, this is the first eye tracking study comparing social visual attention directly in all three clinical groups and TD controls.

In summary, the comorbid group showed significantly reduced social visual attention to faces in comparison to the control group. This effect was consistent across different levels of social complexity and after correction for their reduced total fixation duration and was detected using two representative eye tracking variables. Firstly, the fixation duration on faces was significantly reduced. Secondly, the time needed for the

TABLE 2 | Fixed effects parameter estimates for fixation duration on faces from 73 subjects.

Fixed effect	F value	Effect	Estimate	95% CI		SE	p-value
				Lower	Upper		
		(Intercept)	14.4	13.5	15.3	0.5	<.001
Group	4.65						
		- ADHD vs. TD	–0.3	–2.1	1.4	0.9	0.717
		- ASD vs. TD	2	–0.4	4.3	1.2	0.102
		- ASD + ADHD vs. TD	–2.3	–4.5	–0.2	1.1	0.032
Group × social complexity	4.75						
		ADHD vs. TD × high vs. low	–0.9	–3.4	1.6	1.3	0.493
		ASD vs. TD × high vs. low	–4.9	–7.8	–1.9	1.5	0.001
		ASD + ADHD vs. TD × high vs. low	1.0	–1.8	3.7	1.4	0.480
Social complexity	662.98	high vs. low	–13.7	–14.7	–12.6	0.5	<.001
Total fixation duration	28.64	(covariate)	0.1	0.1	0.2	0.03	<.001
Previous social training	1.59	yes vs. no	1.3	–0.7	3.4	1.1	0.212

TD, Typically Developing; ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; ASD + ADHD, comorbid group with ASD and ADHD; CI, Confidence Interval; SE, Standard Error; vs., versus; x, interaction between two effects.

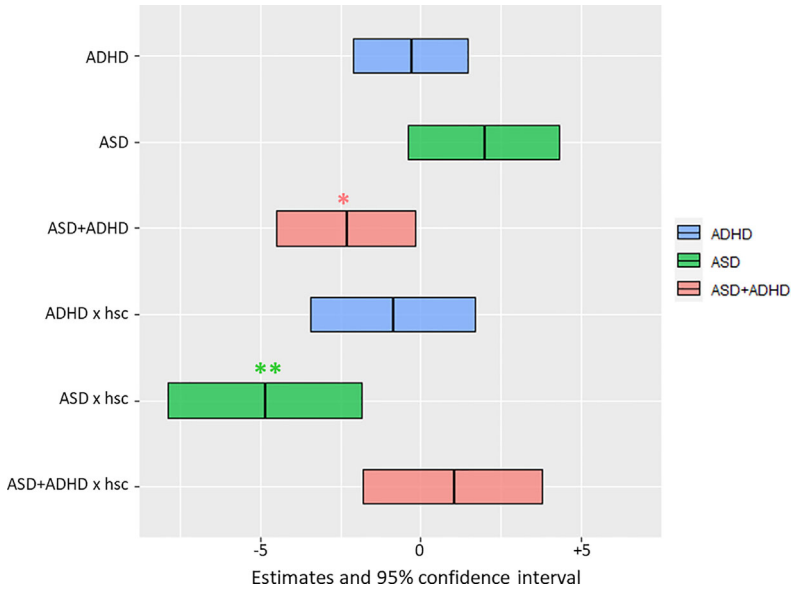

FIGURE 2 | Results of the mixed effects analysis for the region of faces. Mean estimates of the fixed effects with 95% confidence interval are shown as center and border lines of each box, respectively. Their position on the x-axis (in seconds) relative to 0 is a measure of the statistical effect on the fixation duration to faces. Two fixed effects significantly reduce the fixation duration to faces, namely, the ASD + ADHD and the interaction term of ASD x high social complexity. Color coding is explained in the legend. *$p < 0.05$, **$p < 0.01$. Abbreviations: TD, Typically Developing; ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; ASD + ADHD, Autism Spectrum Disorder with comorbid Attention-Deficit/Hyperactivity Disorder; hsc, high social complexity; x, interaction between two effects.

completion of face fixations was significantly prolonged, possibly reflecting a latency in the perception of the social configuration of interacting faces. Moreover, the significant effect of reduced fixation duration on faces was also evident at the early gaze behavior. Interestingly, there was an effect of social complexity on facial fixation duration in the ASD group but not in TD controls; ASD individuals looked less at faces in the socially complex images compared to the socially simple ones. Finally, participants with ADHD did not differ from controls in any of the gaze behavior parameters investigated. Taken together, reduced social visual attention was present in the comorbid group ASD + ADHD, while in the ASD group, it was reduced compared to TD controls when looking at scenes with high as opposed to low social complexity.

The present findings for the comorbid group are new, given that ASD cases have not been previously differentiated from the comorbidity cases in eye-tracking. Our findings are in line with recent non-eye-tracking studies of social cognition that consider this differentiation. Namely, in a study of visual and auditory emotion recognition, the comorbid group found to be somewhat more impaired than the "pure" groups in the speed of emotion recognition in both modalities (74). Elsewhere, autistic symptomatology, based on SRS and ADI-R, was found to be more pronounced in the ASD + ADHD in comparison to ASD and particularly regarding the social interaction subscale (ADI-R) (75). Such effects have been proposed to describe a more severe phenotype in ASD + ADHD (76). Other scenarios refer to comorbidity as a separate nosology (77) or propose the existence of subtypes of these two neurodevelopmental disorders (78). However, given their evolution of symptomatology across developmental ages (79), their genetic origins (80) and the recency of this discussion, more research directly investigating the comorbid ASD + ADHD group is needed to clarify this topic and replicate and extend our findings.

As highlighted in recent reviews on eye-tracking in ASD, social complexity is crucial for the performance of ASD subjects in social visual attention (37). However, only a handful of studies clearly report coexisting ADHD diagnosis. Therefore, findings from such samples should be interpreted with certain caution. Here, subjects with ASD-only were studied at different levels of social complexity and indeed there was a significant interaction between the ASD group and social complexity. This signifies that ASD participants spent less time on faces of people interacting with each other rather than on isolated faces. Yet, the time spent on faces across levels of social complexity was similar to the TD group, which replicates previous findings, where autistic children had the same fixation behavior, in terms of fixation time at faces, as TD children (33). Consequently, the conclusions concerning the importance of social complexity are partially replicated here. Moreover, adding to the existing conclusions, this study suggests that apart from social complexity, the existing comorbidity of ADHD could also play a crucial role in the performance of ASD in social visual attention. Thus, the timely need for reporting ADHD comorbidity as common practice in ASD research is underlined (81).

In the current analysis, latency to isolated faces in ASD participants was similar to TD, replicating previous findings. Particularly, in a comparable study including social images of different social complexity, children with ASD spent a similar amount of time as TD to first fixate to the face AOI (70). In our study, the latency of attention to a group of faces was additionally

investigated and also introduced as a new measurement. Interestingly, the ASD + ADHD group required significantly longer until all four interacting faces were fixated for the first time when contemplating the socially complex scenes, suggesting they may have required longer in order to conceive the configuration of interacting people. Thus, the latency of attention to a group of faces, as presented here, could be meaningful for studying the apprehension of complex social interactions. Thus, it remains to be validated in future studies as a possible sensitive indicator of social visual attention deficits.

Apart from the clinical and theoretical implications of this study discussed above, the data analysis in this eye-tracking study offers various methodological advantages. Firstly, the type of linear regression model used allows for a modularly expandable introduction of explanatory variables, such as the status of previous social competence training and the covariate of total fixation duration. Secondly, with the mixed effects model, the impact of the explanatory variables on the fixation data is differentiated from the inter-individual gazing traits. This approach is essential in psychiatric research even more in the era of the dimensionality of disorders. (82). Thirdly, repeated measures, from two stimuli each, were nested in the two levels of social complexity (83). Finally, eye tracking offers measurable variables that are promising in social attention and are related to real-life social behaviors of neurodevelopmental disorders (84). In conjunction with robust statistical methods, here we compare objective eye tracking measurements for ASD, ADHD, and ASD + ADHD that could eventually provide potential candidates of valid biomarkers for differentiating these disorders. Recently, patterns of visual social attention which were obtained through gaze behavior were associated with caregiver-reported measures of social communication used in clinical trials (19). Thus, gaze measurements, as presented in our study, could serve as biomarkers for early diagnosis, monitoring and further care interventions as recommended (47).

Limitations of this study include moderate participant and stimulus sample sizes, which were partially addressed with the application of mixed effects models. Especially recruitment of ASD-only participants proved challenging. Applying thorough inclusion criteria on datasets, on the one hand ensured good data quality, on the other side caused additional exclusion of participants. Therefore, our study could be considered as a pilot study. In order to reduce the number of comparisons for the eye-tracking variables, the clinical groups were only compared to the control group. Nevertheless, these limitations call for independent replications with different participant and stimulus samples. The original stimuli will be made available upon request. Additionally, there was a male predominance in the clinical samples, which is yet in accordance with the known prevalence of ASD and ADHD.

In conclusion, to the best of our knowledge, this study investigates for the first time social visual attention using the eye tracking method to compare groups of ADHD, ASD, ASD + ADHD and TD participants. Our findings underscore the timely need to investigate social attention in the comorbid group in alignment with the current DSM-V guidelines. In addition, we emphasize that the existence of ADHD comorbidity should be considered as a crucial factor having impact on social visual attention in ASD and therefore its reporting should be a common practice in ASD research. Eye tracking measurements and Free Viewing of real-life social scenes as here presented, could contribute to the investigation of social attention, differentiation of ASD, ADHD, and ASD + ADHD and lead to the development of valid biomarkers. In this way, research on these neurodevelopmental disorders could enable an early diagnosis, gradually allow a thorough understanding of their social challenges, and promote an efficacious assistance to the population, with accurate monitoring and care interventions that will improve their quality of life.

DATA AVAILABILITY STATEMENT

All results presented in this study are included in the article/ **Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethik-Kommission der Albert- Ludwigs-Universität Freiburg Freiburg, Germany. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CI: data collection, data analysis, statistical analyses, and manuscript writing. DS: study design and data collection. MS: statistical analyses and manuscript writing. AR: manuscript writing. LT: manuscript writing. NS: manuscript writing. CF: manuscript writing. MB-S: study design and manuscript writing. GB: statistical analyses and manuscript writing. CK: study design and manuscript writing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Bishop DVM. Which neurodevelopmental disorders get researched and why? *PLoS One* (2010) e15112. doi: 10.1371/journal.pone.0015112
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Arlington, VA: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596
3. Bitta M, Kariuki SM, Abubakar A, Newton CRJC. Burden of neurodevelopmental disorders in low and middle-income countries: A systematic review and meta-analysis. *Wellcome Open Res* (2018) 2:121. doi: 10.12688/wellcomeopenres.13540.3
4. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 Years -Autism and developmental disabilities monitoring network, 11 Sites, United States, 2014. *MMWR Surveill Summ* (2018) 67(No. SS-6):1–23. doi: 10.15585/mmwr.ss6706a1
5. Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, andservice provision. *Lancet Psychiatry* (2018) 5:175–86. doi: 10.1016/S2215-0366(17)30167-0
6. Stevens T, Peng L, Barnard-Brak L. The comorbidity of ADHD in children diagnosed with autism spectrum disorder. *Res Autism Spectr Disord* (2016) 31:11–8. doi: 10.1016/j.rasd.2016.07.003
7. Grzadzinski R, Di Martino A, Brady E, Mairena MA, O'Neale M, Petkova E, et al. Examining autistic traits in children with ADHD: does the autism spectrum extend to ADHD? *J Autism Dev Disord* (2011) 41:1178–91. doi: 10.1007/s10803-010-1135-3
8. Taurines R, Schwenck C, Westerwald E, Sachse M, Siniatchkin M, Freitag C. ADHD and autism: differential diagnosis or overlapping traits? A selective review. *ADHD Atten Deficit Hyperact Disord* (2012) 4:115–39. doi: 10.1007/s12402-012-0086-2
9. Demopoulos C, Hopkins J, Davis A. A Comparison of Social Cognitive Profiles in children with Autism Spectrum Disorders and Attention-Deficit/Hyperactivity Disorder: A Matter of Quantitative but not Qualitative Difference? *J Autism Dev Disord* (2013) 43:1157–70. doi: 10.1007/s10803-012-1657-y
10. Bora E, Pantelis C. Meta-analysis of social cognition in attention-deficit/hyperactivitydisorder (ADHD):Comparison with healthy controls and autistic spectrum disorder. *Psychol Med* (2016) 46:699–716. doi: 10.1017/S0033291715002573
11. Rommelse NNJ, Geurts HM, Franke B, Buitelaar JK, Hartman CA. A review on cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. *Neurosci Biobehav Rev* (2011) 35:1363–96. doi: 10.1016/j.neubiorev.2011.02.015
12. van der Meer JMJ, Oerlemans AM, van Steijn DJ, Lappenschaar MGA, de Sonneville LMJ, Buitelaar JK, et al. Are Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder Different Manifestations of One Overarching Disorder? Cognitive and Symptom Evidence From a Clinical and Population-Based Sample. *J Am Acad Child Adolesc Psychiatry* (2012) 51:1160–72.e3. doi: 10.1016/j.jaac.2012.08.024
13. Ikeda E, Hinckson E, Krägeloh C. Assessment of quality of life in children and youth with autism spectrum disorder: A critical review. *Qual Life Res* (2013) 23:1069–85. doi: 10.1007/s11136-013-0591-6
14. Wehmeier PM, Schacht A, Barkley RA. Social and Emotional Impairment in Children and Adolescents with ADHD and the Impact on Quality of Life. *J Adolesc Heal* (2010) 46:209–17. doi: 10.1016/j.jadohealth.2009.09.009
15. Leitner Y. The Co-Occurrence of Autism and Attention Deficit Hyperactivity Disorder in Children - What Do We Know? *Front Hum Neurosci* (2014) 8:268. doi: 10.3389/fnhum.2014.00268
16. Santosh PJ, Singh J. Drug treatment of autism spectrum disorder and its comorbidities in children and adolescents. *BJPsych Adv* (2016) 22:151–61. doi: 10.1192/apt.bp.115.014597
17. Antshel KM, Polacek C, McMahon M, Dygert K, Spenceley L, Dygert L, et al. Comorbid ADHD and Anxiety Affect Social Skills Group Intervention Treatment Efficacy in Children With Autism Spectrum Disorders. *J Dev Behav Pediatr* (2011) 32:439–46. doi: 10.1097/DBP.0b013e318222355d
18. Cooper M, Martin J, Langley K, Hamshere M, Thapar A. Autistic traits in children with ADHD index clinical and cognitive problems. *Eur Child Adolesc Psychiatry* (2014) 23:23–34. doi: 10.1007/s00787-013-0398-6
19. Murias M, Major S, Davlantis K, Franz L, Harris A, Rardin B, et al. Validation of eye-tracking measures of social attention as apotential biomarker for autism clinical trials. *Autism Res* (2018) 11:166–74. doi: 10.1002/aur.1894
20. Mikami AY, Miller M, Lerner MD. Social functioning in youth with attention-deficit/hyperactivity disorder and autism spectrum disorder: transdiagnostic commonalities and differences. *Clin Psychol Rev* (2019) 68:54–70. doi: 10.1016/j.cpr.2018.12.005
21. Sokolova E, Oerlemans AM, Rommelse NN, Groot P, Hartman CA, Glennon JC, et al. A causal and mediation analysis of the comorbidity between attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). *J Autism Dev Disord* (2017) 47:1595–604. doi: 10.1007/s10803-017-3083-7
22. Salley B, Colombo J. Conceptualizing Social Attention in Developmental Research. *Soc Dev* (2016) 25:687–703. doi: 10.1111/sode.12174
23. Boraston Z, Blakemore SJ. The application of eye-tracking technology in the study ofautism. *J Physiol* (2007) 581:893–8. doi: 10.1113/jphysiol.2007.133587
24. Karatekin C. Eye tracking studies of normative and atypicaldevelopment. *Dev Rev* (2007) 27:283–348. doi: 10.1016/j.dr.2007.06.006
25. Rommelse NNJ, Van der Stigchel S, Sergeant JA. A review on eye movement studies in childhood and adolescent psychiatry. *Brain Cognit* (2008) 68:391–414. doi: 10.1016/j.bandc.2008.08.025
26. Klein C, Seernani D, Ioannou C, Schulz-Zhecheva Y, Biscaldi M, Kavšek M. "Typical and Atypical Development of Eye Movements". In: Klein C, Ettinger U, editors. *Eye Movement Research: An Introduction to its Scientific Foundations and Applications*. Berlin: Springer Publishers (2020). p. 635–701. doi: 10.1007/978-3-030-20085-5_15
27. Falck-Ytter T, Bölte S, Gredebäck G. Eye tracking in early autism research. *J Neurodev Disord* (2013) 5:28. doi: 10.1186/1866-1955-5-28
28. Jones W, Carr K, Klin A. Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-old toddlers with autism spectrum disorder. *Arch Gen Psychiatry* (2008) 65:946–54. doi: 10.1001/archpsyc.65.8.946
29. Klin A, Jones W, Schultz R, Volkmar F, Cohen D. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Arch Gen Psychiatry* (2002) 59:809–16. doi: 10.1001/archpsyc.59.9.809
30. Hanley M, McPhillips M, Mulhern G, Riby DM. Spontaneous attention to faces in Asperger syndrome using ecologically valid static stimuli. *Autism* (2012) 17:754–61. doi: 10.1177/1362361312456746
31. Rice K, Moriuchi JM, Jones W, Klin A. Parsing Heterogeneity in Autism Spectrum Disorders: Visual Scanning of Dynamic Social Scenes in School-Aged Children. *J Am Acad Child Adolesc Psychiatry* (2013) 51:238–48. doi: 10.1016/j.jaac.2011.12.017.Parsing
32. Elison JT, Sasson NJ, Turner-Brown LM, Dichter GS, Bodfish JW. Age trends in visual exploration of social and nonsocial information in children with autism. *Res Autism Spectr Disord* (2012) 6:842–51. doi: 10.1016/j.rasd.2011.11.005
33. Van Der Geest JN, Kemner C, Verbaten MN, Van Engeland H. Gaze behavior of children with pervasive developmental disorder toward human faces: a fixation time study. *J Child Psychol Psychiatry* (2002) 43:669–78. doi: 10.1111/1469-7610.00055
34. Fletcher-Watson S, Leekam SR, Benson V, Frank MC, Findlay JM. Eye-movements reveal attention to social information in autism spectrum disorder. *Neuropsychologia* (2009) 47:248–57. doi: 10.1016/j.neuropsychologia.2008.07.016
35. Freeth M, Chapman P, Ropar D, Mitchell P. Do Gaze Cues in Complex Scenes Capture and Direct the Attention ofHigh Functioning Adolescents with ASD? *Evid Eye-tracking* (2009) 40:534–47. doi: 10.1007/s10803-009-0893-2
36. Frazier TW, Strauss M, Klingemier EW, Zetzer EE, Hardan AY, Eng C, et al. A Meta-Analysis of Gaze Differences to Social and Nonsocial Information Between Individuals With and Without Autism. *J Am Acad Child Adolesc Psychiatry* (2017) 56:546–55. doi: 10.1016/j.jaac.2017.05.005
37. Chita-Tegmark M. Attention Allocation in ASD: a Review and Meta-analysis of Eye-Tracking Studies. *Rev J Autism Dev Disord* (2016) 3:209–23. doi: 10.1007/s40489-016-0077-x
38. Karatekin C, Asarnow RF. Exploratory Eye Movements to Pictures in Childhood-Onset Schizophrenia and Attention-Deficit / Hyperactivity Disorder (ADHD). *J Abnorm Child Psychol* (1999) 27:35–49. doi: 10.1023/A:1022662323823
39. Serrano VJ, Owens JS, Hallowell B. Where Children With ADHD Direct Visual Attention During Emotion Knowledge Tasks: Relationships to

Accuracy, Response Time, and ADHD Symptoms. *J Atten Disord* (2015) 22:752–63. doi: 10.1177/1087054715593632
40. Muszkat M, De Mello CB, Muñoz POL, Lucci TK, David VF, Siqueira JO, et al. Face scanning in autism spectrum disorder and attention deficit/hyperactivity disorder: Human versus dog face scanning. *Front Psychiatry* (2015) 6:150. doi: 10.3389/fpsyt.2015.00150
41. Uekermann J, Kraemer M, Abdel-Hamid M, Schimmelmann BG, Hebebrand J, Daum I, et al. Social cognition in attention-deficit hyperactivity disorder (ADHD). *Neurosci Biobehav Rev* (2010) 34:734–43. doi: 10.1016/j.neubiorev.2009.10.009
42. Santosh P, Mijovic A. Social impairment in Hyperkinetic Disorder. *Eur Child Adolesc Psychiatry* (2004) 13:141–50. doi: 10.1007/s00787-004-0372-4
43. Baribeau DA, Doyle-Thomas KAR, Dupuis A, Iaboni A, Crosbie J, McGinn H, et al. Examining and comparing social perception abilities acrosschildhood-onset neurodevelopmental disorders. *J Am Acad Child Adolesc Psychiatry* (2015) 54:479–86. doi: 10.1016/j.jaac.2015.03.016
44. Tye C, Asherson P, Ashwood KL, Azadi B, Bolton P, McLoughlin G. Attention and inhibition in children with ASD, ADHD and co-morbid ASD + ADHD: an event-related potential study. *Psychol Med* (2014) 44:1101–16. doi: 10.1017/S0033291713001049
45. Oerlemans AM, Van Der Meer JMJ, Van Steijn DJ, De Ruiter SW, De Bruijn YGE, De Sonneville LMJ, et al. Recognition of facial emotion and affective prosody in children withASD (+ADHD) and their unaffected siblings. *Eur Child Adolesc Psychiatry* (2014) 23:257–71. doi: 10.1007/s00787-013-0446-2
46. Strimbu K, Tavel J. The maturometer - Instrumental test and redesign. *Curr Opin HIV AIDS* (2010) 5:463–6. doi: 10.1097/COH.0b013e32833ed177.What
47. Frye RE, Vassall S, Kaur G, Lewis C, Karim M, Rossignol D. Emerging biomarkers in autism spectrum disorder: a systematicreview. *Ann Transl Med* (2019) 7:792–792. doi: 10.21037/atm.2019.11.53
48. Rommelse NNJ, Franke B, Geurts HM, Hartman CA, Buitelaar JK. Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder. *Eur Child Adolesc Psychiatry* (2010) 19:281–95. doi: 10.1007/s00787-010-0092-x
49. Seernani D, Ioannou C, Damania K, Spindler K, Hill H, Foulsham T, et al. Studying global processing in autism andattention-deficit/hyperactivity disorder with gaze movements: The example of a copying task. *PLoS One* (2020) 15:e0224186. doi: 10.1371/journal.pone.0224186
50. Rühl D, Bölte S, Feineis-Matthews S, Poustka F. Diagnostische Beobachtungsskala für Autistische Störungen(ADOS). *Zeitschrift für Kinder- und Jugendpsychiatrie und Psychotherapie* (2004). 32:45–50.
51. Bölte S, Rühl D, Schmötzer G, Poustka F. *Diagnostisches interview für autismus - revidiert. German version of the autism diagnostic interview - revised (ADI-R)*. Bern: Huber (2005).
52. Falkmer T, Anderson K, Falkmer M, Horlin C. Diagnostic procedures in autism spectrum disorders: A systematic literature review. *Eur Child Adolesc Psychiatry* (2013) 22:329–40. doi: 10.1007/s00787-013-0375-0
53. Biscaldi M, Paschke-Müller M, Rauh R, Schaller UM. Evaluation des Freiburger TOMTASS. *Z für Psychiatr Psychol und Psychother* (2016) 64:269–75. doi: 10.1024/1661-4747/a000288
54. Paschke-Müller MS, Biscaldi M, Rauh R, Fleischhaker C, Schulz E. *TOMTASS - Theory-of-Mind-Training bei Autismusspektrumstörungen*. Springer Berlin Heidelberg: Berlin, Heidelberg (2017). doi: 10.1007/978-3-662-53216-4
55. Virues-Ortega J, Julio FM, Pastor-Barriuso R. The TEACCH program for children and adults with autism: Ameta-analysis of intervention studies. *Clin Psychol Rev* (2013) 33:940–53. doi: 10.1016/j.cpr.2013.07.005
56. Conners C. *Conners 3rd edition: Manual*. Canada Multi-Health Syst: Toronto, Ontario (2008).
57. Marshall P, Hoelzle J, Nikolas M. Diagnosing Attention-Deficit/Hyperactivity Disorder (ADHD) in young adults: a qualitative review of the utility of assessment measures and recommendations for improving the diagnostic process. *Clin Neuropsychol* (2019) 2:1–34. doi: 10.1080/13854046.2019.1696409
58. Achenbach T, Rescorla L. *Manual for the ASEBA school-age forms & profiles: Child behaviorchecklist for ages 6-18, teacher's report form, youth self-report*. Burlington, VT: University of Vermont (2001).
59. Raiker JS, Freeman AJ, Perez-Algorta G, Frazier TW, Findling RL, Youngstrom EA. Accuracy of Achenbach Scales in the Screening of Attention-Deficit/Hyperactivity Disorder in a Community Mental Health Clinic. *J Am Acad Child Adolesc Psychiatry* (2017) 56:401–9. doi: 10.1016/j.jaac.2017.02.007
60. Constantino JN, Davis SA, Todd RD, Schindler MK, Gross MM, Brophy SL, et al. Validation of a brief quantitative measure of autistic traits: Comparison of the social responsiveness scale with the Autism Diagnostic Interview-Revised. *J Autism Dev Disord* (2003) 33:427–33. doi: 10.1023/A:1025014929212
61. Döpfner M, Görtz-Dorten A, Lehmkuhl G, Breuer D, Goletz H. *Diagnostik-System für psychische Störungen nach ICD-10 und DSM-IV für Kinder und Jugendliche*. Bern: Huber (2008).
62. Klein C, Fischer B, Fischer B, Hartnegg K. Effects of methylphenidate on saccadic responses in patients with ADHD. *Exp Brain Res* (2002) 145:121–5. doi: 10.1007/s00221-002-1105-x
63. World Medical Association declaration of Helsinki. Ethical principles for medical research involving human subjects. *JAMA - J Am Med Assoc* (2013) 310:2191–4. doi: 10.1001/jama.2013.281053
64. Weiß R. *Grundintelligenztest Skala 2—Revision (CFT 20-R) [Culture Fair Intelligence Test 20-R—Scale 2]*. Göttingen: Hogrefe (2006).
65. Lang PJ, Bradley MM, Cuthbert BN. *International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual. Report No.: Technical Report A-6*. Gainesville, FL: University of Florida.
66. Holmqvist K, Nyström M, Andersson R, Dewhurst R, Jarodzka H, van de Weijer J. *Eye tracking: a comprehensive guide to methods and measures*. Oxford: Oxford University Press (2017).
67. SensoMotoric Instruments. BeGaze Manual version 3.1. *SensoMotoric Instruments*. Teltow (2012).
68. Grossman RB, Zane E, Mertens J, Mitchell T. Facetime vs. Screentime: Gaze Patterns to Live and Video Social Stimuli in Adolescents with ASD. *Sci Rep* (2019) 9:12643. doi: 10.1038/s41598-019-49039-7
69. Shi L, Zhou Y, Ou J, Gong J, Wang S, Cui X, et al. Different visual preference patterns in response to simple andcomplex dynamic social stimuli in preschool-aged children with autism spectrum disorders. *PLoS One* (2015) 10:e0122280. doi: 10.1371/journal.pone.0122280
70. Sumner E, Leonard HC, Hill EL. Comparing Attention to Socially-Relevant Stimuli in Autism SpectrumDisorder and Developmental Coordination Disorder. *J Abnorm Child Psychol* (2018) 46:1717–29. doi: 10.1007/s10802-017-0393-3
71. Bates D, Mächler M, Bolker BM, Walker SC. Fitting linear mixed-effects models using lme4.*J Stat Softw* (2015) 67:1–48. doi: 10.18637/jss.v067.i01
72. Boisgontier MP, Cheval B. The anova to mixed model transition. *Neurosci Biobehav Rev* (2016) 68:1004–5. doi: 10.1016/j.neubiorev.2016.05.034
73. Anagnostou E, Skarlatou V, Mergner T, Anastasopoulos D. Idiothetic signal processing and spatial orientation in patientswith unilateral hippocampal sclerosis. *J Neurophysiol* (2018) 120:1256–63. doi: 10.1152/jn.00016.2018
74. Waddington F, Hartman C, de Bruijn Y, Lappenschaar M, Oerlemans A, Buitelaar J, et al. Visual and auditory emotion recognition problems as familial cross-disorder phenomenon in ASD and ADHD. *Eur Neuropsychopharmacol* (2018) 28:994–1005. doi: 10.1016/j.euroneuro.2018.06.009
75. Sprenger L, Bühler E, Poustka L, Bach C, Heinzel-Gutenbrunner M, Kamp-Becker I, et al. Impact of ADHD symptoms on autism spectrum disorder symptomseverity. *Res Dev Disabil* (2013) 34:3545–52. doi: 10.1016/j.ridd.2013.07.028
76. Antshel KM, Russo N. Autism Spectrum Disorders and ADHD: Overlapping Phenomenology,Diagnostic Issues, and Treatment Considerations. *Curr Psychiatry Rep* (2019) 21:34. doi: 10.1007/s11920-019-1020-5
77. Chantiluke K, Christakou A, Murphy CM, Giampietro V, Daly EM, Ecker C, et al. Disorder-specific functional abnormalities during temporal discounting in youth with Attention Deficit Hyperactivity Disorder (ADHD), Autism and comorbid ADHD and Autism. *Psychiatry Res Neuroimaging* (2014) 223:113–20. doi: 10.1016/j.pscychresns.2014.04.006
78. Rommelse N, Buitelaar JK, Hartman CA. Structural brain imaging correlates of ASD and ADHD across the lifespan: a hypothesis-generating review on developmental ASD-ADHD subtypes. *J Neural Transm* (2017) 124:259–71. doi: 10.1007/s00702-016-1651-1
79. Hartman CA, Geurts HM, Franke B, Buitelaar JK, Rommelse NNJ. Changing ASD-ADHD symptom co-occurrence across the lifespan withadolescence as

crucial time window: Illustrating the need to go beyond childhood. *Neurosci Biobehav Rev* (2016) 71:529–41. doi: 10.1016/j.neubiorev.2016.09.003
80. Hellmer K, Nyström P. Infant acetylcholine, dopamine, and melatonin dysregulation: Neonatal biomarkers and causal factors for ASD and ADHD phenotypes. *Med Hypotheses* (2017) 100:64–6. doi: 10.1016/j.mehy.2017.01.015
81. Gillberg C, Fernell E. Autism Plus Versus Autism Pure. *J Autism DevDisord* (2014) 44:3274–6. doi: 10.1007/s10803-014-2163-1
82. Hengartner MP, Lehmann SN. Why Psychiatric Research Must Abandon Traditional Diagnostic Classification and Adopt a Fully Dimensional Scope: Two Solutions to a Persistent Problem. *Front Psychiatry* (2017) 8:101. doi: 10.3389/fpsyt.2017.00101
83. Judd CM, Westfall J, Kenny DA. Treating stimuli as a random factor in social psychology: A new andcomprehensive solution to a pervasive but largely ignored problem. *J Pers Soc Psychol* (2012) 103:54–69. doi: 10.1037/a0028347
84. van Rijn S, Urbanus E, Swaab H. Eyetracking measures of social attention in young children: How gazepatterns translate to real-life social behaviors. *Soc Dev* (2019) 28:564–80. doi: 10.1111/sode.12350

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Mapping the Network of Social Cognition Domains in Children With Autism Spectrum Disorder Through Graph Analysis

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Children with autism spectrum disorder (ASD) are characterized by difficulties in social cognition (SC) domains. The aim of this study is to build an SC network to explore associations among interacting elements within this cognitive construct. We used a graph analysis to explain how individual SC domains relate to each other and how these relations may differ between ASD and typically developing (TD) groups. Seventy-six children with ASD and 81 TD children, matched for verbal mental age, were subjected to three SC measures. Our results showed that TD children exhibited an SC network characterized by a single domain (i.e., social cognition), while children with ASD demonstrated communicating node communities where social information processing measured by the Social Information Processing Interview (SIPI) represents a key point in understanding network differences between groups.

Keywords: autism spectrum disorder, graph analysis, network, social cognition, verbal mental age

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INTRODUCTION

Social cognition (SC) is an adaptive human function (1, 2) that includes cognitive domains encompassing the capacity to process the social world (such as emotional processing, attention, social stimuli encoding, etc.). It emerges in early childhood through the development of "theory of mind" [ToM; (3)], that is, the capacity to understand mental and emotional states of other people (2). The development of SC competencies follows a certain sequential order in typically developing (TD) children (3, 4). Children with autism spectrum disorder (ASD) display the same progressive order, but this appears to be delayed in terms of age at attainment (3, 5). In conformance with this view, recent literature (3, 6) has suggested the ASD profile is best described in terms of a delay in the development of these social abilities, as opposed to a total lack of SC competencies. This view has important implications, bringing into focus the need for early rehabilitation programs geared toward improving social competencies, attenuating social deficits in children with autism, and reducing the child's isolation. In fact, prevalence of ASD in the general population is estimated worldwide to be around 1% both from screening and register-based studies (7). We know that SC domains do not operate in isolation, yet it remains undefined how difficulty in this complex social construct influences interactions among different social domains. The interrelationship among SC domains is crucial to developing social behaviors that are adequate to their surrounding context and to maintaining social relationships. According to Ibrahim et al. (8), one method of exploring associations among interacting elements within a complex system

as SC involves their separation into networks that can be characterized and quantified through graphical theoretical analysis. The graph analysis explains how individual variables such as SC outcomes relate to each other, how these relations may differ between groups, and how information may be exchanged. The current study applies graph theory to social behavioral data in children with ASD in order to better understand which social domains are important in an interacting network compared to TD children.

In constructing the network, we consider that SC is a complex structure that could involve many domains, in this case, nodes that—according to Happé and Frith (9)—can be understood as a complex network diagram that includes distinct components. The main SC component that appears to be compromised in ASD concerns ToM. The ToM ability required a good capacity to understand emotions, and it can affect social information processing. TD children begin to consolidate ToM ability at the age of 4–5 years (3, 9). Around the age of 6 years, this ability starts to become more elaborate and allow the development of prosocial behavior. These abilities must communicate effectively with each other to allow their proper development. In individuals with ASD, delayed development of SC abilities could compromise the construction of effective networks with consequent impairment of all their social skills.

Our study aims to investigate a simplified model of Happé and Frith's (9) theoretical framework, based on observed data, in order to graphically represent their idea of SC network and relations among components. Moreover, graphical analysis allows the devising and testing of connections between components with associated path properties (8).

In order to obtain a more simplified network that could lead to a better understanding of interactions among elements, we focused our approach on underlying differences between ASD and TD, taking into consideration that ToM is the main core of ASD symptoms (10). In this study, we used three SC tests: (1) a simplified version of the Eyes Task [ET; (11)]; (2) the Comic Strip Task [CST; (12)], a well-known test assessing different components of ToM, i.e., intentions, emotions, and beliefs; and (3) the Social Information Processing Interview [SIPI; (13, 14)] to evaluate the capacity to process social information and display adequate social behavior. While the CST is based on seeing social scenes, the ET is focused on the understanding of others by their gaze. Even if two tests evaluated the same construct, they used a different kind of information and analysis for their contribution within the network; they could show whether they effectively work in the same way or if the kind of information is elaborated in a different manner. We decided to include the results of the SIPI in the network because it is based on Crick and Dodge's (15) model and can summarize many nodes of Happè and Frith's (9) map. In fact, the processes described by Crick and Dodge (15) are related to many dimensions, i.e., social schemas and rules, self and other evaluations, evaluation of goal and arousal regulation, that are used to determine SIPI scores.

A topographic view of the interaction of these domains in ASD could lead to a greater understanding of the associations between social deficits and ASD symptomatology, providing new opportunities for diagnosis and treatment. This study is the first to use graph theory measures to investigate the SC network in children with ASD. For this reason, we investigated the global SC network in children with ASD using TD children as a control.

METHODS

Participants

The participant group in our study includes 76 children with ASD selected by the Reference Regional Center for Autism, Abruzzo Region Health System, L'Aquila, Italy [mean ± standard deviation chronological age (CA) = 9.21 ± 2.65 years; 70 males and six females] and 81 TD children recruited from a local primary school in the same region (mean ± SD CA = 6.39 ± 1.69 years; 70 males and 11 females) for a total of 157 children. Groups were matched by verbal mental age (VMA) through the Test for Reception of Grammar-Version 2 (TROG-2; 14; TD-VMA = 7.11 ± 2.09; ASD-VMA = 7.43 ± 2.72). Inclusion criteria for the ASD population were: (1) a diagnosis of ASD made by the Autism Diagnostic Observation Schedule-Second Version [ADOS-2; (16)] and (2) no other neurological disorders. Required for inclusion in the TD group was the absence of any neurological or psychological disorder. Demographic data of samples are reported in **Table 1**.

Criterion for Group Matching

In our study, the children with autism had a CA higher than TD children because we chose to match the two groups on VMA assessed with the TROG-2 (17). The matching leads to chronologically older ASD [$t_{(155)} = -7.89$, $p < 0.01$] and to homogeneous groups in relation to their VMA [$t_{(155)} = -0.82$, $p = 0.41$].

According to recent literature (3), children with ASD showed a delay in developing SC abilities based on CA, whereas VMA appears to be a good predictor of ToM abilities altogether (18) and in children with autism (3). Indeed, Pino et al. (3) showed that ToM scores on the VMA in the ASD group had a

TABLE 1 | Demographic data of the sample and clinical information concerning the ASD group.

	TD group ($n = 81$) Mean (SD)	ASD group ($n = 76$) Mean (SD)	t df(1, 155)	p
DEMOGRAPHIC DATA				
Chronological age	6.39 (1.69)	9.21 (2.65)	−7.89	<0.01
Verbal mental age	7.11 (2.09)	7.43 (2.72)	−0.82	0.41
CLINICAL INFORMATION				
ADOS-social communication and social interaction	–	9.48 (2.93)	–	–
ADOS-repetitive and stereotyped behaviors	–	1.29 (1.2)	–	–
ADOS total scores	–	10.78 (3.11)	–	–

ADOS, Autism Diagnostic Observation Schedule; ADS, autism spectrum disorder; TD, typically developing.

significant relationship between this variable and mental states (both positive and negative), as measured with the ET and the intentions component of the CST. In addition, Hobson (19) showed that children with ASD succeeded on ToM tasks as could be expected from their mental age; thus, it can be argued that ToM tests require a specific cognitive ability, which could correspond to VMA.

Social Cognition Measures

Eyes Task-Simplified (11)

This measure contains 56 black-and-white photos of children's eye region, portraying either mental states or primary emotions. The expressions included as positive primary emotions (PPE-ET) were happy or surprised, sad and angry were used for negative primary emotions (NPE-ET), while excited and thinking represented positive mental state (PMS-ET), and worried and shy were used for negative mental states (NMS-ET)—for a total of four emotional states and four mental states. Each stimulus involved one image (children's eye region), one target word on the left and the other with a target word on the right edge of the slide. Participants were asked to indicate which word best described the picture presented (e.g., "Look at this child—Is this child happy or angry?"). Testing lasted ∼15 min based on the randomized presentation of the items. Accuracy was measured on a 0–7 scale based on the participant's selection of one of two choices in seven comparisons per target emotion/mental state [for example: 1. happy vs. surprised; 2. happy vs. sad; 3. happy vs. angry; 4. happy vs. excited; 5. happy vs. thinking; 6. happy vs. worried; 7. happy vs. shy; for details, including an example of an image of the test, see (11)].

Comic Strip Task (20)

The CST is a recent 21-item measure developed to assess three aspects of ToM: beliefs (B-CST), intentions (I-CST), and emotions (E-CST). Each subscale includes five items, each comprising a five-picture comic strip illustrating everyday social scenarios involving interpersonal interactions familiar to young children, for example, a birthday party or play at the park. In addition, it contains a control subscale (two items for each subcomponent of ToM) comprising non-social scenarios, albeit in settings similar to the other comic strips. According to the procedure proposed by Sivaratnam et al. (12), prior to the administration of the CST, six images depicting basic emotions (happy, sad, angry, frightened, surprised, and confused) were presented to ensure that the child was able to recognize basic emotions at the level required by the task. Specifically, the child was required to name at least four out of six images correctly to proceed with the ToM test. The CST subscales (Intentions–Beliefs–Emotions) were administered in the same order in both groups. For each item, children are shown three pictures that tell a social story, after which they are presented with two pictures containing alternative endings to the story and asked to select the one they think best completes the story. One option indicates a lack of understanding of others' mental states and is scored 0; the other indicates the presence of such understanding and is scored 1. For example, as could be seen in Sivaratnam et al. (12), item 5, "Recognition surprise," from the Emotions subscale, in the first three figures is represented the protagonist involved in a surprise birthday party, where he is given gifts; then the child must choose whether: (1) the protagonist will be angry and he will run away or (2) the protagonist will be happy and he will celebrate with his friends. Each ToM subscale has a maximum score of 5, with a total test score of 15, with higher scores indicating superior ToM ability [for details, including an example of an image of the test, see (12)].

Social Information Processing Interview (13, 14)

The SIPI is an interview based on a storybook easel depicting a series of vignettes in which a protagonist is either rejected by two other peers or provoked by another peer. Each type of vignette is combined with each type of peer intent to generate four stories: (1) a non-hostile peer entry rejection story, (2) an ambiguous peer entry rejection story, (3) an accidental provocation story, and (4) an ambiguous provocation story. According to Ziv et al. (14), the scores correspond to four of the five mental steps of social information processing proposed by Crick and Dodge's (15) model: (1) Encoding, (2) Interpretation of cues, (3) Response construction, and (4) Response evaluation.

An example of an SIPI story is the following: Michael is watching the other children playing. Michael walks up to the other children and asks them: "Can I play with you?" The children say: "Sorry. The teacher said only two can play in the block area" [for details, see (14)]. The encoding component evaluates the level of detail that the child recalls across the four stories. Thus, the examiner asks the child: "Tell me what happened in the story, from the beginning to the end." A score of 0 is given to a child who recalls no correct details for each story, and a score of 1 is given to a child who correctly recalls all the details in each story, and then, a sum of the scores is calculated, so scores could range from 0 (no correct coding in four stories) to 4 (all correct coding in four stories). The interpretation component evaluates the hostile attribution to others' behavior (the question is "Do you think the other children who didn't let Michael play are mean or not mean?"). The range for this score is 0–1 for each story, with higher scores representing higher levels of hostile attribution bias. The score in the interpretation component is inversely encoded compared with the other SIPI components; that is, a higher score indicates a major tendency to consider the behavior of other children as hostile. Regarding the response construction component, as reported by Ziv and Sorongon [(13), p. 7] in their paper, the score is derived from the child's responses to the open-ended item, "What would you say or do if this happened to you? The answers are used to create three, mutually exclusive flag variables (coded 0, 1) for each story: competent flag, aggressive flag, and avoidant flag. For example, if the child's response is coded as "competent," then he or she is given a "1" for the competent flag, a "0" for the aggressive flag, and a "0" for the avoidant flag. The final response construction score is then calculated by subtracting the aggressive and avoidant scores from the competent score. The original range of this score is −4 (only avoidant or aggressive responses) to 4 (only competent responses). However, to avoid negative scale scores, the scale was modified such that the presented possible range for this score is

0 (only avoidant or aggressive responses) to 8 (only competent responses)" [(12), p. 7; (21)].

For the response evaluation step, the scores are made from a combination of 36 Response Evaluation questions (4 stories × 3 competent/aggressive/avoidant presented responses × 3 questions per presented response).

An example of a question for the response evaluation of an SIPI story is "Michael could kick apart the blocks and say to the other children, 'if I can't play, then you can't play either,' (1) 'Is this a good thing or a bad thing for Michael to say?,' (2) 'If you do that, do you think the other children would like you?,' and (3) 'Do you think the other children would let you play if you do that?"' If a child evaluates as positive an aggressive behavior, the score is 0. For example, child could respond that Michael said a good thing and that other children would let Michael play with them after his aggressive behavior, in this case, the given score is 0 (21).

Statistical Analysis

Comparison Between Groups

The *T*-test was used to test the differences between the groups (ASD, TD) regarding demographic parameters and the measures for the components of the ET (positive primary emotions, negative primary emotions, positive mental states, and negative mental states) and for response evaluation of the SIPI subscale. The Mann–Whitney test was used to test differences between ASD and TD regarding the CST subscale (emotions, beliefs, and intention) and for the SIPI subscale of encoding, interpretation, and response construction). Bonferroni's correction has been made ($\alpha = 0.05$).

Network Analysis

Graphs give a better way of dealing with abstract concepts like relationships and interactions; they provide an intuitive way of thinking these concepts (22, 23). Ibrahim et al. (8) propose that graph theory concepts are useful in the analysis of complex networks. By using graph theory, we can visualize and analyze relationships between SC domains. In graph theory, variables are termed "nodes," which are connected *via* "edges." Edges can be weighted: an edge with a higher weight is more strongly connected with a node than an edge with a lower weight. Moreover, edges can be directed, meaning that the edge between nodes A and B is different from the edge between nodes B and A. In our study, the SC measures constitute the nodes of the network, with the partial correlations between them as weighted and undirected edges. In graph analysis, there are several properties that can be inferred from a network. Some of the canonical centrality indices are represented by strength, betweenness, and closeness (24).

Network Analysis: Construction of the Network

Two graphs were constructed, one for the ASD group and one for the TD group, while nodes were represented by psychological domains that represent SC components (SC measures previously explained). Networks were estimated according to the Gaussian graphical model (25), in which edges are interpreted as partial correlation coefficients. We estimated the Gaussian graphical model using graphical least absolute shrinkage and selection operator (LASSO) (26), which estimates the (inverse) partial covariance matrix of a set of variables, penalizing small covariances by setting small covariances to zero. The optimal strength of the penalty term was estimated using the BIC (27). As some variables are ordinals, polychoric, polyserial, and Pearson correlations were used; moreover, only significant correlations were maintained.

After obtaining one network for each group, we evaluated several canonical proprieties (24) such as *strength*, *betweenness*, and *closeness* of each node.

Strength is a weighted measure of degree between a node and any other node connected to it, given by the formula:

$$k_i = \sum_{j \in N} w_{ij}$$

where k represents the strength, and w represents the weight between the nodes i and j; in this case, w_{ij} was set as the correlation coefficient. This value represents a local connectivity of the node indicating how its connection with adjacent nodes is strong.

Betweenness represents how many times a node serves as a bridge between two other nodes; it is given by the formula:

$$b_i = \sum_{j<k} \frac{p_{jk}(i)}{p_{jk}}$$

where p_{jk} represents the number of shortest paths between nodes j and k, and $p_{jk}(i)$ is the number of shortest paths between j and k that pass through i. The higher this value is, the greater number of shortest paths passing through a node, indicating how that node is important in the average path between two nodes.

Closeness is the average length of the shortest path between a node and any other node; it can be considered as a measure of how long it will take to spread information to other nodes.

$$L_i^{-1} = \frac{n-1}{\sum_{j \in N j \neq i} d_{ij}}$$

where d is the shortest path length between nodes i and j, and n is the number of nodes. The more central a node is, the lower its total distance is from all other nodes. It can be considered a measure of how information from a node reaches other nodes. Closeness differentiates with strength by the fact that it indicates how it relates to all other nodes in the network, not just the adjacent ones.

Betweenness, closeness, and strength represent centrality measures of the network that reveal the relative importance of nodes in the network, whether high centrality suggests to strongly affect other nodes due to their strong connection (28). Thus, centrality measures represent the degree in which a node influences other nodes in the network. However, even if they share this common feature, betweenness, closeness, and strength represent different forms of influence. We indicate that strength represents local connectivity as it measures its influence on the adjacent nodes. Betweenness indicates how that node is used

to connect other nodes in the network, and finally, closeness represents how far a node is from all other nodes. This difference relies on how they are computed, whether betweenness is a measure that indicates how many times a node is located within the shortest path between two other nodes, strength is computed by examining how many connections are attached to each node, and closeness indicates how far a node is from all other nodes (29).

Network Analysis: Group Comparisons

In order to evaluate differences between ASD and TD networks, every network was non-parametric bootstrapped 1,000 times, obtaining for each bootstrap measures of strength, betweenness, and closeness of each node. Whereupon statistically significant differences were evaluated by the z test and adjusted by Bonferroni's correction ($\alpha = 0.05$).

We used the *bootnet* package (30) from R (31) to perform the calculations.

Community Detection

Subsets of nodes that are densely connected to each other but less with others are referred to as communities (32). Modularity is a measure that indicates the quality of a particular division of the network (33). Modularity values range from −1 to 1, where a value of 0 indicates that the division is not better than random, while 1 theoretically indicates strong community structures; in practice, values for such networks fall between 0.3 and 0.7 (33).

There are different algorithms to detect graph communities; in our research, we used that proposed by Blondel et al. (34), which assigns a different community to each node of the network, then a node is moved to the community of its neighbors to achieve the highest positive contribution to modularity. This procedure is then repeated for all nodes until it obtains no further improvement. We used this method, as it has shown that it performs well in terms of accuracy (35). Communities were detected for each network using the *igraph* package (36).

RESULTS

Comparison Between Groups

The *T*-test and Mann–Whitney test showed that children with ASD obtained lower scores in all components of the SIPI: interpretation ($U = 2{,}083.50$; $p < 0.001$), response evaluation [$t_{(155)} = -3.01$, $p = 0.03$], and response construction ($U = 767.50$; $p < 0.001$) compared to the TD children, with the exception of encoding ($U = 2{,}414.50$; $p = 0.06$). Regarding CST, the ASD group had lower scores in the emotions ($U = 2{,}030.50$; $p < 0.001$) and beliefs ($U = 1{,}367.50$; $p < 0.001$) components; there was no difference between the groups in the intentions component ($U = 2{,}782.50$; $p = 0.26$).

Finally, regarding ET, children with ASD showed difficulties in the negative mental states component [$t_{(155)} = -2.97$; $p = 0.03$]; however, there were no significant differences in the positive mental states component [$t_{(155)} = -1.50$; $p = 0.13$], the primary emotions component with negative valence [$t_{(155)} = -0.18$; $p = 0.85$], or the positive valence [$t_{(155)} = 1.33$; $p = 0.18$] compared to the TD group.

Visualization of the Networks

Networks are represented in **Figure 1**, nodes represent SC components, lines between nodes represent correlations between measures, while widths of lines represent the strength of a correlation. Red and green lines represent positive (green) and negative (red) correlations. The node's distance represents closeness.

Graph Measures

Graph analysis results are reported in **Table 2** (which also contains the z tests performed). However, it was possible to evaluate significant differences between closeness and strength measures. Statistical analysis shows significant differences between the two networks regarding all the closeness and strength measures, where the graph of the TD sample reveals global greater values in each node for closeness and strength. Nodes in ASD's network showed greater betweenness values compared to nodes in TD's network except for NPE-ET and E-SIPI, which instead showed lower values compared to TD's nodes.

Community Detection

Communities detected are presented in **Figure 2**. Modularity estimated for the TD communities was low ($Q = 0.07$), indicating that the community's divisions were not better than random, suggesting that there are no communities in the network. In community detection for the ASD network though, we estimated a value of $Q = 0.39$, indicating that the network could be considered as divided into communities. ASD communities in the network are (a) I-SIPI, PMS-ET, NMS-ET, PPE-ET, NPE-ET, and RE-SIPI; (b) E-CST, B-CST, I-CST, and RC-SIPI; and (c) E-SIPI.

DISCUSSION

In the present study, we employed graph theory to map the structure of the SC network in children with ASD compared to TD children. Specifically, the aim was to build a network of SC domains/competencies to explore associations among interacting elements within this complex cognitive construct. Thus, we modeled the SC measures of children with ASD and TD as a complex system of interactions and further applied graph analysis to define important features therein for both groups.

Our results show that nodes in the ASD network show an overall higher betweenness compared to those in the TD network (except for the E-SIPI node and NPE-ET node, which showed a higher betweenness for the TD group). Nodes in the TD network showed an overall higher closeness and strength compared to the ASD network.

Community detection in the ASD network found three communities of nodes: the first community was composed of a single component, i.e., the E-SIPI node (Encoding) that is a community *per se*. This result suggests that people with ASD can encode social information, but this social information would not be utilized by the entire network. This is confirmed by the finding that this node in ASD showed lower scores in all the centrality measures compared to TD.

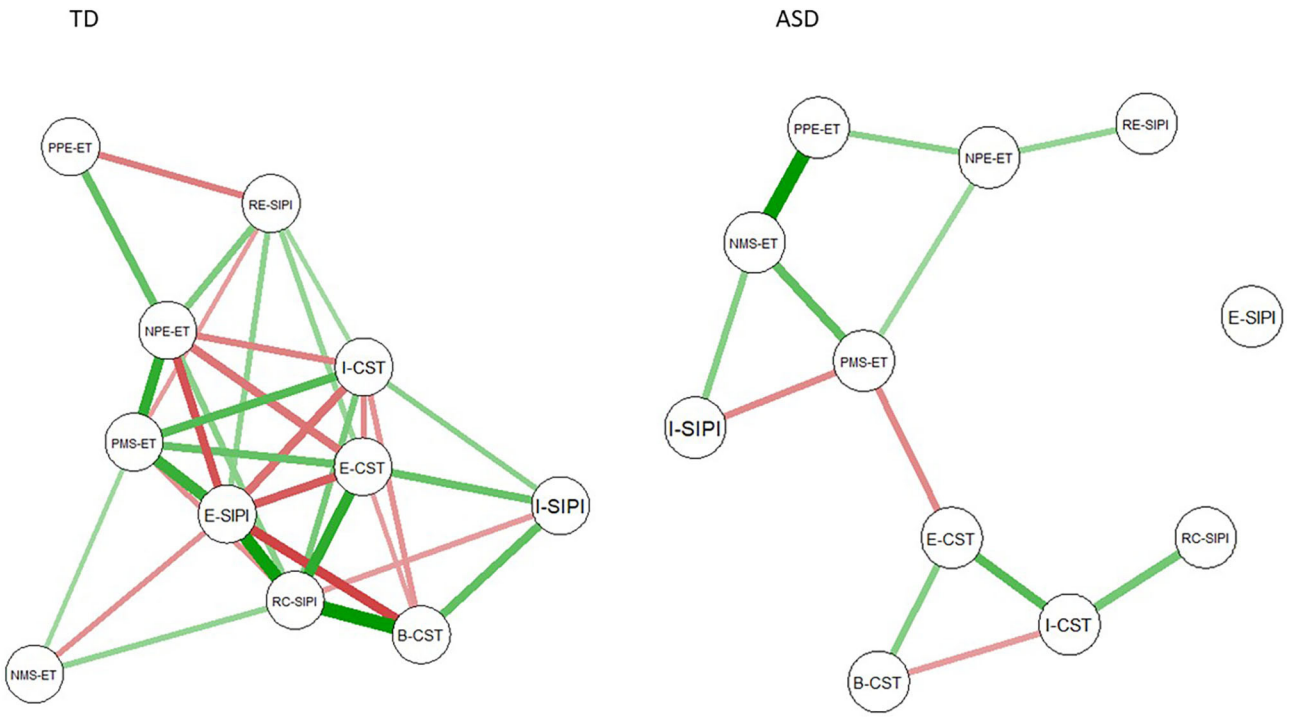

FIGURE 1 | Graphs of typically developing (TD) and autism spectrum disorder (ASD) populations. Each node represents a social cognition (SC) domain. Strength is represented by the link's thickness, and closeness by the nodes' distance. Green and red links represent positive and negative correlation coefficients, respectively. B-CST, Belief-Comic Strip Task; E-CST, Emotions-Comic Strip Task; I-CST, Intentions-Comic Strip Task; NPE-ET, Negative primary emotions-Eyes Task; PPE-ET, Positive primary emotions-Eyes Task; NMS-ET, Negative mental states-Eyes Task; PMS-ET, Positive mental states-Eyes Task; E-SIPI, Encoding-Social information processing interview; I-SIPI, Interpretation-Social information processing interview; RC-SIPI, Response construction-Social information processing interview; RE-SIPI, Response evaluation-Social information processing interview.

The second community was composed of the CST subdomains, namely, the E-CST node (Emotions), the B-CST node (Beliefs), and the I-CST (Intentions), to which is added an SIPI component: the RC-SIPI node (response construction), indicating that the construction of the social response is strictly related to the understanding of intentions, beliefs, and emotions. In the response construction, the child is asked: "to put himself/herself in the shoes" of the main character of the story and try to explain how he/she would act in the same situation (6). This ability is densely connected with the construction of a response in a social scenario.

The third community obtained was composed of domains as the ET such as NMS-ET (Negative Mental States), PMS-ET (Positive Mental States), PPE-ET (Positive Primary Emotions), NPE-ET (Negative Primary Emotions), and nodes representing domains evaluated by the SIPI names I-SIPI (Interpretation) and RE-SIPI (Response Evaluation). This community could indicate that the interpretation of the scene, as well as the assessment of whether the response given by the other is right or wrong, is closely related to the interpretation of information also of a visual type (interpretation of mental states based on visual cues). Specifically, the RE-SIPI component is crucial for processing social cues and subsequently social behavior, whereas I-SIPI component evaluates the tendency to attribute hostile intentions to other people in positive social situations and *vice versa*.

Furthermore, while the ET and CST are grouped in the same community, the components of the SIPI are divided among three communities, suggesting that the information required to complete this particular task must make more transitions between SC skills.

Indeed, *betweenness* represents the number of paths that pass through a node, higher betweenness in ASD, and the existence of communities could indicate that, to reach a determined node, information passes through and is influenced by other nodes before reaching it. Betweenness is a measure based on the concept of shortest path, which is the path between node A and node B with the minimum intermediary nodes. To clarify the results based on this concept, we can refer to the ASD network in **Figure 1**. If, for example, we take the PMS-ET and E-CST nodes, we can see that they form a "bridge" between two agglomerations of nodes, so regardless of the length of the shortest path, any path between the two agglomerates (which we have found are communities) will have to go through those nodes, resulting in a high betweenness for both. The same reasoning can be made for the other nodes of the two communities. E-SIPI node shows low betweenness since it is not connected in the network. The TD network has a more "balanced" situation, even though we have a betweenness that is not as wide as on most ASD nodes. Moreover, this kind of spread of information characterizes the communication between communities of nodes in ASD's

TABLE 2 | Significant differences between groups (ASD and TD) for social cognition measures and canonical properties of graph analysis (betweenness, closeness, and strength) for each node (i.e., social cognition components).

Social cognition measures	Measures score mean (SD)/ median [1st quartile−3rd quartile]		Betweenness mean (SD)		z	Closeness mean (SD)		z	Strength mean (SD)		z
	ASD	TD	ASD	TD		ASD	TD		ASD	TD	
COMIC STRIP TASK											
Belief (B-CST)	1 [1–2]*	4 [2–4]*	4.33 (7.27)	2.28 (3.96)	−7.78*	0.01 (0.01)	0.04 (0.02)	27.95*	1.12 (0.72)	4.10 (2.80)	32.52*
Emotions (E-CST)	4 [4–4.75]*	5 [4–5]*	10.55 (10.55)	4.57 (6.03	−15.55*	0.01 (0.01)	0.04 (0.02)	28.48*	1.56 (0.78)	4.46 (2.71)	32.42*
Intentions (I-CST)	4 [3–5]	4 [3–5]	9.75 (10.90)	2.23 (4.48)	−20.19*	0.01 (0.01)	0.04 (0.02)	27.95*	1.26 (0.48)	4.16 (2.78)	32.43*
EYES TASK											
Negative primary emotions (NPE-ET)	12.11 (2.06)	12.16 (1.27)	4.88 (8.32)	8.43 (8.96)	31.26*	0.01 (0.01)	0.04 (0.02)	31.26*	0.98 (0.54)	4.27 (2.67)	38.08*
Positive primary emotions (PPE-ET)	11.52 (2.39)	11.08 (1.65)	9.77 (10.17	1.37 (3.84)	19.60*	0.01 (0.01)	0.03 (0.02)	19.60*	1.49 (0.66)	3.05 (3.01)	15.87*
Negative mental states (NMS-ET)	10.6 (2.56)*	11.64 (1.71)*	13.29 (10.28)	0.70 (2.50)	18.64*	0.01 (0.01)	0.03 (0.02)	18.64*	1.70 (0.67)	3.00 (3.13)	12.81*
Positive mental states (PMS-ET)	10.26 (2.40)	10.76 (1.69)	12.57 (12.65)	3.27 (5.07)	28.31*	0.01 (0.01)	0.04 (0.02)	28.31*	1.44 (0.63)	4.30 (2.69)	32.58*
SOCIAL INFORMATION PROCESSING INTERVIEW											
Encoding (E-SIPI)	4 [3–4]	4 [3–4]	3.99 (7.34)	6.94 (7.42)	8.94*	0.01 (0.01)	0.04 (0.02)	35.70*	0.86 (0.57)	4.84 (2.55)	48.03*
Interpretation (I-SIPI)	3 [2–3]*	3 [3–4]*	7.18 (9.65)	2.39 (4.89)	−13.99*	0.01 (0.01)	0.04 (0.02)	23.10*	1.36 (0.69)	3.45 (2.92)	22.10*
Response construction (RC-SIPI)	2 [1–3]*	4 [3–5]*	9.93 (10.71)	6.68 (7.12)	−7.98*	0.01 (0.01)	0.04 (0.02)	31.87*	1.38 (0.69)	4.83 (2.49)	42.14*
Response evaluation (RE-SIPI)	19.71 (2.15)*	29.73 (1.09)*	5.16 (7.92)	1.45 (3.48)	−13.57*	0.01 (0.01)	0.04 (0.02)	24.91*	0.95 (0.60)	3.43 (3.02)	25.43*

*ADS, autism spectrum disorder; TD, typically developing. *p < 0.05.*

network. The characteristic spread of information highlighted by our analysis could suggest that, within the SC network in ASD, a compensatory mechanism intervenes. However, this compensatory mechanism seems to become less efficient when one is facing a more complex social scenario, as the one presented in the SIPI (characterized by the simulation of a peer-to-peer social situation).

In a recent study, it was found that processing and understanding of complex social information measured through the SIPI could well-differentiate between children with ASD and TD rather than CST and ET (37). According to Pino et al. (3), intentions and emotion comprehension are lower-level competencies; these skills are learned earlier and are necessary for the construction of more complex abilities (6).

Our findings confirm that SIPI represents a complex task for ASD, thus the altered segregation and the altered use of information concerning this task may be related to such difficulties. SIPI is a complex task that is more similar to social context compared to the other tasks. Since it is based on the model of Crick and Dodge (15), planning a correct social response involves the use of several capacities (e.g., multiple evaluations, regulations, schemas, or rules). As seen in **Figure 1**, we found that the Encoding node is separated from the rest of the network, thus it presents lower centrality measures (strength, betweenness, and closeness) compared to TD. When a child is involved in a social situation, through encoding, he or she can give an interpretation of the social scene thus construct and make a response (15). Cooper et al. (38) have found a dissociation between encoding and recollection in people with ASD; our results support an impairment in the encoding process, which characterized people with ASD, which would consequently also involve other social skills. Specifically, our results suggest that individual with ASD seems to use other sources of information during the interpretation or the construction of a social response rather than a proper mechanism of encoding.

From community detection, we found that the TD network presents a network without communities, i.e., there are no subsets of nodes that are densely connected with each other; moreover, they present higher values of closeness (which indicates how information directly reaches other nodes) and strength (which represents how locally the connection is strong with adjacent

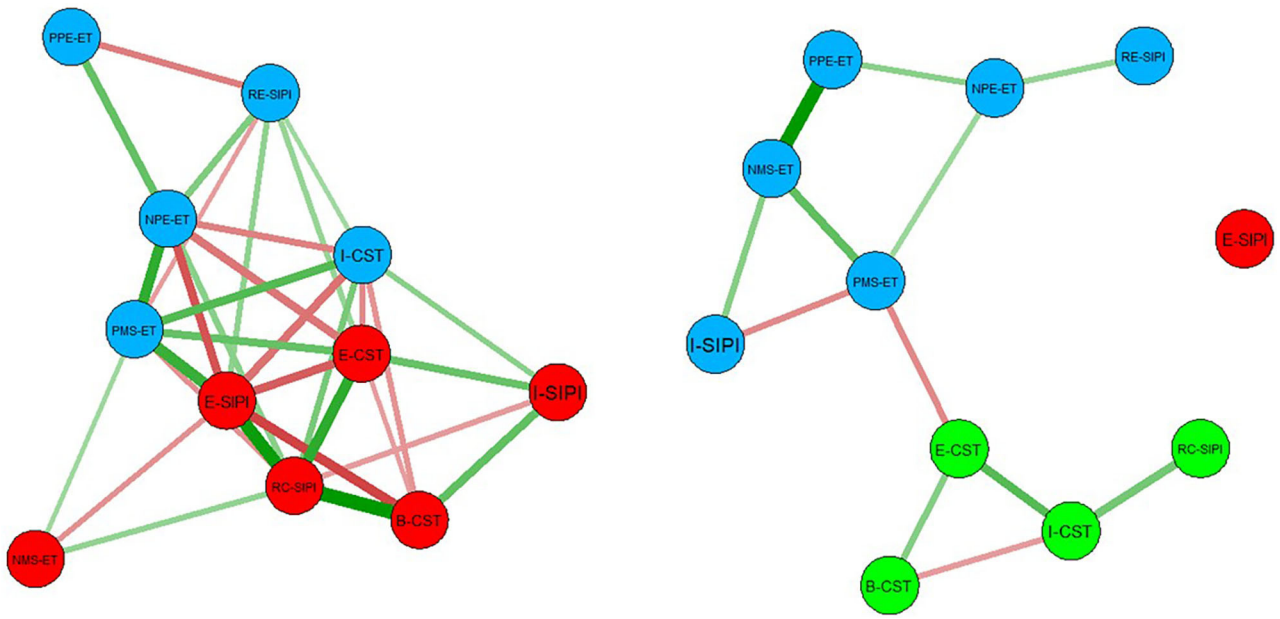

FIGURE 2 | Subset of nodes found by community detection, nodes colored with the same color represent communities found for each network.

nodes). Taken together, these results suggest that, in the TD network, communication between nodes is direct and has major weight compared to the ASD nodes communication. Moreover, as the TD network does not present multiple communities, the SC skills measured by the assessed tasks, only for TD, would compose a single domain, i.e., SC.

Even if these results must be interpreted with caution, it is important to know that the ASD network and the TD network fit the theoretical SC network proposed by Happé and Frith (9); further, our approach highlighted properties of the network that differentiate ASD and TD SC.

As recent literature has found that ASD is characterized by a delay of social abilities (3, 6) and VMA appears to be a good predictor of ToM ability (3, 18), our ASD sample was determined to have the same mental age as the TD group.

Our research confirms the results of Pino et al. (3) and Hobson (19), as matching group by VMA has yielded the same results in components of SC measured by test scores; specifically, they do not show significant differences in Intentions, as measured by the CST; in Primary Emotions with negative and positive valence, as measured by the ET; and Positive mental states. On the contrary, the two groups differ in negative mental state perception. The role of emotional valence in ASD is still being debated. Several studies suggest that the processing of negative emotions is most difficult for individuals with ASD (39–41). Ashwin et al. (42) consider the difficulty of processing negative emotions in ASD to be linked to an atypical function and structure of the amygdala. In their study, individuals with ASD were less accurate on the emotion recognition task compared to controls, but only for the negative basic emotions. According to Mazza et al. (40), emotional contagion for negative emotions of other people (like sadness, distress, suffering, anger) is important for adaptive social behavior. The lack of sharing experience when other people have negative emotions leads to a failure of appropriate empathic behavior in ASD people. In addition, the two groups showed differences in understanding emotions and beliefs, but not in the Intention component of the CST. We suggest that is consistent with the suggestion that the ability to understand others' beliefs and emotions is more complex with respect to the ability to understand the intentions of other people (3, 9). The latter ability occurs earlier in development as it is already present, to a certain extent, in TD infants (9). Thus, it is possible that in children with ASD, this ability becomes available later, and at the age of about 6 or 7 years, they gain the ability to understand the intentions of other people (3).

SC comprises various functions such as emotional processing, imitation, pretend play, ToM, empathy, and so on (9), but in this study, we consider only a part of this complex construct, and this can represent a limitation of our research. In the literature, at least part of the interest in ToM abilities is associated with the idea that people with ASD suffer from "mind-blindness" (3, 43). Social difficulty compromises interpersonal relationships and leads to social isolation in individuals with ASD. For this reason, it is important to study the SC network in the ASD group to create their SC profile and thereby understand how relations among its domains/components may affect their social behavior.

Limitations

It is important to know that our research presents some considerable limitations. It must be pointed out that results must be interpreted with caution as our analysis describes connectivity between nodes/domains but did not give information with regard to how information is processed by nodes or the direction of the information flow that follows.

In fact, our results do not express how a node elaborates information in the network (e.g., filtering, selecting, select salient feature, etc.) that literature and future research could elaborate, although it is important to highlight that this approach clarifies important features of the network's connections. Another important limitation was that our samples were composed mostly of males. Moreover, our network is a simplified version of the Happé and Frith (9) SC network; thus, implementing other nodes in the model could lead to a better understanding of connections between SC domains.

Future Directions

Future research could investigate specific contributions that SC domains provide in the network, deepening our understanding of under what processes social information passes between one domain and another. According to Vagnetti et al. (44), future research should be directed toward understanding how node processes effectively contribute to the network (e.g., by integrating or controlling information) and how edges change over time. Indeed, these structures could be time-dependent, especially during early development, and it would be interesting to understand when the structure of SC becomes fixed. In addition, it would also be interesting to investigate how intervention in ASD could change the network, e.g., connections and/or their weight, and it would be interesting to know if a variant version of functioning could mitigate social difficulties associated with ASD. It would be further interesting to consider a longitudinal study that would explore if and how the SC network structure becomes time-dependent.

We support the idea that a rehabilitation intervention could try to work on the strength of the edges to improve the network connections.

Our results showed that ASD domains of the SC network were isolated compared to TD, which were connected. The TD network reflects the theoretical SC network model proposed by Happé and Frith (9), where components are connected to each other.

Network indices comparison between the two groups shows a different communication role and statistical weight of the SC network nodes. These differences deserve a better understanding because they could provide an explanation of social functioning difficulties in ASD as well as their social isolation.

CONCLUSION

In conclusion, our research has found a connected SC network in children with ASD and TD, although important differences emerged in nodal communication—a phenomenon possibly related to the SC deficits presented by ASD.

While the TD SC network is characterized by a single domain, we found that ASD is characterized by node communities, thus higher betweenness for ASD nodes reflects the communication between communities, while higher strength and closeness for the TD highlight important contributions of each node in the network. SIPI represents a key point in understanding differences between groups. Our findings suggest that, for ASD, social information encoding performs a reduced contribution in the network; moreover, some types of information (measured by CST and ET) seem more relevant depending on the process involved (Response construction or Interpretation and Response evaluation).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ASL L'AQUILA—PROTOCOL NUMBER 186061/17. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

INFORMED CONSENT

Informed consent was obtained from parents and oral assent from children in order to collect demographic and score variables.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

REFERENCES

1. Pinkham AE, Hopfinger JB, Pelphrey KA, Piven J, Penn DL. Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. *Schizophr Res*. (2008) 99:164–75. doi: 10.1016/j.schres.2007.10.024
2. Mazza M, Lucci G, Pacitti F, Pino MC, Mariano M, Casacchia M, et al. Could schizophrenic subjects improve their social cognition abilities only with observation and imitation of social situations? *Neuropsychol Rehabil*. (2010) 20:675–703. doi: 10.1080/09602011.2010.486284
3. Pino MC, Mazza M, Mariano M, Peretti S, Dimitriou D, Masedu F, et al. Simple mindreading abilities predict complex theory of mind: developmental delay in autism spectrum disorders. *J Autism Dev Disord*. (2017) 47:2743–56. doi: 10.1007/s10803-017-3194-1
4. Wellman HM, Liu D. Scaling of theory-of-mind tasks. *Child Dev*. (2004) 75:523–41. doi: 10.1111/j.1467-8624.2004.00691.x
5. Broekhof E, Ketelaar L, Stockmann L, van Zijp A, Bos MG, Rieffe C. The understanding of intentions, desires and beliefs in young children with autism spectrum disorder. *J Autism*

Dev Disord. (2015) 45:2035–45. doi: 10.1007/s10803-015-2363-3
6. Mazza M, Mariano M, Peretti S, Masedu F, Pino MC, Valenti M. The role of theory of mind on social information processing in children with autism spectrum disorders: a mediation analysis. *J Autism Dev Disord*. (2017) 47:1369–79. doi: 10.1007/s10803-017-3069-5
7. Valenti M, Vagnetti R, Masedu F, Pino MC, Rossi A, Scattoni ML, et al. Register-based cumulative prevalence of Autism Spectrum Disorders during childhood and adolescence in Central Italy. *Epidemiol Biostat Public Health*. (2019) 16. Available online at: https://ebph.it/article/view/13226
8. Ibrahim GM, Morgan BR, Vogan VM, Leung RC, Anagnostou E, Taylor MJ. Mapping the network of neuropsychological impairment in children with autism spectrum disorder: a graph theoretical analysis. *J Autism Dev Disord*. (2016) 46:3770–7. doi: 10.1007/s10803-016-2929-8
9. Happé F, Frith U. Annual research review: towards a developmental neuroscience of atypical social cognition. *J Child Psychol Psychiatry*. (2014) 55:553–77. doi: 10.1111/jcpp.12162
10. Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a "theory of mind"? *Cognition*. (1985) 21:37–46. doi: 10.1016/0010-0277(85)90022-8
11. Franco F, Itakura S, Pomorska K, Abramowski A, Nikaido K, Dimitriou D. Can children with autism read emotions from the eyes? The eyes test revisited. *Res Dev Disabil*. (2014) 35:1015–26. doi: 10.1016/j.ridd.2014.01.037
12. Sivaratnam CS, Cornish K, Gray KM, Howlin P, Rinehart NJ. Brief report: assessment of the social-emotional profile in children with autism spectrum disorders using a novel comic strip task. *J Autism Dev Disord*. (2012) 42:2505–12. doi: 10.1007/s10803-012-1498-8
13. Ziv Y, Sorongon A. Social information processing in preschool children: relations to sociodemographic risk and problem behavior. *J Exp Child Psychol*. (2011) 109:412–29. doi: 10.1016/j.jecp.2011.02.009
14. Ziv Y, Hadad BS, Khateeb Y. Social information processing in preschool children diagnosed with autism spectrum disorder. *J Autism Dev Disord*. (2014) 44:846–59. doi: 10.1007/s10803-013-1935-3
15. Crick NR, Dodge KA. A review and reformulation of social information-processing mechanisms in children's social adjustment. *Psychol Bull*. (1994) 115:74. doi: 10.1037/0033-2909.115.1.74
16. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop S. *Autism Diagnostic Observation Schedule–Second edition (ADOS-2)*. Los Angeles, CA: Western Psychological Services (2012).
17. Bishop DVM. *TROG-2 Test for Reception of Grammar-2*. London: Pearson (2003).
18. Happé FG. An advanced test of theory of mind: Understanding of story characters' thoughts and feelings by able autistic, mentally handicapped, and normal children and adults. *J. Autism Dev. Disord*. (1994) 24:129–54. doi: 10.1007/BF02172093
19. Hobson RP. Early childhood autism and the question of egocentrism. *J Autism Dev Disord*. (1984) 14:85–104. doi: 10.1007/BF02408558
20. Cornish K, Rinehart N, Gray K, Howlin P. *Comic Strip Task*. Melbourne, VIC: Monash University Developmental Neuroscience and Genetic Disorders Laboratory and Monash University Centre for Developmental Psychiatry and Psychology (2010).
21. Pino MC, Mariano M, Peretti S, D'Amico S, Masedu F, Valenti M, et al. When do children with autism develop adequate social behaviour? Cross-sectional analysis of developmental trajectories. *Eur J Dev Psychol*. (2018) 17:71–87. doi: 10.1080/17405629.2018.1537876
22. Kellermann TS, Bonilha L, Lin KK, Hermann BP. Mapping the landscape of cognitive development in children with epilepsy. *Cortex*. (2015) 66:1–8. doi: 10.1016/j.cortex.2015.02.001
23. Shirinivas SG, Vetrivel S, Elango NM. Applications of graph theory in computer science an overview. *Int J Eng Sci Technol*. (2010) 2:4610–21.
24. Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*. (2010) 52:1059–69. doi: 10.1016/j.neuroimage.2009.10.003
25. Lauritzen SL. *Graphical Models*. Oxford: Clarendon Press (1996).
26. Friedman JH, Hastie T, Tibshirani R. Sparse inverse covariance estimation with the graphical lasso. *Biostatistics*. (2008) 9:432–41. doi: 10.1093/biostatistics/kxm045
27. Schwarz G. Estimating the dimension of a model. *Ann Stat*. (1978) 6:461–4. doi: 10.1214/aos/1176344136
28. Borsboom D, Cramer A, Schmittmann VD, Epskamp S, Waldorp LJ. The small world of psychopathology. *PloS ONE*. (2011) 6:e27407. doi: 10.1371/journal.pone.0027407
29. Opsahl T, Agneessens F, Skvoretz J. Node centrality in weighted networks: generalizing degree and shortest paths. *Soc Netw*. (2010) 32:245–51. doi: 10.1016/j.socnet.2010.03.006
30. Epskamp S, Borsboom D, Fried EI. Estimating psychological networks and their accuracy: a tutorial paper. *Behav Res Methods*. (2018) 50:195–212. doi: 10.3758/s13428-017-0862-1
31. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing (2017). Available online at: https://www.R-project.org/
32. Boccaletti S, Latora V, Moreno Y, Chavez M, Hwang D.-U. Complex networks: structure and dynamics. *Phys Rep*. (2006) 424:175–308. doi: 10.1016/j.physrep.2005.10.009
33. Newman ME, Girvan M. Finding and evaluating community structure in networks. *Phys Rev*. (2004) 69:026113. doi: 10.1103/PhysRevE.69.026113
34. Blondel VD, Guillaume JL, Lambiotte R, Lefebvre E. Fast unfolding of communities in large networks. *J Stat Mech Theor E*. (2008) 10:P10008. doi: 10.1088/1742-5468/2008/10/P10008
35. Yang Z, Algesheimer R, Tessone CJ. A comparative analysis of community detection algorithms on artificial networks. *Sci Rep*. (2016) 6:30750. doi: 10.1038/srep30750
36. Csardi G, Nepusz T. The igraph software package for complex network research. *Int J Complex Syst*. (2006) 1695:1–9.
37. Pino MC, Masedu F, Vagnetti R, Attanasio M, Di Giovanni C, Valenti M, et al. Validity of social cognition measures in the clinical services for autism spectrum disorder. *Front Psychol*. (2020) 11:4. doi: 10.3389/fpsyg.2020.00004
38. Cooper RA, Plaisted-Grant KC, Baron-Cohen S, Simons JS. Eye movements reveal a dissociation between memory encoding and retrieval in adults with autism. *Cognition*. (2017) 159:127–38. doi: 10.1016/j.cognition.2016.11.013
39. Howard MA, Cowell PE, Boucher J, Broks P, Mayes A, Farrant A, et al. Convergent neuroanatomical and behavioural evidence of an amygdala Hypothes is of autism. *Neuroreport*. (2000) 11:2931–5. doi: 10.1097/00001756-200009110-00020
40. Mazza, M, Pino, MC, Mariano M, Tempesta D, Ferrara M, De Berardis D, et al. Affective and cognitive empathy in adolescents with autism spectrum disorder. *Front Hum Neurosci*. (2014) 8:791. doi: 10.3389/fnhum.2014.00791
41. Humphreys T, Polick AS, Howk LL, Thaxton JR, Ivancic AP. An evaluation of repeating the discriminative stimulus when using least-to-most Prompting to teach intraverbal behavior to children with autism. *J Appl Behav Anal*. (2013) 46:534–8. doi: 10.1002/jaba.43
42. Ashwin C, Chapman E, Colle L, Baron-Cohen S. Impaired recognition of negative basic emotions in autism: a test of the amygdala theory. *Soc Neurosci*. (2006) 1:349–63. doi: 10.1080/17470910601040772
43. Baron-Cohen S, Bowen DC, Holt RJ, Allison C, Auyeung B, Lombardo MV, et al. The "reading the mind in the eyes" test: complete absence of typical sex difference in∼ 400 men and women with autism. *PLoS ONE*. (2015) 10:e0136521. doi: 10.1371/journal.pone.0136521
44. Vagnetti R, Pino MC, Masedu F, Peretti S, Le Donne I, Rossi R, et al. Exploring the social cognition network in young adults with autism spectrum disorder using graph analysis. *Brain Behav*. 10:e01524. doi: 10.1002/brb3.1524

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Predictors of Change in Play-Based Communication and Behavior Intervention for High-Risk ASD: The Role of Mother-Child Dyadic Synchrony

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Background: Interindividual variability is important in the evolution of adaptative profiles of children with ASD having benefited from an early intervention make up for deficits in communication, language and social interactions. Therefore, this paper aimed to determine the nature of factors influencing the efficacy variability of a particular intervention technique i.e., "Play-based communication and behavior intervention" (PCBI).

Methods: The participants comprised 70 13–30-month-old toddlers with ASD enrolled in PCBI for 12 weeks. The Autism Treatment Evaluation Checklist (ATEC) was used to evaluate the efficacy of PCBI. Video recordings of 5 min of free-play before and after PCBI were used to examine behaviors of mothers and children and parent-child dyadic synchrony. Hierarchical multiple regression analyses and machine learning algorithms were performed to explore the effect of these potential predictors (mothers' factors, children's factors and videotaped mother-child interaction) of intervention efficacy.

Results: The hierarchical regression analysis and the machine learning algorithms indicated that parenting stress, level of completion of training at home and mother-child dyadic synchrony were crucial factors in predicting and monitoring the efficacy of PCBI.

Conclusions: In summary, the findings suggest that PCBI could be particularly beneficial to children with ASD who show a good performance in the mother-child dyadic synchrony evaluation. A better dyadic mother-child synchrony could enhance the PCBI efficacy through adapted emotional and behavioral responses of the mother and the child and has a beneficial influence on the child's psychological development.

Keywords: autism, intervention efficacy, predictors, mother-child dyadic synchrony, parenting stress, play-based communication and behavior intervention

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by difficulties in social communication and restricted/repetitive behavior or interests (1). Evidence of brain development and key stages of neural plasticity in infancy lends strong support to the importance of very early interventions (2). The first 2 years after birth is a critical period marked by the rapid development of cognition and language (3, 4). Children later diagnosed with ASD may present some deficits in these abilities (5), and the gap between these children and typically developing peers widens at 3–5 years of age (6). Studies have shown that early intervention is efficacious in modifying cognitive and social-communicative outcomes and potentially improving developmental trajectories in toddlers with ASD (4, 7). However, the majority of established interventions have been suggested for use with preschoolers and school-aged children, with very few interventions suitable for children under 2 years old (5).

The play-based communication and behavior intervention model (PCBI) is a manualized evidence-based intervention established by the Nanjing Brain Hospital affiliated with Nanjing Medical University. PCBI is a parent education play-based applied behavior analysis (ABA) model that fosters parental behavior management and parents' communication ability with their children. The characteristic of PCBI is to train parents or other caregivers to effectively master the key intervention techniques applicable to children with ASD, while the feature of ABA is to train ASD children directly. Our team's previous work confirmed that PCBI can significantly improve the development level of children with ASD and reduce ASD symptoms [effect size = 0.88, (8)]. In our previous study, 74 toddlers were randomly assigned to receive PCBI or ABA intervention from highly experienced and credentialed therapists. After 12 weeks of intervention, both groups had a significant increase in the developmental quotient (language behavior ability and personal-social behavior ability) and a decrease in the subscale scores (social contact, perception and behavior) of the Autism Treatment Evaluation Checklist (ATEC) (8).

Empirical support for early intervention has emphasized the importance of this treatment. However, outcomes vary widely due to the influence of child and family characteristics. For example, there is evidence that parents of children with ASD may experience high levels of parenting stress (9, 10), which can have a negative influence on the effectiveness of early interventions and can also be influenced by early interventions (11–13). In addition, parent-child dyadic synchrony, which refers to the co-constructed states of parent-child-dyad interaction characterized by harmonious and mutually responsive emotional exchanges and behavior, is a key component of parent-child interaction and can have positive implications for child development (14, 15). The conceptualizations of parent-child dyadic synchrony encompass an array of interactive behaviors, such as responsiveness, reciprocity and shared emotion evaluated during face-to-face interactions (16). The development of children's emotional regulation occurs through repeated emotional experiences with parents, and shared emotion, as an aspect of dyadic synchrony that lays the foundation for the development of subsequent self-regulation, may differ between children with ASD and typically developing children (17–19). Although parent-child dyadic synchrony plays an important role in children's development, studies have only recently focused on it and regarded it as an important indicator of parent-child relationship quality (20), and few researchers have suggested that parent-child synchrony should be considered a factor in the efficacy of interventions for children with ASD.

Because early intervention requires considerable time and funding, it is crucial to select the target group that is most likely to derive maximal benefit from the intervention. Thus, the primary purpose of this study was to extend our previous work to investigate all the potential predictors of the efficacy of PCBI, including maternal variables (parenting stress and self-efficacy level), child variables (developmental level, ASD symptoms and intervention efficacy change) and mother-child interaction factors (mother and child behaviors during interaction).

METHODS

Participants

A total of 70 children (55 boys and 15 girls) ranging in age between 13 and 30 months and their mothers (between the ages of 25 and 42 years) who received PCBI at the Children's Mental Health Research Center of the Nanjing Brain Hospital affiliated with Nanjing Medical University from October 2017 to February 2019 were enrolled in this study. Because this is a preliminary study aiming to examine the clinical reliability/validity of the protocol, all the participants received PCBI without a control group.

The participants were 70 children with ASD or at high risk of ASD (i.e., who displayed symptoms of autism but were under 24 months of age) between the ages of 8 and 30 months old at intake. Inclusion criteria included: met criteria for ASD in a clinical assessment based on both the Autism Diagnostic Observational Schedule (ADOS) and the Autism Diagnostic Interview (ADI-R) at intake, or met risk criteria for ASD at intake (under 24 months of age) on two screeners and met criteria for ASD later at the age of 24 months. Participants with any genetic syndromes or neurological conditions; premature children and those with complications after birth; a history of craniocerebral trauma; chronic medical conditions; or visual, hearing or motor impairments were not included in this study. This study was approved by the Nanjing Brain Hospital affiliated with the Nanjing Medical University Ethics Committee, and informed consent was obtained from the parents or legal guardians of the participants.

Screening Tools and ASD Diagnosis

All the children were screened at enrollment and at the end of intervention by the M-CHAT and the Autism Behavior Checklist [ABC, (21)]. The M-CHAT is a 23-item parent questionnaire developed to screen children ranging in age from 16 to 30 months old (22). The reliability of M-CHAT is 94% in the Chinese population (23). The ABC is a well-established parent report

checklist used to screen and diagnose autism. The higher the subscale and total ABC score are, the more significant the ASD symptoms are. Participant who did not reach the evaluation age of the screening tools when entering the group will be evaluated at the end of the intervention. The reliability and validity of ABC scale in the Chinese population are nearly 100% (24).

The ADOS is a semistructured, standardized diagnostic observational instrument that provides the diagnosis of ASD based on the DSM-IV algorithm. The ADOS is designed to assess autism symptoms in communicative behaviors, social reciprocity, repetitive behaviors and play (25). All the children received ADOS module 1 and ADI-R (26) to inform the ASD diagnosis, and the assessment was conducted at age 2 for participants under 2 years of age at the end of the intervention.

Intervention

The caregivers received two and a half days of parent training before participating in PCBI to gain some understanding of the importance of early intervention and parental involvement. The PCBI consisted of 12 parent-child sessions, with one 1-h session per week. The staff-child ratio was 1:1. In sessions 1-11, the caregivers were coached in each of eleven intervention techniques from PCBI, addressing one new skill each week and improving those taught previously. The 11 skills were as follows: (a) behavioral training, focusing on positive behavior; (b) behavioral training, dealing with problem behavior; (c) behavioral training, developing training plans; (d) behavioral training, executing training plans; (e) communication training, facilitating joint attention; (f) communication training, responding to joint attention; (g) communication training, promoting speech development; (h) communication training, creating a language environment; (i) communication training, teaching simple game skills; (j) communication training, teaching functional play skills; and (k) communication training, teaching pretend play skills. Session 12 was devoted to maintenance after treatment and discussion of the follow-up training plan. The 60-min period of a session was roughly divided into three sections, each of which was 20 min long. In the first 20 min, the mother demonstrated the skills from the last lesson and the training at home, and the therapist provided feedback and suggestions. In the second 20 min, the therapist introduced some theoretical knowledge to the mother and used a demo game to interact with the child. During the last 20 min, the mother interacted with the child based on the interactive skills just observed, and the therapist provided timely guidance and feedback.

To ensure the effectiveness of the training, mothers were required to complete a feedback form about the lesson, continue training at home every day and submit a 10-min video recording about the training every week. The therapist rated the video clips and provided timely guidance and feedback to the parents. Only the mother with a score over 80 were considered to have mastered the lesson.

Child Measures

Developmental Measures

The Gesell Developmental Schedules (27) is a standardized early developmental quotient (DQ) assessment that provides an overall index of ability on the following five subscales: adaptive behavior, gross motor behavior, language behavior, fine motor behavior and personal-social behavior. All the children were administered the Gesell at baseline and after intervention.

Efficacy Assessment

The Autism Treatment Evaluation Checklist [ATEC, (28)] was used to measure the efficacy of PCBI. It has been successfully used to assess the effectiveness of treatments and progress after intervention in ASD (29–31). The ATEC is designed to be self-administered by parents and elicits parent concerns in four domains: speech/language/communication (14 items, scores range from 0 to 28), health/physical behavior (25 items, scores range from 0 to 75), sensory/cognitive awareness (18 items, scores range from 0 to 36), and sociability (20 items, scores range from 0 to 40) (32). The total scores of these four subscales range from 0 to 180, and a higher subscale and total score indicate greater impairment in children. The reliability of ATEC is 75% and the validity is 92% in the Chinese population (33).

Parent Measures

The Parenting Stress Index Short Form (PSI-SF) is a Likert-based 5-point self-report questionnaire with 36 items used to evaluate parenting stress (34). The PSI-SF consists of three subscales, parenting distress (PD), difficult child (DC) and parent-child dysfunctional interaction (PCDI), as well as a total stress scale. It has been used in previous studies with children with ASD and shows good reliability and validity (35, 36).

The General Self-Efficacy Scale (GSES) is widely implemented worldwide and was developed to measure an individual's self-efficacy level (37). Self-efficacy is defined as an individual's belief about his or her ability to control events related to the individual to meet a specified level of performance. A Chinese version (38) that consisted of 10 questions was used in this study.

Acceptability and Fidelity

Mother-perceived acceptability is especially important for interventions when the mother is the primary interventionist. Satisfaction questionnaires were used to assess parental satisfaction with the intervention after each session. The therapist monitored treatment fidelity by rating mother's performance in correctly implementing techniques and adhering to intervention procedures during each session via a Likert-based 10-point rating system. We also evaluated the completion level of training at home via videotaped observation ratings.

Mother-Child Interaction

Mother-child interaction was assessed and videotaped with the mother and child sitting on a floor mat in a laboratory room (3×3 m^2) at baseline and after intervention. The free play-based setting included a standard set of toys, such as cause-and-effect toys, books, dolls, balls, toy cars, toys for imaginative play (e.g., blocks), and a small towel for peekaboo games. At the beginning of the experiment, the child was given 3 min to independently explore three toys selected by the mother. Then, the mother was asked to engage in play with all the toys if the child wished as

they normally would for the next 10 min (see **Figure 1**). Mother-child interaction was video recorded for later coding by a desktop computer, and four cameras were fixed to the wall. Because the toddlers varied widely in the way they explored the toys independently and the interaction in the last 5 min was relatively more stable, coding focused on the last 5 min of toddlers' free play with their mothers.

Interaction Coding

Videotapes of the last 5 min of the mother-child interaction were rated on a 5-s interval basis using the Observer XT 12.0 behavioral coding software. The coding was performed by two independent coders. Interrater reliability was tested by coding 20% of the video recordings independently using Cohen's kappa interrater agreement coefficient. Cohen's kappa averaged 0.80 for mother and child behaviors. The coding schemes were designed with reference to the work of Guo et al. (18).

The coders rated mother and child behavior using 1- to 3-point rating scales, including positive engagement, negative engagement, disengagement, child-object engagement, and mother-child dyadic synchrony. *Mother positive engagement* refers to mothers expressing positive or neutral affect, vocalizations and behavior to interact with toddlers, such as playing an active imaginative game with a full smile on the face. *Mother negative engagement* refers to mothers expressing angry, hostile, irritable, or negative vocalizations to children as well as intruding on children's exploration. *Mother disengagement* refers to mothers expressing boredom or disinterest and avoiding interaction with their child. *Child positive engagement* refers to toddlers maintaining free play with their mothers by showing positive or neutral affect, vocalizations and positive body posture. *Child negative engagement* refers to toddlers expressing impatience, anger, distressed vocalizations and negative body posture to protest against their mothers, such as crying and pushing their mothers away. *Child disengagement* refers to toddlers withdrawing from a joint activity by expressing sadness or anxiety. *Child-object engagement* refers to toddlers focusing on exploring toys independently and without interacting with their mothers. *Mother-child dyadic synchrony* means that both mothers and children are in a positive state of engagement at the same time.

Statistical Analysis

Data analyses were performed using SPSS 23.0. We evaluated changes in the mothers' variables, including the PSI-SF and GSES scores as well as the acceptability and fidelity of PCBI between baseline (T1) and postintervention (T2). The mother-child interaction variables and children's variables such as developmental level, ASD symptoms and intervention efficacy change were also assessed. Paired *t*-tests was used for data that obey normal distribution and non-parametric test was used for variables did not obey normal distribution. Next, hierarchical multiple regression analyses were performed to explore the effect of these potential predictors of intervention efficacy. All the variables were divided into two categories (children's and mothers' factors, mother-child interaction factors) to examine the main predictors in each category.

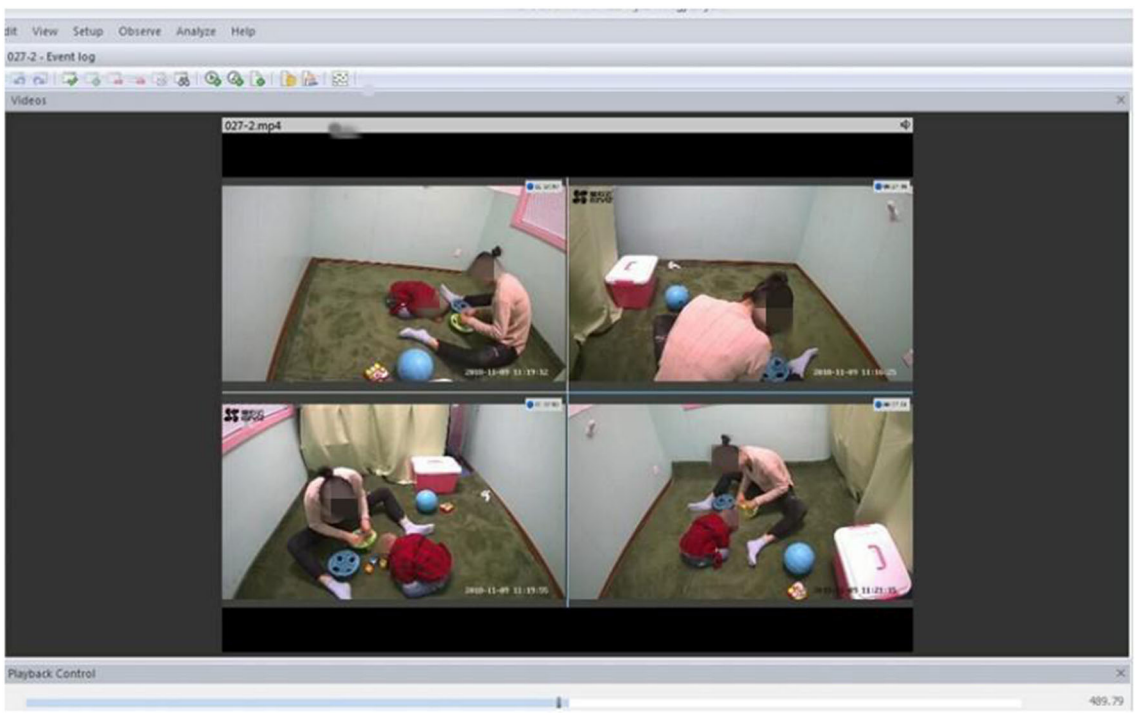


FIGURE 1 | This figure provides an illustration of free play.

We also used machine learning algorithms to verify the factors that can predict the efficacy of intervention. LASSO regression, support vector machine (SVM), ridge regression (RR) and random forest (RF) algorithms were applied to develop regression modes in this study. Machine learning techniques were completed using Python (Python 3.6.5) and MATLAB's Statistics (MATLAB R2018a). We considered all the variables of mothers and children and the mother-child interaction as features, including the age of the mother and child; the subscale and total score on the ABC, Gesell, PSI-SF, and GSES; and both mothers' and children's behaviors during the videotaped mother-child interactions. A 5-fold cross-validation method was used for internal validation to ensure an unbiased estimate of the classifier performance. It consisted of dividing the entire group of 70 children randomly into 5 subsets of equal size; then, 4-folds were used as the training dataset and the remaining fold as the testing dataset. Then, all the features were sorted according to the weight, and the top five features were listed for each regression model. Root mean square error (RMSE) and R^2 were used to describe and estimate the performance of the regression models. RMSE represents the differences between predicted and observed values, and R^2 measures how well the model fits the predicted values; the better the model is, the closer the R^2 is to 1. RMSE and R^2 are defined via the following formulas:

$$RMSE = \sqrt{\frac{\sum_{i=1}^{N}(Y_i - X_i)^2}{N}},$$

$$R^2 = 1 - \frac{SS_{\text{res}}}{SS_{tot}} = 1 - \frac{\sum_i (X_i - Y)^2}{\sum_i (X_i - \overline{X})^2}$$

RESULTS

Child Outcomes

The child outcome variables at baseline (T1) and postintervention (T2) are shown in **Figure 2**. Toddlers made statistically significant improvements in the Gesell subscales, including change in adaptive behavior DQ ($t = 3.01$, $p = 0.004$), language behavior DQ ($t = 5.16$, $p < 0.001$), fine motor behavior DQ ($t = 2.23$, $p = 0.029$) and personal-social behavior DQ ($t = 2.61$, $p = 0.011$), but they did not exhibit a significant change in Gesell gross motor behavior DQ before and after intervention ($t = 0.01$, $p = 0.994$). The subscale and total ABC scores ($z = 6.20$, $p < 0.001$) significantly decreased from intake to T2. In addition, the ATEC indicated that PCBI was effective, and the score decreased in this period of intervention ($t = 9.05$, df = 69, $p < 0.001$, Cohen's $d = 0.74$).

Parent Outcomes

Figure 3 presents the means and standard deviations for mother outcomes at T1 and T2. Paired t-tests clearly revealed that during PCBI, parenting stress decreased in the total level of PSI ($z = 2.86$, $p = 0.004$) as well as on the mother-child dysfunctional interaction ($z = 3.43$, $p = 0.001$) subscale. However, no significant change was observed for the mother's self-efficacy level at preintervention and postintervention ($z = 0.99$, $p = 0.318$).

Mother-Child Interaction Outcomes

Table 1 presents the change in mother-child interaction coding data for mothers and children. During PCBI, the rate of mothers' positive engagement ($z = 2.59$, $p = 0.010$) significantly increased, and mothers' disengagement ($z = 3.24$, $p = 0.001$) decreased. The rate of child positive engagement ($z = 5.52$, $p < 0.001$) also showed a statistically significant increase, while the degree of child-object engagement ($z = 4.38$, $p < 0.001$) was reduced. In addition, mother-child dyadic synchrony was significantly improved after intervention ($z = 5.44$, $p < 0.001$).

Summary of Hierarchical Regression Analysis for Variables Predicting the Intervention Effect (Change in ATEC Score)

As shown in **Table 2**, hierarchical multiple regression analyses of the children's and mothers' factors revealed that the completion level and change in the PSI score contributed significantly to the intervention effect (change in ATEC score). The completion level explained ∼70% of the change in the ATEC score, with a change in the PSI score making a marginally unique contribution to the change in the ATEC score after controlling for the completion level.

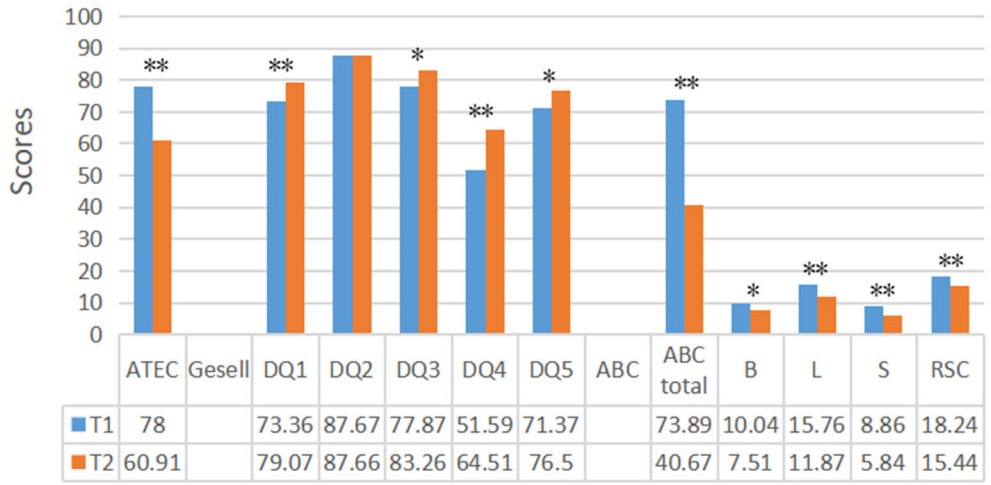
The regression on mother-child interaction variables indicated that change in child positive engagement and change in mother-child dyadic synchrony contributed significantly to the change in the ATEC score (**Table 3**). Change in child positive engagement explained ∼30% of the change in the ATEC score, with change in mother-child dyadic synchrony making a significant contribution to the model.

Performance of the Regression Models

Table 4 shows the importance rankings of the top 5 variables for different algorithms for predicting the efficacy of PCBI. The best performance was found for the SVM model ($R^2 = 0.75$, RMSE = 0.59), and the worst performance was found for the RR model ($R^2 = 0.53$, RMSE = 0.70). Based on R^2 and RMSE, the performance of different models can be ranked from strongest to weakest as follows: SVM > RF > LASSO > RR. Therefore, the SVM was selected as the best regression model for this study. As shown in **Table 4**, different machine-learning algorithms produced similar but different rank orderings because each method fit a different type of regression model. Mothers' factors, especially the completion level and mothers' stress (the subscale and total score of PSI) at baseline, seemed to be consistently important predictors. In addition to maternal variables, mother-child dyadic synchrony at baseline, which was ranked second place by the SVM model, was an important predictor in this study.

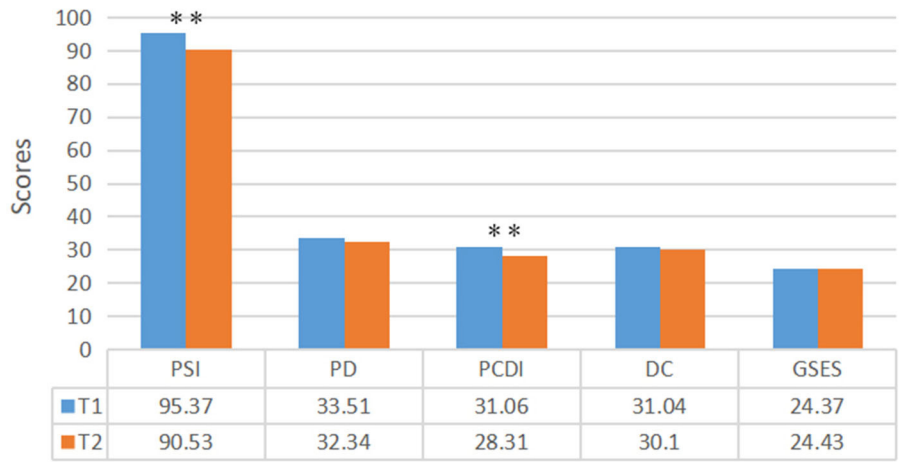
DISCUSSION

Our first outcome verified a finding of our previous work, namely, that PCBI is effective for children with ASD aged 13–30 months (8). Analyses of the changes over 12 weeks of PCBI suggest that toddlers, as a group, improved in their developmental and autism symptoms with respect to gains in adaptive behavior, language behavior, fine motor behavior and



	ATEC	Gesell	DQ1	DQ2	DQ3	DQ4	DQ5	ABC	ABC total	B	L	S	RSC
T1	78		73.36	87.67	77.87	51.59	71.37		73.89	10.04	15.76	8.86	18.24
T2	60.91		79.07	87.66	83.26	64.51	76.5		40.67	7.51	11.87	5.84	15.44

FIGURE 2 | Outcome of children's variables at baseline (T1) and postintervention (T2). T1, preintervention; T2, postintervention; DQ1, Adaptive behavior; DQ2, Gross Motor behavior; DQ3, Language behavior; DQ4, Fine motor behavior; DQ5, Personal-social behavior; ATEC, The Autism Treatment Evaluation Checklist; ABC, The Autism Behavior Checklist; B, L, S, and RSC, the subscales of ABC. *$p < 0.05$; **$p < 0.01$.



	PSI	PD	PCDI	DC	GSES
T1	95.37	33.51	31.06	31.04	24.37
T2	90.53	32.34	28.31	30.1	24.43

FIGURE 3 | Outcome of mothers' variables at baseline (T1) and postintervention (T2). T1, preintervention; T2, postintervention; PSI-SF, The Parenting Stress Index Short Form; PD, PCDI, and DC, the subscales of PSI-SF; GSES, The General Self-Efficacy Scale. **$p < 0.01$.

personal-social behavior skills and decreases in the ATEC, ABC and subscale scores. In addition, we used video-recorded mother-child interactions to investigate the behaviors of children and mothers and found a significant gain in the level of child positive engagement and a reduction in child-object engagement. This finding is consistent with a study of parent delivery of the Early Start Denver Model intervention, which also conducted a 12-week intervention and found improvement of developmental skills (39). Previous studies have demonstrated that children with ASD have unstable structures of dyadic interactions and may have difficulty sustaining positive emotional states (18). However, the dyadic regulation ability of children with ASD in this study improved significantly. These results indicate that PCBI is an effective intervention method that can not only raise children's developmental levels but also enhance their emotional regulation and effective social interaction abilities. In addition, these children will be followed up and reassessed every year to check if the improvements were consolidated and generalized to other fields of their everyday life and now this work is ongoing.

TABLE 1 | Outcome of mother-child interaction variables at baseline (T1) and postintervention (T2).

	T1	T2	Change scores	*z*	*P*
Mothers					
Positive engagement	53.54 ± 8.78	56.66 ± 5.29	3.11 ± 8.41	2.59	0.010
Negative engagement	3.81 ± 6.80	1.96 ± 4.04	−1.86 ± 7.52	1.57	0.117
Disengagement	2.50 ± 3.94	1.17 ± 1.98	−1.33 ± 3.21	3.24	0.001
Children					
Positive engagement	9.16 ± 8.29	16.30 ± 11.47	7.14 ± 9.39	5.52	< 0.001
Negative engagement	3.46 ± 8.97	3.06 ± 7.79	−0.40 ± 10.19	0.20	0.845
Disengagement	5.51 ± 8.04	5.94 ± 7.28	0.43 ± 8.93	0.09	0.932
Child-object engagement	41.81 ± 13.17	34.54 ± 12.79	−7.27 ± 14.82	4.38	< 0.001
Dyadic engagement	9.03 ± 8.34	16.00 ± 11.56	6.97 ± 9.42	5.44	< 0.001

Data are expressed as the mean ± SD. T1, preintervention; T2, postintervention.

TABLE 2 | Summary of hierarchical regression analysis for children's and mothers' factors predicting intervention effect (change in ATEC score).

Predictor variables (factors of mothers and children)	Model 1			Model 2			Model 3		
	B	SE B	β	B	SE B	β	B	SE B	β
Mothers' age	0.33	0.50	0.08	0.18	0.26	0.05	0.19	0.25	0.05
ABC total score T1	0.07	0.04	0.21	−0.01	0.02	−0.03	−0.12	0.02	−0.05
Change in Children's DQ	−0.07	0.15	−0.06	0.04	0.08	0.03	0.05	0.08	0.04
Completion level				−15.69	1.27	−0.87**	−15.02	1.25	0.83*
Change in PSI score							0.17	0.07	0.17**
R^2		0.06			0.74		0.76		
F		1.25			41.45**		37.41**		
R^2 change		0.06			0.68		0.03		
F change		1.25			152.60**		6.32*		

*$p < 0.05$; **$p < 0.01$.

Our second finding was that parenting stress decreased after 12 weeks of intervention. Previous reports demonstrated that mothers of children with ASD often experience much more stress than mothers of children with any other health problems, and parenting stress is related to child outcomes (11, 40, 41). In addition, mothers' self-efficacy was found to be an important factor affecting mothers' stress by adjusting the influence of children's behavior problems on mothers' anxiety and depression. The less satisfied mothers of children with ASD are, the higher the levels of pressure they experience (13, 42, 43). Consistent with these studies, we also found a negative correlation between mothers' self-efficacy and stress, although no significant difference in satisfaction was found between baseline and postintervention. In addition, the mother-child interaction videotapes showed an improvement in mothers' interaction skills, such as an increase in the level of positive engagement and a reduction in the level of negative engagement. This result indicates that PCBI can not only contribute to reducing mothers' stress but also improve mothers' skills in interacting with their children.

The main purpose of this study was to investigate and obtain preliminary data on the characteristics of toddlers who are more likely to benefit from PCBI. Available evidence indicates that many factors may impact the outcome of the intervention, including the characteristics of the mother and child (44–48). Thus, this study analyzed the main predictors from the perspective of mothers and children. Both the machine learning algorithms and hierarchical multiple regression indicated that maternal factors, such as mothers' stress and completion level of training at home, might be associated with the outcome of the intervention. Interestingly, mothers' stress, which was a predictor in this study, often emerges as a predictor in other reports focused on different intervention models (12, 13, 49), suggesting that more attention should be paid to the stress of mothers of children with ASD. In addition, the regression analysis of this study showed that the change in PSI score mediated the completion level of training at home and the ATEC scores. This might be interpreted as indicating that mothers with less stress were better able to complete their homework; in other words, stress may have affected their ability to perform the training at home.

The results of machine learning algorithms and hierarchical multiple regression suggest that PCBI might be particularly beneficial to children with ASD who show good performance in mother-child dyadic synchrony. Thus, the efficacy of PCBI

TABLE 3 | Summary of hierarchical regression analysis for mother-child interaction factors predicting intervention effect (change in ATEC score).

Predictor variables (mother-child interaction factors)	Model 1			Model 2			Model 3		
	B	SE B	β	B	SE B	β	B	SE B	β
Change in mother negative engagement	−0.04	0.26	−0.02	-1.16	1.26	−0.55	-0.79	1.15	−0.38
Change in mother disengagement	0.33	0.61	0.07	-0.83	1.36	−0.17	-0.70	1.24	−0.14
Change in child negative engagement	0.27	0.20	0.17	-0.01	0.18	−0.01	-0.15	0.17	−0.10
Change in child disengagement	0.04	0.23	0.02	-0.19	0.20	−0.11	-0.23	0.18	−0.13
Child-object engagement	0.18	0.14	0.17	-0.02	0.13	−0.02	0.26	0.13	−0.24
Change in mother positive engagement				-0.94	1.25	−0.50	-0.51	1.14	−0.27
Change in child positive engagement				-0.94	0.20	−0.56**	-0.45	0.22	−0.29*
Change in mother-child dyadic synchrony							-0.93	0.26	−0.54**
R^2		0.05			0.31		0.43		
F		0.63			4.01**			5.85**	
R^2 change		0.05			0.26			0.12	
F change		0.63			11.90**			13.22**	

*$p < 0.05$; **$p < 0.01$.

TABLE 4 | Model fits for different algorithms and variable importance rankings.

	R^2	RMSE	Variable rank				
			1	2	3	4	5
LASSO	0.59	0.63	Completion level	Mother negative engagement	DC score (T1)	GSES score (T1)	Dyadic emotion engagement (T1)
SVM	0.75	0.59	Completion level	Dyadic emotion engagement (T1)	Change in dyadic emotion engagement	DC score (T1)	Child positive engagement (T1)
RR	0.53	0.70	Completion level	DC score (T1)	PD score (T1)	Dyadic emotion engagement (T1)	Change in adaptive behavior DQ
RF	0.61	0.57	Completion level	Change in adaptive behavior DQ	Satisfaction	Child positive engagement (T1)	PSI score (T1)

LASSO, LASSO regression; SVM, support vector machine; RR, ridge regression; RF, random forest; PD and DC, the subscales of the Parenting Stress Index Short Form.

can be improved through the improvement of mother-child dyadic synchrony. Dyadic synchrony refers to the emotional and behavioral responsivity of the mother and the child to each other and can make a positive contribution to children's development (50). The potential mechanism of this result might be that the improvement of mother-child dyadic synchrony may improve children's development as well as their behavior and communication ability. In addition, according to previous studies that demonstrated that the maternal psychological state, such as depression and stress, contributes to poorer dyadic synchrony (50), two crucial predictors in this study, mother-child dyadic synchrony and mothers' stress, may have mutual influences on each other and work together to affect the efficacy of PCBI. Consistent with our findings, Hobson et al. (51) indicated that parent-child dyadic synchrony was a mediating factor to predict child communication outcomes. Guo et al. (18) highlighted that children with ASD were more likely to exhibit emotion dysregulation; the problem of emotion dysregulation should be considered when an intervention is implemented. Our results indicated that mother-child dyadic synchrony was a crucial factor in predicting and monitoring the efficacy of the intervention that should be considered in future clinical interventions.

This study has a number of strengths, including the focus on both maternal and child characteristics as well as the analysis of video-recorded parent-child interactions and the use of machine learning algorithms. However, this study also has several limitations. First, the caregivers investigated in this study were the mothers of the children with ASD; the results cannot be generalized to fathers. Second, PCBI is the main intervention for children of this age in our team, and all the participants received PCBI without a control group; thus, it is unclear whether the findings are specific to responses to PCBI. It would be necessary to conduct a randomized control trial to test whether these predictors response to the PCBI only. Third, this study focused on short-term efficacy and factors likely to affect children's response to intervention. Longitudinal studies are needed to determine whether gains are maintained after a number of years and translate to meaningful cognitive,

academic and social differences between children who accessed the intervention and those who did not. It is also necessary to analysis of each individual profile in our future work to provide a more specific intervention to each child.

In conclusion, this study indicated that mother-child dyadic synchrony, parenting stress of mothers and the completion level of training at home are important predictors of PCBI efficacy. In addition, the findings suggested that PCBI can contribute to reducing mothers' stress and improve the interaction skills between mothers and children with ASD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Nanjing Brain Hospital affiliated with the Nanjing Medical University Ethics Committee, and informed consent was obtained from the parents or legal guardians of the participants. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JW and XK conceived and designed the study. LF, JW, MF, XX, TX, JF, NQ, CL, and YD performed the experiments. LF and JW analyzed experimental results. LF wrote the paper. LF, JW, and XK reviewed and edited the manuscript. All authors read and approved the manuscript.

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REFERENCES

1. American Psychiatric Association 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edn. Arlington, VA: American Psychiatric Publishing (2013).
2. Wolff JJ, Gu H, Gerig G, Elison JT, Styner M, Gouttard S, et al. Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am J Psychiatr.* (2012) 169:589–600. doi: 10.1176/appi.ajp.2011.11091447
3. Beuker KT, Rommelse NN, Donders R, Buitelaar JK. Development of early communication skills in the first two years of life. *Infant Behav Dev.* (2013) 36:71–83. doi: 10.1016/j.infbeh.2012.11.001
4. Webb SJ, Jones EJ, Kelly J, Dawson G. The motivation for very early intervention for infants at high risk for autism spectrum disorders. *Int J Speech Lang Pathol.* (2014) 16:36–42. doi: 10.3109/17549507.2013.861018
5. Bradshaw J, Steiner AM, Gengoux G, Koegel LK. Feasibility and effectiveness of very early intervention for infants at-risk for autism spectrum disorder: a systematic review. *J Autism Dev Disord.* (2015) 45:778–94. doi: 10.1007/s10803-014-2235-2
6. Shattuck PT, Durkin M, Maenner M, Newschaffer C, Mandell DS, Wiggins L, et al. Timing of identification among children with an autism spectrum disorder: findings from a population-based surveillance study. *J Am Acad Child Adolesc Psychiatr.* (2009) 48:474–83. doi: 10.1097/CHI.0b013e31819b3848
7. Landa RJ. Efficacy of early interventions for infants and young children with, at risk for, autism spectrum disorders. *Int Rev Psychiatr.* (2018) 30:25–39. doi: 10.1080/09540261.2018.1432574
8. Feng M, Xiao X, Xiao T, Fu J, Weng J, Qiu N, et al. Effect of play-based communication and behavior intervention on toddlers with autism spectrum disorder. *Chin J Appl Clin Pediatr.* (2019) 34:604–8. doi: 10.3760/cma.j.issn.2095-428X.2019.08.011
9. Baker-Ericzn MJ, Brookman-Frazee L, Stahmer A. Stress levels and adaptability in parents of toddlers with and without autism spectrum disorders. *Res Pract Pers Severe Disabil.* (2005) 30:194–204. doi: 10.2511/rpsd.30.4.194
10. Zaidman-Zait A, Mirenda P, Duku E, Vaillancourt T, Smith IM, Szatmari P, et al. Impact of personal and social resources on parenting stress in mothers of children with autism spectrum disorder. *Autism Int J Res Pract.* (2017) 21:155–66. doi: 10.1177/1362361316633033
11. Osborne LA, McHugh L, Saunders J, Reed P. Parenting stress reduces the effectiveness of early teaching interventions for autistic spectrum disorders. *J Autism Dev Disord.* (2008) 38:1092–103. doi: 10.1007/s10803-007-0497-7
12. Rollins PR, John S, Jones A, De Froy A. Pathways early ASD intervention as a moderator of parenting stress on parenting behaviors: a randomized control trial. *J Autism Dev Disord.* (2019) 49:4280–93. doi: 10.1007/s10803-019-04144-4
13. Ozturk Y, Vivanti G, Uljarevic M, Dissanayake C, Victorian, ASELCC Team. Treatment-related changes in children's communication impact on maternal satisfaction and psychological distress. *Res Dev Disabil.* (2016) 56:128–38. doi: 10.1016/j.ridd.2016.05.021
14. Harrist AW, Waugh RM. Dyadic synchrony: its structure and function in children's development. *Dev Rev.* (2002) 4:555–92. doi: 10.1016/S0273-2297(02)00500-2
15. Kochanska G. Mutually responsive orientation between mothers and their young children: implications for early socialization. *Child Dev.* (1997) 68:94–112. doi: 10.2307/1131928
16. Zeegers M, Potharst ES, Veringa-Skiba IK, Aktar E, Goris M, Bögels SM, et al. Evaluating mindful with your baby/toddler: observational changes in maternal sensitivity, acceptance, mind-mindedness, dyadic synchrony. *Front Psychol.* (2019) 10:753. doi: 10.3389/fpsyg.2019.00753
17. Butler EA, Randall AK. Emotional coregulation in close relationships. *Emot Rev.* (2013) 5:202–10. doi: 10.1177/1754073912451630
18. Guo Y, Garfin DR, Ly A, Goldberg WA. Emotion coregulation in mother-child dyads: a dynamic systems analysis of children with and without autism spectrum disorder. *J Abnormal Child Psychol.* (2017) 45:1369–83. doi: 10.1007/s10802-016-0234-9
19. Lozier LM, Vanmeter JW, Marsh AA. Impairments in facial affect recognition associated with autism spectrum disorders: a meta-analysis. *Dev Psychopathol.* (2014) 26:933–45. doi: 10.1017/S0954579414000479
20. Hammer AT, Grau JM, Silberman SG, Smith EN. Dyadic synchrony among young latina mothers and their toddlers: the role of maternal and child behavior. *Infant Behav Dev.* (2019) 57:101378. doi: 10.1016/j.infbeh.2019.101378
21. Krug DA, Arick J, Almond P. Behavior checklist for identifying severely handicapped individuals with high levels of autistic behavior. *J Child Psychol Psychiatr Alli Discip.* (1980) 21:221–9. doi: 10.1111/j.1469-7610.1980.tb01797.x
22. Robins DL, Fein D, Barton ML, Green JA. The modified checklist for autism in toddlers: an initial study investigating the early detection of autism and

pervasive developmental disorders. *J Autism Dev Disord.* (2001) 31:131–44. doi: 10.1023/a:1010738829569
23. Gong Y, Liu J, Guo Y, Song W, Jia M, Li C. Validity and reliability of the Chinese simplified version of the modified checklist for autism in toddlers. *Chin Ment Health J.* (2015) 29:121–4. doi: 10.3969/j.issn.1000-6729.2015.02.008
24. Yang X, Huang Y, Jia M, Chen S. Report of autism behavior scale. *Chin Ment Health J.* (1993) 7:279–80. CNKI:SUN:ZXWS.0.1993-06-017
25. Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord.* (2000) 30:205–23. doi: 10.1023/A:1005592401947
26. Lord C, Rutter M, Le Couteur A. Autism diagnostic interview-revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord.* (1994) 24:659–85. doi: 10.1007/BF02172145
27. Ball RS. The gesell developmental schedules: arnold gesell (1880-1961). *J Abnormal Child Psychol.* (1977) 5:233–9. doi: 10.1007/BF00913694
28. Rimland B, Edelson M. *Autism Treatment Evaluation Checklist*. San Diego, CA: Autism Research Institute (1999).
29. Hadoush H, Nazzal M, Almasri NA, Khalil H, Alafeef M. Therapeutic effects of bilateral anodal transcranial direct current stimulation on prefrontal and motor cortical areas in children with autism spectrum disorders: a pilot study. *Autism Res.* (2020) 13:828–36. doi: 10.1002/aur.2290
30. Magiati I, Moss J, Yates R, Charman T, Howlin P. Is the autism treatment evaluation checklist a useful tool for monitoring progress in children with autism spectrum disorders? *J Intellect Disabil Res.* (2011) 55:302–12. doi: 10.1111/j.1365-2788.2010.01359.x
31. Yang Y, Wang H, Xue Q, Huang Z, Wang Y. High-frequency repetitive transcranial magnetic stimulation applied to the parietal cortex for low-functioning children with autism spectrum disorder: a case series. *Front Psychiatr.* (2019) 10:293. doi: 10.3389/fpsyt.2019.00293
32. Geier DA, Kern JK, Geier MR. A comparison of the autism treatment evaluation checklist (ATEC) and the childhood autism rating scale (CARS) for the quantitative evaluation of autism. *J Ment Health Res Intellect Disabil.* (2013) 6:255–67. doi: 10.1080/19315864.2012.681340
33. Fang H, Ren Y, Li C, Ke X. Reliability and validity of the Chinese version of autism treatment evaluation checklist. *Sichuan Ment Health.* (2019) 32:518–22. doi: 10.11886/scjsws20190902002
34. Abidin RR. Parenting stress and the utilization of pediatric services. *Children's Health Care.* (1983) 11:70–73. doi: 10.1207/s15326888chc1102_5
35. Haskett ME, Ahern LS, Ward CS, Allaire JC. Factor structure and validity of the parenting stress index-short form. *J Clin Child Adolesc Psychol.* (2006) 35:302–12. doi: 10.1207/s15374424jccp3502_14
36. Reitman D, Currier RO, Stickle TR. A critical evaluation of the parenting stress index-short form (PSI-SF) in a head start population. *J Clin Child Adolesc Psychol.* (2002) 31:384–92. doi: 10.1207/S15374424JCCP3103_10
37. Schwarzer R, Born A. Optimistic self beliefs: assessment of general perceived self e-cacy in thirteen cultures. *Word Psychol.* (1997) 3:177–90.
38. Wang CK, Hu ZF, Liu Y. Evidences for reliability validity of the chinese version of general self e-cacy scale. *Chin J Appl Psychol.* (2001) 7:37–40.
39. Rogers SJ, Estes A, Lord C, Vismara L, Winter J, Fitzpatrick A, et al. Effects of a brief early start denver model (ESDM)-based parent intervention on toddlers at risk for autism spectrum disorders: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatr.* (2012) 51:1052–65. doi: 10.1016/j.jaac.2012.08.003
40. Blacher J, McIntyre LL. Syndrome specificity and behavioural disorders in young adults with intellectual disability: cultural differences in family impact. *J Intellect Disabil Res.* (2006) 50:184–98. doi: 10.1111/j.1365-2788.2005.00768.x
41. Reed P, Osborne LA, Corness M. Brief report: relative effectiveness of different home-based behavioral approaches to early teaching intervention. *J Autism Dev Disord.* (2007) 37:1815–21. doi: 10.1007/s10803-006-0306-8
42. Hastings RP, Brown T. Behavior problems of children with autism, parental self-efficacy, mental health. *Am J Ment Retardat.* (2002) 107:222–32. doi: 10.1352/0895-8017(2002)107<0222:BPOCWA>2.0.CO;2
43. Ozturk Y, Riccadonna S, Venuti P. Parenting dimensions in mothers and fathers of children with autism spectrum disorders. *Res Autism Spectr Disord.* (2014) 8:1295–306. doi: 10.1016/j.rasd.2014.07.001
44. Kasari C, Gulsrud A, Freeman S, Paparella T, Hellemann G. Longitudinal follow-up of children with autism receiving targeted interventions on joint attention and play. *J Am Acad Child Adolesc Psychiatr.* (2012) 51:487–95. doi: 10.1016/j.jaac.2012.02.019
45. Perry A, Cummings A, Geier JD, Freeman NL, Hughes S, Managhan T, et al. Predictors of outcome for children receiving intensive behavioral intervention in a large, community-based program. *Res Autism Spectr Disord.* (2011) 5:592–603. doi: 10.1016/j.rasd.2010.07.003
46. Flanagan HE, Perry A, Freeman NL. Effectiveness of large-scale community-based intensive behavioral Intervention: A waitlist comparison study exploring outcomes and predictors. *Res Autism Spectr Disord.* (2012) 6:673–82. doi: 10.1016/j.rasd.2011.09.011
47. Magiati I, Charman T, Howlin P. A two-year prospective follow-up study of community-based early intensive behavioural intervention and specialist nursery provision for children with autism spectrum disorders. *J Child Psychol Psychiatry.* (2007) 48:803–12. Available online at: https://acamh.onlinelibrary.wiley.com/doi/abs/10.1111/j.1469-7610.2007.01756.x
48. Makrygianni MK, Reed P. A meta-analytic review of the effectiveness of behavioural early intervention programs for children with autistic spectrum disorders. *Res Autism Spectr Disord.* (2010) 4:577–93. doi: 10.1016/j.rasd.2010.01.014
49. Strauss K, Vicari S, Valeri G, D'Elia L, Arima S, Fava L. Parent inclusion in early intensive behavioral intervention: the influence of parental stress, parent treatment fidelity and parent-mediated generalization of behavior targets on child outcomes. *Res Dev Disabil.* (2012) 33:688–703. doi: 10.1016/j.ridd.2011.11.008
50. Skuban EM, Shaw DS, Gardner F, Supplee LH, Nichols SR. The correlates of dyadic synchrony in high-risk, low-income toddler boys. *Infant Behav Dev.* (2006) 29:423–34. doi: 10.1016/j.infbeh.2006.02.004
51. Hobson JA, Tarver L, Beurkens N, Hobson RP. The relation between severity of autism and caregiver-child interaction: a study in the context of relationship development intervention. *J Abnormal Child Psychol.* (2016) 44:745–55. doi: 10.1007/s10802-015-0067-y

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Emotional vs. Neutral Face Exploration and Habituation: An Eye-Tracking Study of Preschoolers With Autism Spectrum Disorders

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Diminished orienting to social stimuli, and particularly to faces, is a core feature of autism spectrum disorders (ASDs). Impaired face processing has been linked to atypical attention processes that trigger a cascade of pathological development contributing to impaired social communication. The aim of the present study is to explore the processing of emotional and neutral faces using an eye-tracking paradigm (the emotional faces task) with a group of 24 children with ASD aged 6 and under and a group of 22 age-matched typically developing (TD) children. We also measure habituation to faces in both groups based on the presentation of repeated facial expressions. Specifically, the task consists of 32 pairs of faces, a neutral face and an emotional face from the same identity, shown side by side on the screen. We observe differential exploration of emotional faces in preschoolers with ASD compared with TD. Participants with ASD make fewer fixations to emotional faces than their TD peers, and the duration of their first fixation on emotional faces is equivalent to their first fixation on neutral faces. These results suggest that emotional faces may be less interesting for children with ASD. We also observe a habituation process to neutral faces in both children with ASD and TD, who looked less at neutral faces during the last quarter of the task compared with the first quarter. By contrast, TD children show increased interest in emotional faces throughout the task, looking slightly more at emotional faces during the last quarter of the task than during the first quarter. Children with ASD demonstrate neither habituation nor increased interest in the changing emotional expressions over the course of the task, looking at the stimuli for equivalent time throughout the task. A lack of increased interest in emotional faces may suggest a lack of sensitivity to changes in expression in young children with ASD.

Keywords: emotional faces, habituation, eye-tracking, preschoolers, ASD, face exploration

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INTRODUCTION

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders characterized by persistent deficits in social communication and interactions, as well as restricted and repetitive patterns of behavior, interests, or activities. Symptoms of autism are present early in development and are known to cause variable functional impairment (1). Diminished orienting to faces and

reduced eye contact are two striking behavioral hallmarks of autism. Faces are highly salient but complex social stimuli that are essential to social interactions (2). A recent review and meta-analysis of eye-tracking studies confirmed overall reduced attention to social stimuli and impaired face orienting in individuals with ASD compared with typically developing (TD) controls (3). Some authors have suggested this lack of social orientation as a potential trigger for the developmental cascade that contributes to autistic symptoms (4).

Eye tracking is a non-invasive tool, facilitating the detailed characterization of looking behavior (5–7). It is especially useful for screening and detecting early visual exploration abnormalities. Several authors have suggested that eye-tracking measurements may be useful for the diagnosis of ASD (6) or as predictors of outcome (8). For example, Frazier et al. (6) created an eye-tracking-based autism risk index including time spent on different biological and social stimuli. They found that the autism risk index was strongly associated with the severity of autistic symptoms among children between 3 and 8 years old, according to Autism Diagnostic Observation Schedule—Second Edition (ADOS-2) severity scores. To study predictors of outcome, Franchini et al. (8) reproduced a visual preference paradigm by presenting biological and geometric motion side by side during eye tracking. The authors showed that children with ASD who preferred biological motion at the age of 3 showed drastic reductions in the severity of their autistic symptoms 1 year later than did preschoolers who preferred geometric motion (8).

Eye-tracking technology also is an extremely useful tool for understanding autistic symptoms and face exploration behavior in children with ASD. An eye-tracking study detected atypical face exploration for preschoolers with ASD, noting that they looked less at the inner facial features of neutral faces and more at the external facial features than did TD children (9). Two other studies suggested that children with ASD looked significantly less at the eyes and more at the mouth than TD children when viewing social scenes (10, 11). Given the potential for early emergence of autistic symptoms, a few studies have explored face exploration in 2- to 6-month-old infants at risk for ASD, with inconsistent results (12–14). Jones and Klin (13) showed that infants later diagnosed with ASD demonstrate decreased fixations on the eyes within the first 2–6 months of life (13). However, a longitudinal study by Young et al. (14) showed that none of the infants with lower rates of gazing at the eye region at age 6 months had any signs of autism at 18 months (14). Moreover, context appears to modify how toddlers with ASD process faces (15). The authors showed that children with ASD spent less time looking at whole faces and lip movements than did their peers solely in the context of a direct interaction (15).

The mechanisms underlying impaired face processing in ASD are not yet fully understood. Face exploration in ASD appears to change to some degree based on the emotion expressed on the face and whether the face is static or dynamic [for a review, see (16)]. A recent study among adults with ASD linked impaired face exploration with specific deficits in emotion exploration (17), and emotion exploration has been related to difficulties in the recognition of different emotions (18). A few studies have explored emotion recognition in preschoolers with ASD, using either facial or vocal stimuli, with mixed results. Some studies do not point to significantly impaired emotion recognition in individuals with ASD (19), whereas others identify impaired emotion recognition overall or for specific emotions (18), depending on the type of stimuli (18) and characteristics related to the participants (20).

A growing body of work has focused on attentional processes, such as habituation or visual disengagement, and their contributions to socio-communicative impairments in autism (21–24). Hypotheses for explaining both decreased social interest and the developmental cascade of socio-communicative impairments have emerged from recent work exploring attention deficits in children with ASD (21–24). Studies demonstrate impaired visual disengagement, which can result in sticky attention in the absence of habituation to stimuli (25–28). Habituation is defined as the diminishing of a response to a repeated stimulus (29) and is referred to as repetition suppression in neuroimaging studies (30). Some authors have suggested that impaired habituation to sensory stimuli in children with ASD may result in stimulus overload (21, 22). Overwhelmed by their surroundings, children with ASD may have trouble evaluating both the salience and relevance of stimuli, including social cues (21, 22). As a result, social stimuli can be labeled "unpleasant" and, consequently, avoided, contributing to socio-developmental impairment in children with ASD (21, 22). These results are supported by neuroimaging studies. Ewbank et al. (31) showed repetition suppression, with reduced blood oxygenation level-dependent (BOLD) response, and changes in connectivity between the occipital face area and the fusiform face area in neurotypical adults while looking at repeated identical faces (31). The same authors later observed decreased repetition suppression in the fusiform face area in adults with ASD looking at repeated faces (32). Other neuroimaging studies also point to reduced habituation involving the amygdala in individuals with ASD, related to more severe social impairment (33, 34).

During eye tracking, habituation is typically defined by a progressive decrease in looking time at a stimulus when it is repeated (35). However, despite its relevance, surprisingly few eye-tracking studies have investigated differential habituation in children with ASD (35) or habituation to faces (36). A recent eye-tracking study compared habituation responses with sensitivity to novelty in ASD, Williams syndrome, and TD preschool children based on repeated vs. novel geometric stimuli presented side by side (35). The TD and Williams syndrome groups showed reduced attention to the repeating stimuli and increased attention to the novel stimuli over time, while the ASD group showed a similar decrease in attention to both stimuli. Correspondingly, another study showed slow visual habituation to faces in children with severe autism (36). The authors defined habituation when the average of two consecutive visual fixations dropped below 50% of the average of the same child's longest two fixations. Children with ASD needed more trials than controls to habituate to faces compared with houses. To the best of our knowledge, previous studies have never compared habituation with neutral vs. emotional faces in children with ASD. Through the repetition of 32 pairs of neutral and emotional faces, we were able to observe changes in participants' attention to faces and whether

TABLE 1 | ASD (Autism Spectrum Disorder) and TD (Typically Developing) groups characteristics.

	ASD group	TD group	*p*-value [$t_{(df)}$]
N (Gender)	24 (Males = 22/Females = 2)	22 (Males = 16/Females = 6)	0.128 (Fisher's exact-test)
Age Mean ± SD (Range)	3.92 ± 1.18 years old (1.88–5.63 years old)	4.12 ± 1.08 years old (1.77–5.84 years old)	0.547 [$t_{(44)} = 0.61$]

habituation to neutral and emotional faces is different between children with ASD and their TD peers.

The aim of this eye-tracking study is two-fold. First, we describe the exploration patterns of emotional and neutral static faces stimuli in children younger than 6 years with ASD and their age-matched TD peers. Namely, we look at the time spent on the faces and inner facial features (eyes and mouth), as well as the number of fixations children made to these areas of interest (see section Emotional and Neutral Face Exploration paragraph for details). The number of fixations, together with fixation duration, allows us to explore whether the child fixates the same part of a stimulus for a prolonged time or whether he/she explores it by making several fixations within the stimulus. This is especially interesting since a "sticky" pattern of exploration is described as one of the early signs of ASD in children (37).

Commensurate with results from previous work (3), we hypothesize that children with ASD will show decreased orienting to faces, especially to emotional vs. neutral faces, than will TD children. We also hypothesize that children with ASD will present a differential exploration pattern, depending on whether a stimulus is emotional or neutral, as compared with TD participants. Specifically, we expect that children with ASD will spend less time looking at the eyes and more time on the mouth than TD children, with a decreased number of fixations in each area of interest (AOI). Second, we will measure habituation during face exploration. In the current study, we define habituation as a significant decrease in the time spent on faces during the last quarter of the task compared with the time spent on faces during the first quarter of the task (see section Habituation paragraph for details). According to recent theories and previous results (35, 36), we hypothesize that children with ASD will show reduced habituation to faces, both emotional and neutral, spending a similar amount of time looking at faces throughout the task.

MATERIALS AND METHODS

Participants

The present study included 24 participants with ASD (2F), 1.88–5.63 years old (3.92 ± 1.18), and 22 TD children (6F), 1.77–5.84 years old (4.12 ± 1.08) (**Table 1**). Both groups did not differ by age ($p = 0.547$) or gender ($p = 0.128$).

Participants with ASD were recruited through local ASD-specialized therapeutic centers and parent associations. For participants with ASD, the clinical diagnosis was confirmed using either the ADOS-Generic (ADOS-G) (38) or the ADOS-2 (Second Edition) (39) (**Table 2**). The ADOS consists of a series of structured and semi-structured tasks involving social interactions between an examiner and a child. It serves as a standardized tool for diagnosing ASD and quantifies observations in three domains of behavior: communication, social interaction, and repetitive/restricted behaviors or interests. The version (module) of the ADOS is selected according to a child's age and language level. Therefore, the ADOS module differed between participants. Accordingly, the ADOS Calibrated Severity Score served as a standardized measure of symptom severity across modules (40). Calibrated Severity Scores also were obtained for the Social Affect (SA-SS) and the Restricted Interests and Repetitive Behaviors domains (RRB-SS). The 22 participants with typical development were recruited through announcements in the Geneva community. They also were assessed using the ADOS-G or ADOS-2 to ensure the absence of ASD symptoms prior to their inclusion in the TD cohort. All TD children had a Total Severity Score of 1 (the minimum), except for one child who had a score of 2. Children also were excluded from the TD group if they presented any neurological/psychiatric problems or learning disabilities according to a parent interview and questionnaire, or if they had a sibling or first-degree relative diagnosed with ASD. The study was approved by the Local Research Committee, the Commission Centrale d'Ethique de Recherche (CCER) in Geneva, Switzerland, and written informed consent was obtained from a parent of all the participants prior to inclusion in the study. All participants are part of the Geneva Autism Cohort, a cohort of preschoolers followed up longitudinally (8, 41).

TABLE 2 | ADOS calibrated severity scores and best estimate intellectual quotient for ASD (autism spectrum disorder) and TD (typically developing) groups.

	ASD group	TD group	*p*-value [$t_{(df)}$]
Total ADOS severity score Mean ± SD	7.21 ± 1.84	1.05 ± 0.21	<0.001 [$t_{(44)} = 15.59$]
ADOS social affect severity score Mean ± SD	6.08 ± 1.93	1.09 ± 0.42	<0.001 [$t_{(44)} = 11.85$]
ADOS restricted interests and repetitive behaviors severity score Mean ± SD	8.92 ± 1.38	2.09 ± 1.82	<0.001 [$t_{(44)} = 14.39$]
Best estimate intellectual quotient Mean ± SD	81.51 ± 26.00	122.90 ± 17.43	<0.001 [$t_{(44)} = 6.29$]

ADOS, Autism Diagnostic Observation Schedule.

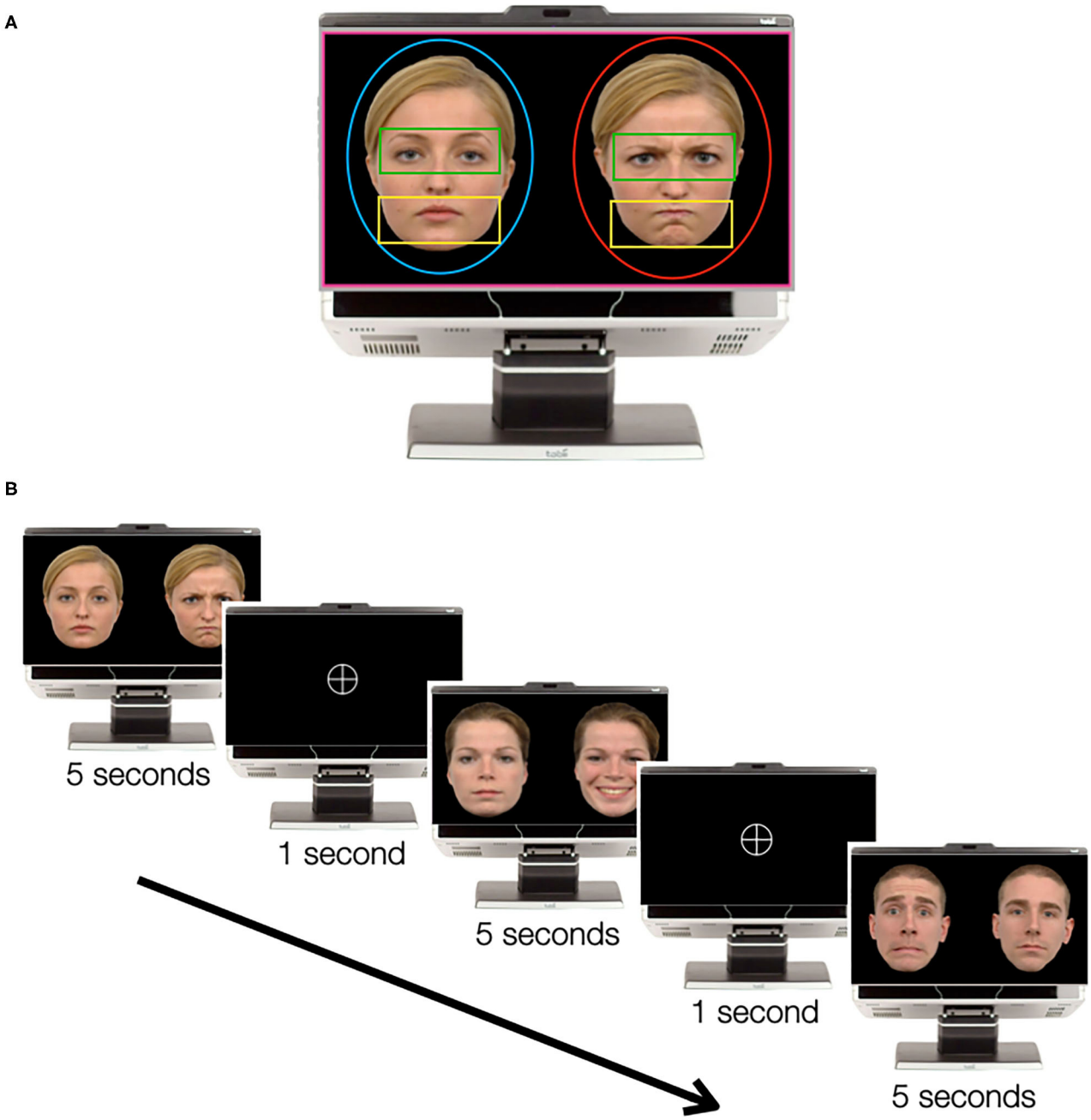

FIGURE 1 | The emotional faces task. **(A)** Example of one pair of faces with area of interest (AOI). AOI representation: screen in pink, neutral face in blue, emotional face in red, eyes in green, and mouth in yellow. The pair of faces was extracted from the Radboud Faces Database (47). **(B)** Example of the order of the stimuli, with three pairs of faces and two turning wheels between the faces.

A total of 59 pre-schoolers (all under the age of 6) participated in the current study (31 children with ASD and 28 TD children). Five children with ASD were subsequently excluded because they did not sufficiently attend to stimuli presented during eye tracking. To be included in the statistical analysis, participants needed to attend to at least 50% of trials (16 stimuli) for at least 50% of the presentation duration of each stimulus (2.5 s). We further excluded data from three children (two with ASD) due to a failure in the eye-tracking calibration procedure detected during a visual inspection of the recording (see section Procedures and Experimental Measures paragraph for details). Consequently, to keep the ASD and TD groups matched for gender, we had to exclude five TD girls. After a total of 13 children (7 with ASD) were excluded, the final groups comprised

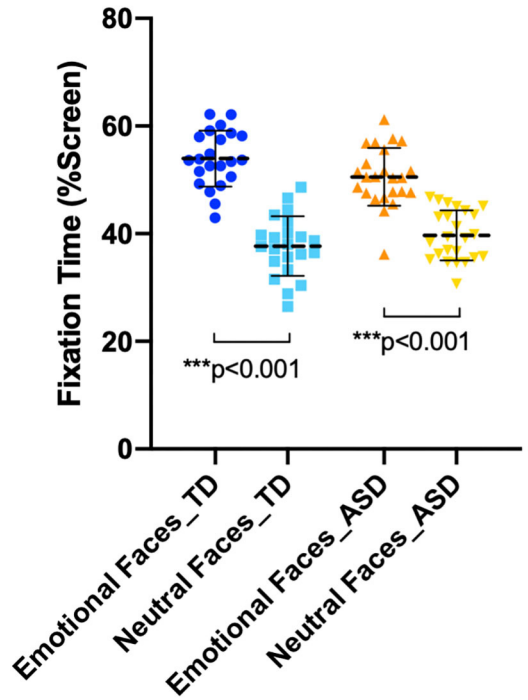

FIGURE 2 | Fixations to emotional and neutral faces in autism spectrum disorder (ASD) and typically developing (TD) group. TD group (on the left) and ASD group (on the right) both looked significantly less at neutral faces than emotional faces.

24 participants with ASD and 22 TD children. Children with ASD who were excluded due to failed eye tracking did not differ on severity of autism symptoms as compared with those who were included in the final sample (mean ADOS Total Severity Score: included participants = 7.21 ± 1.84 and excluded participants = 6.29 ± 2.28).

Cognitive functioning was assessed using several standardized tools. With the use of an approach previously described by our team (42) and commensurate with other studies (43), cognitive tools were selected according to age, language level, symptom severity, and participants' abilities to attend to demanding cognitive tasks. We established a Best Estimate Intellectual Quotient (BEIQ), based on either the Wechsler Pre-school and Primary Scale of Intelligence, fourth edition (WPPSI-IV) (44), the Mullen Scales of Early Learning (MSEL) composite score (45), or the Psycho-Educational Profile, third edition (PEP-3) (46). The WPPSI-IV is a standardized intelligence test for young children, aged between 2.5 and 7 years 7 months. It is used to determine the child's intelligence quotient (IQ) and includes five composite domain scores: the Verbal Comprehension Index score, the Visual-Spatial Index score, the Fluid Reasoning Index score, the Working Memory Index score, and the Processing Speed Index score. The MSEL is a standardized assessment used to measure cognitive functioning in children from the ages of 0 to 68 months. The scale includes five subdomains: Visual Reception, Fine and Gross Motor Skills, and Receptive and Expressive Language. The total composite score gives an estimate of overall intelligence. By comparison, the PEP-3 is a standardized tool for assessing developmental level in children with developmental disorders, and ASD in particular, between the ages of 2 and 7.5 years. It includes the same five domains as the MSEL but combines non-verbal and verbal intelligence scores into a Verbal/Preverbal Cognition score and includes an additional Imitation Skills Index.

Choice between the different scaled scores was as follows: whenever possible, we used the Full-Scale IQ (FSIQ) score from the WPPSI-IV (ASD $N = 0$, TD $N = 3$). For participants with lower cognitive abilities or if the FSIQ derived from the WPPSI-IV was not quantifiable, we used either the MSEL or the PEP-3, depending on when participants were tested for the study. The MSEL was added to our study protocol in 2015 and was used for participants who were evaluated after that date. Thus, the MSEL was used to calculate the BEIQ for 19 participants with ASD and 14 TD participants. The Verbal/Preverbal Cognition scale of the PEP-3 was used to calculate the BEIQ for five participants with ASD and five TD participants. Ten of 24 (42%) participants with ASD obtained a BEIQ score below 70 (range 49.0–68.0). The ASD group had a significantly lower mean BEIQ than the TD group ($p < 0.001$; **Table 2**).

Procedure and Experimental Measures

Participants were seated on a chair or on their parent's laps, ∼60 cm from the screen. Gaze data were acquired and analyzed using TX300 Tobii eye-tracker software with a 300-Hz sampling rate (https://www.tobiipro.com). The stimuli were presented on a 1,200 × 1,920 pixel video monitor and subtended at a minimal horizontal visual angle of 7.82° and a minimal vertical visual angle of 2.86° for the smallest AOI. All participants were administered a five-point calibration procedure to verify eye motion and gaze presence before beginning the task. Calibration was repeated until the eye tracker correctly detected child's gaze.

The emotional faces task comprised a sequence of 32 stimuli, each composed of two adult faces presented side by side on the screen for a duration of 5 s. Each stimulus included a neutral face and an emotional face taken from the same person/identity. Thus, the task included a total of four emotion expressions (anger, fear, happiness, and sadness), with eight different identities expressing each emotion. Emotions were mixed throughout the task. The face stimuli were all part of the Radboud Faces Database (47), and all emotions were expressed at the same intensity according to the database. Between each stimulus, a rotating wheel was displayed in the center of the screen for 1 s to recenter participants' visual attention. Two additional seconds of the rotating wheel to center participants' attention was required (1 s before the beginning of the task and 1 s at the end of the task). Total task duration was 3 min 13 s. Children did not receive any viewing instruction prior to the task. All participants viewed the sequence of face stimuli in the same order.

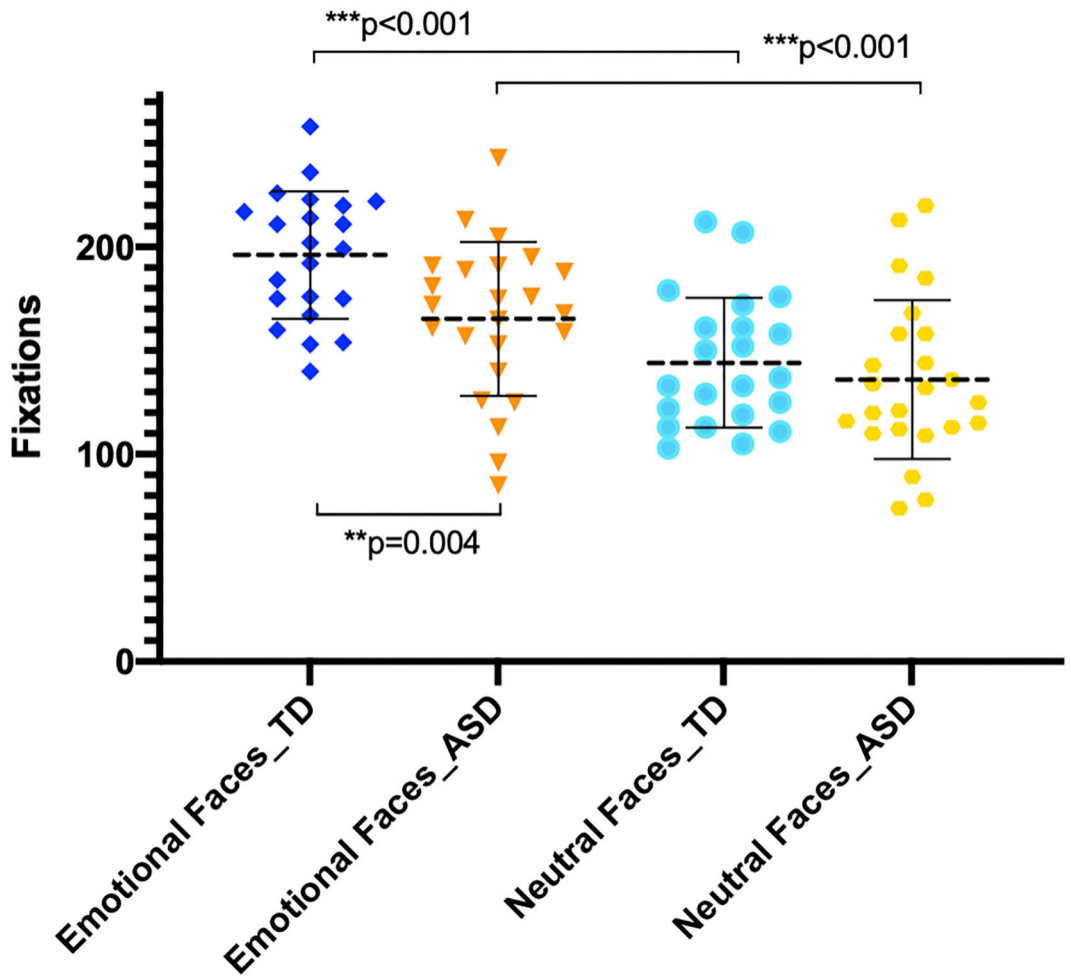

FIGURE 3 | Number of fixations on emotional and neutral faces. Autism spectrum disorder (ASD) group (orange) made less fixations to emotional faces than typically developing (TD) group (dark blue).

Data Analysis

To quantify the time spent looking at key regions of the faces, we drew an oval-shaped face AOI on each of the side-by-side faces (see **Figure 1**) and added rectangular-shaped AOI for the eye and mouth regions. We also drew an AOI containing the whole screen to quantify screen attendance (see the following paragraph). The size of the AOI containing the screen and the faces was equivalent for all stimuli. AOI containing the eyes and mouths was adjusted according to the physiognomy of each identity and thus equals for the two faces in each stimulus.

Data analysis was performed using IBM SPSS Statistics for Macintosh, Version 24.0 (IBM Corp., Armonk, NY), and graphs were plotted using GraphPad Prism for Macintosh, Version 8 (GraphPad Software, La Jolla, CA, USA; www.graphpad.com). Normality of distribution was tested with D'Agostino–Pearson test for all the variables. Screen attendance was measured using total time spent on the screen and the number of visits on the screen, allowing us to quantify the amount of time that children looked at the screen after looking away. We used an unpaired *t*-test to compare screen attendance between groups.

Fixation time spent on each group of AOI (all faces, emotional faces, neutral faces, eyes, and mouth) was calculated for the ASD and TD groups. Fixations were defined according to the Tobii IV-T Fixation filter (48), using a velocity threshold of 30° within a velocity window length of 20 ms. Adjacent fixations were merged. The maximum time between all fixations was 75 ms, and the maximum angle between all fixations was 0.5°. Despite the fact that screen attendance was comparable in both groups, we still controlled for overall time spent on the screen during stimulus presentation by calculating the percentage of time children fixated on each AOI group relative to overall time spent on the screen.

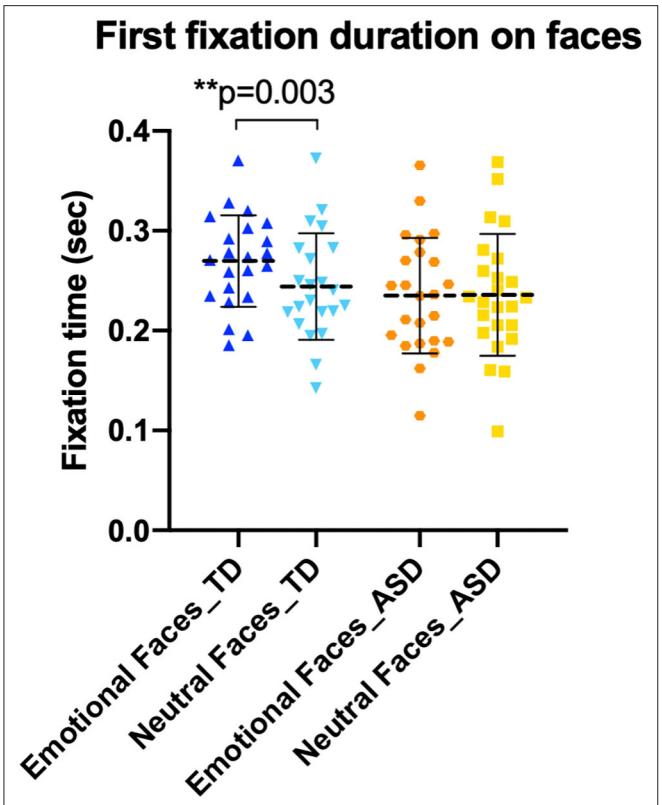

FIGURE 4 | First fixations to emotional and neutral faces. Typically developing (TD) children showed longer first fixation on emotional faces (dark blue) than on neutral faces (light blue).

Emotional and Neutral Face Exploration

A one-way multivariate analysis of variance (MANOVA) was run to determine the effect of diagnosis on fixation duration on emotional and neutral faces. We then compared the overall number of fixations within and between ASD and TD groups, using paired and unpaired *t*-tests, respectively. We used the same approach for duration of first fixations on the neutral face and the emotional face of each stimulus.

To test for differences in the exploration of emotional and neutral faces, we calculated fixation time on the eyes and the mouth of emotional and neutral faces in both groups. Effect of diagnosis on fixation duration by region (eyes or mouth) was then tested using a one-way MANOVA. To end, we tested the interaction between fixation duration for the four emotional expressions and diagnosis, using a two-way ANOVA. Then we performed *post-hoc* analysis using Tukey's multiple comparisons test for fixation duration on each emotion between the ASD and TD groups.

We used Pearson correlations (data were normally distributed) to detect potential relationships between ADOS Total Severity Score and our eye-tracking measures (fixation duration on the screen and on emotional and neutral faces, first fixation duration on emotional and neutral faces, and number of fixations on emotional and neutral faces).

Habituation

In the context of the present study, habituation was defined as the difference in time spent on the first quarter of the task (first eight stimuli) compared with the last quarter (last eight stimuli). We calculated fixation duration on each stimulus (including both the emotional and neutral faces), as well as on each emotional/neutral face. The sums were adjusted according to overall time spent on the screen during the first quarter and the last quarter, respectively. We compared the differences in both groups, using paired *t*-tests, and we applied a Bonferroni correction for multiple comparison.

RESULTS

The difference in total time spent on the screen between the ASD ($M = 124.95$ s, SD = 16.87) and TD groups ($M = 132.02$ s, SD = 13.26) was not statistically significant [$t_{(44)} = 1.57$, $p = 0.124$], nor was the difference in the number of visits to the screen between the ASD ($M = 35.58$, SD = 5.22) and TD groups ($M = 36.27$, SD = 4.81) [$t_{(44)} = 0.46$, $p = 0.645$].

Emotional and Neutral Face Exploration

Overall, participants with ASD spent an equivalent amount of time looking at faces ($M = 90.25\%$, SD = 4.03) as compared with TD participants ($M = 91.65\%$, SD = 2.59) [$t_{(44)} = 1.34$, $p = 0.170$].

A one-way MANOVA tested the effect of diagnosis on the exploration of emotional and neutral faces [fixation duration on emotional faces ASD group ($M = 50.56\%$, SD = 5.37) and TD group ($M = 53.96\%$, SD = 5.20); fixation duration on neutral faces ASD group ($M = 39.69\%$, SD = 4.63) and TD group ($M = 37.69\%$, SD = 5.55)] (**Figure 2**). There was a tendency toward a main effect of diagnosis on the combined dependent variables [$F_{(2, 43)} = 2.501$, $p = 0.094$; Wilks' lambda = 0.896; partial $\eta^2 = 0.104$]. Follow-up univariate ANOVA showed that the two groups were statistically different in the total time spent exploring emotional faces [$F_{(1)} = 4.749$, $p = 0.035$; partial $\eta^2 = 0.097$], but not neutral faces [$F_{(1, 44)} = 1.769$, $p = 0.190$; partial $\eta^2 = 0.039$].

Both groups made more fixations to emotional faces than to neutral faces (**Figure 3**). Participants with ASD made significantly more fixations to emotional faces ($M = 165.30$, SD = 37.15) than neutral faces ($M = 136.00$, SD = 38.39) [$t_{(23)} = 4.99$, $p < 0.001$]. The TD group also fixated more on emotional faces ($M = 196.10$, SD = 30.79) than neutral faces ($M = 144.10$, SD = 31.40) [$t_{(21)} = 7.11$, $p < 0.001$]. However, when we compared both groups, the ASD group made significantly less fixations to emotional faces than the TD group [$t_{(44)} = 3.05$, $p = 0.004$]. No between-group difference was detected in the number of fixations to neutral faces [$t_{(df)} = 0.78$, $p = 0.438$].

We did not observe a significant difference [$t_{(23)} = 0.10$, $p = 0.924$] in the first fixation duration between emotional ($M = 0.24$ s, SD = 0.06) and neutral faces ($M = 0.24$ s, SD = 0.06) in the ASD group (**Figure 4**). However, there was a significant difference [$t_{(21)} = 3.44$, $p = 0.003$] in the duration of first fixations between emotional ($M = 0.27$ s, SD = 0.05) and neutral faces ($M = 0.24$ s, SD = 0.05) in the TD group.

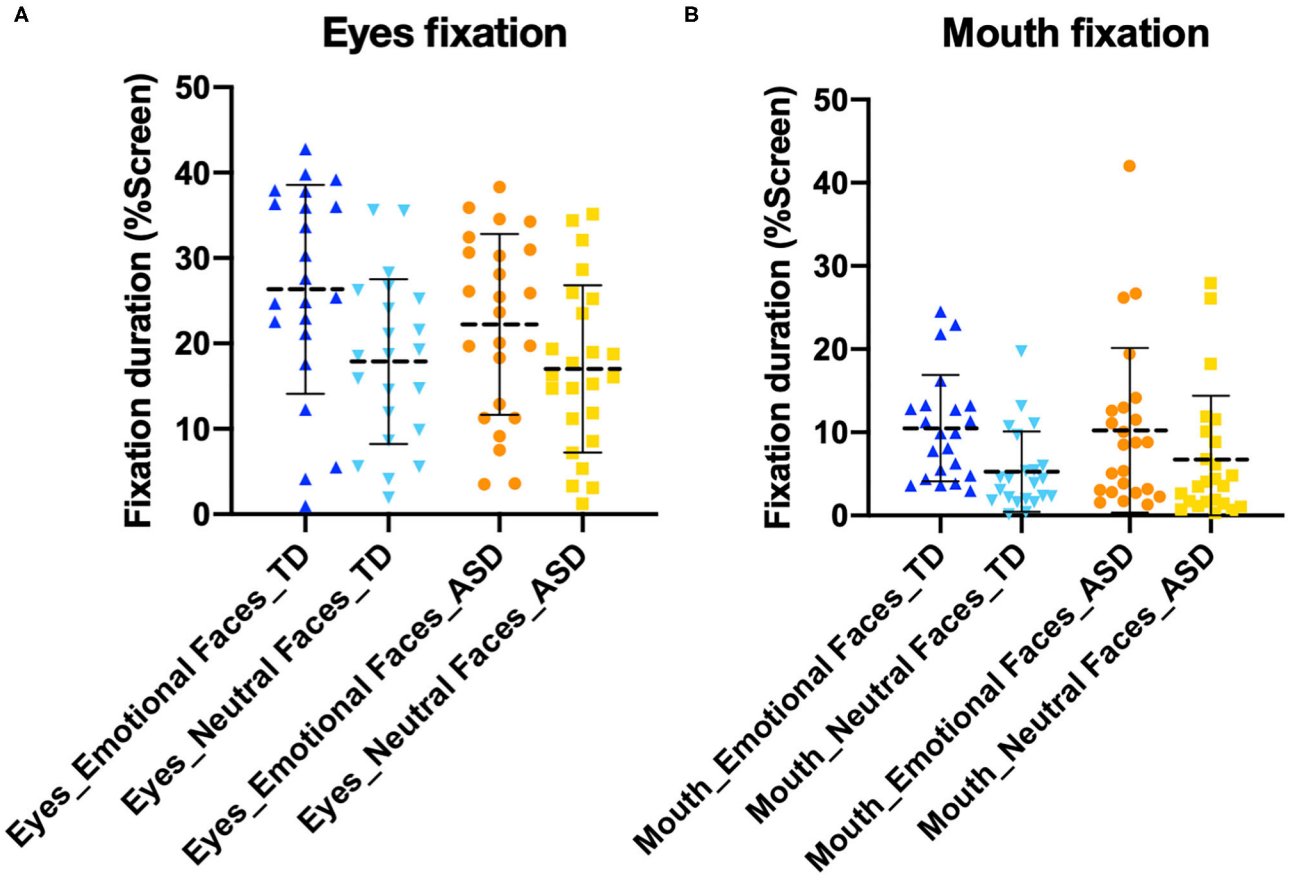

FIGURE 5 | Fixations to **(A)** eyes and **(B)** mouth. There was no difference between the typically developing (TD) and autism spectrum disorder (ASD) groups.

We did not observe an effect of diagnosis on time spent on facial features (**Figure 5**). In other words, we did not observe a significant difference between time spent on the eyes and mouth, between ASD and TD [$F_{(2,\ 43)} = 0.389$, $p = 0.680$]. Concerning the four different emotions, there was no significant difference in time spent on emotions between the ASD and TD groups, nor did we observe an interaction between expression (anger, fear, happiness, and sadness) and diagnosis [$F_{(3,\ 176)} = 0.52$, $p = 0.671$] per a two-way ANOVA (**Figure 6**).

We did not observe any significant correlations between the ADOS Total Severity Score and our eye-tracking measures in the ASD group (all $p \geq 0.105$).

Habituation

We then looked at habituation to faces over the course of the task and found a significant effect of time spent on neutral faces (**Figure 7**). The ASD group spent less time on neutral faces during the first quarter of the task ($M = 42.99\%$, SD $= 7.28$) than during the last quarter ($M = 36.45\%$, SD $= 9.42$) [$t_{(23)} = 3.06$, $p = 0.006$]. The TD group also spent less time on neutral faces during the first quarter of the task ($M = 41.61\%$, SD $= 5.69$) than the last quarter ($M = 34.59\%$, SD $= 8.43$) [$t_{(21)} = 3.71$, $p = 0.001$].

However, no significant effect of time spent on emotional faces was observed in either group of children after having applied a Bonferroni correction (p significant if ≤ 0.025). The ASD group looked slightly less at emotional faces during the first quarter of the task ($M = 49.28\%$, SD $= 8.15$) than the last quarter ($M = 51.89\%$, SD $= 12.19$); however, the difference was not statically significant [$t_{(23)} = 1.05$, $p = 0.306$]. TD children also looked slightly less at emotional faces during the first quarter of the task ($M = 51.56\%$, SD $= 5.67$) than the last quarter ($M = 56.02\%$, SD $= 7.79$), but the difference was not statically significant [$t_{(21)} = 2.25$, $p = 0.035$]. Both groups looked significantly more at the background of the screen behind the faces during the last quarter of the task than the first quarter (ASD group $p = 0.008$; TD group $p < 0.001$).

DISCUSSION

Contrary to expectations, our results are not commensurate with previous studies showing altered orienting to faces in preschoolers with ASD compared with TD preschoolers. Further, we did not observe differences in time spent on the eyes or the mouth between subject groups. As suggested by Falck-Ytter and Von Hofsten in a review of literature, the finding that individuals

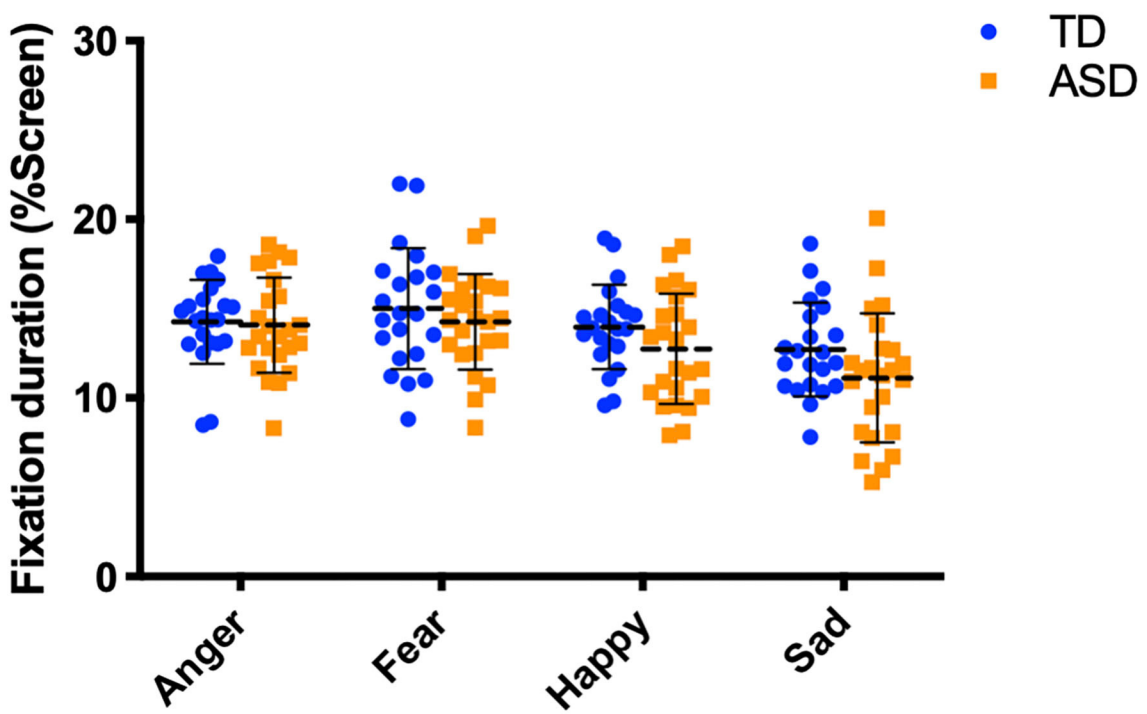

FIGURE 6 | Fixations to the four different emotions. There was no difference between the typically developing (TD) (blue) and autism spectrum disorder (ASD) (orange) groups.

with ASD look less at the eyes and more at the mouth than did TD peers is not consistent between eye-tracking studies of children (49). While it is most frequent among studies based on dynamic stimuli (10, 11), a recent eye-tracking study using dynamic face stimuli and based on large samples of toddlers with ASD, TD, and developmental delay did not show decreased fixations to the eye region in toddlers with autism (50). Moreover, the authors did not observe a correlation between time spent on the eyes and clinical data related to autism severity, language level, or cognitive skills.

In addition, we did not observe a preference pattern between emotional expressions in either participant group. While some studies have observed impairments in emotion recognition and processing in children with ASD (18, 20), to the best of our knowledge, no clear consensus has emerged from the many studies regarding differences in emotion exploration in children with ASD. However, several studies have suggested that "negative" emotions such as fear and anger may be less salient for children with ASD (51–53). For example, a recent eye-tracking study showed that high-functioning children with ASD perceive fear as less intense than their TD peers (52). Moreover, a recent magnetoencephalography study demonstrated differences in electrical activity in children with ASD while looking at happy vs. angry faces, suggesting reduced salience or perhaps an underdeveloped response to anger (51). Finally, an electroencephalography (EEG) study suggested that boys with ASD are less able to detect angry and fearful faces than their TD peers in the absence of group differences on sadness or happiness (53).

Despite a lack of group differences in time spent, we found that our ASD subjects tended to explore emotional faces differently than the TD group. Indeed, ASD participants completed less fixations, as well as shorter first fixations, to emotional faces than TD children, stressing the need for understanding subtle differences in exploration pattern in this population. This may indicate that preschoolers with ASD visually engage less frequently with emotional faces in the absence of a clear difference in the total time spent on the emotional faces, pointing to a somewhat "stickier" pattern of attention. There were no observable intra-group differences in the duration of our ASD group's first fixations on emotional and neutral faces, whereas the duration of first fixations to emotional faces was significantly longer than on neutral faces in the TD group. This could suggest that emotional faces are perceived as less appealing and less salient for children with ASD. This finding is in line with a recent pupillometry study, in which a lack of pupil dilatation was reported in children with ASD while looking at objects, as well as static and dynamic faces (54). The authors attributed this lack of difference to an insensitivity toward event-related pupil dilatation, suggesting an abnormal physiological reaction and reduced arousal to socially salient stimuli in ASD.

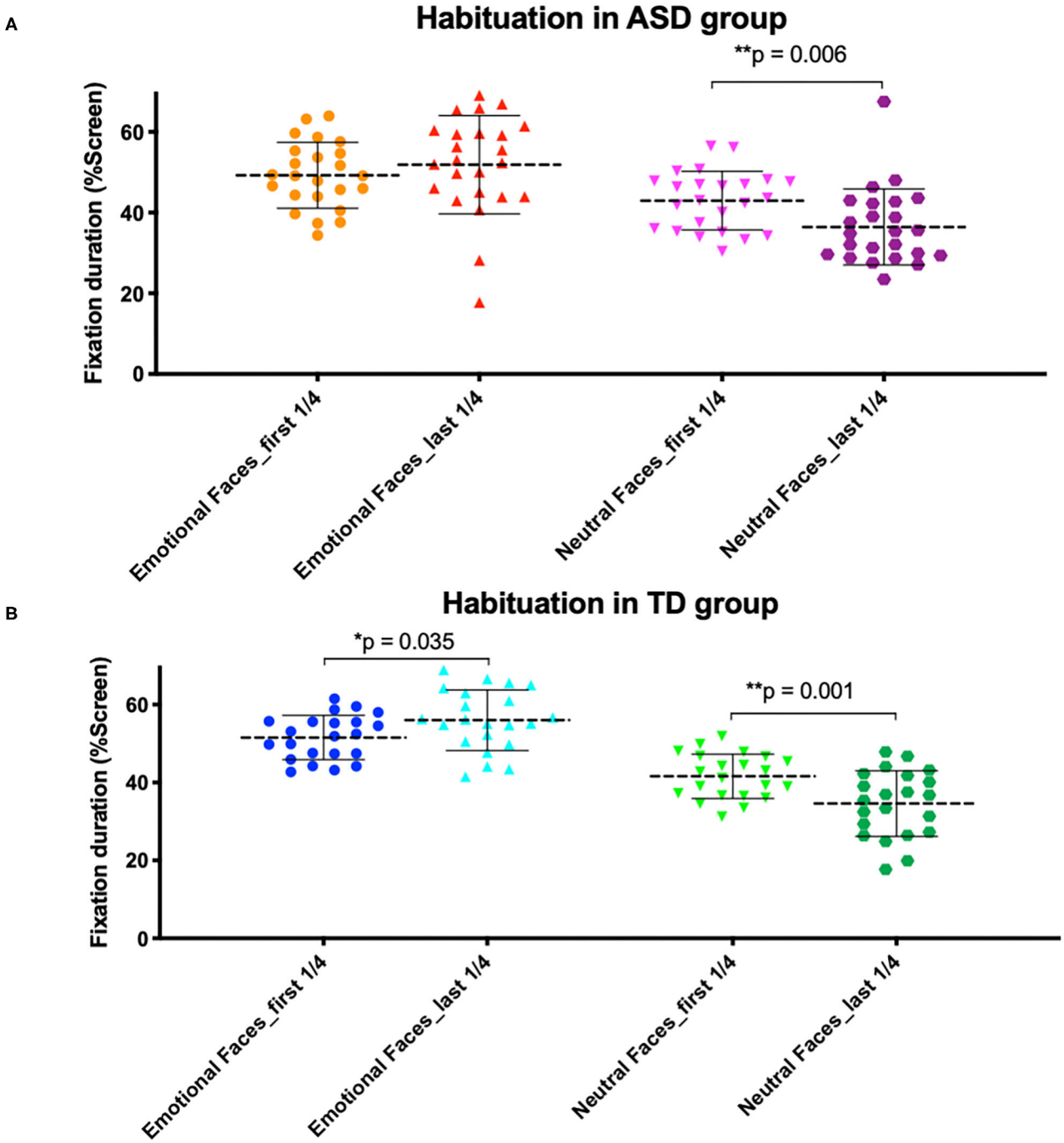

FIGURE 7 | Habituation to emotional and neutral faces in **(A)** autism spectrum disorder (ASD) and **(B)** typically developing (TD) group. **(A)** The ASD group looked less at neutral faces throughout the task. **(B)** The TD group looked less at neutral faces throughout the task but looked more at emotional faces.

Our habituation analysis of looking time over the course of the task revealed that ASD participants' attention to emotional faces does not improve during the task, as expected, despite the novel element of changes in emotional expression between stimuli. In both groups, we found that children attended less to neutral faces over the course of the task, whereas time spent looking at emotional faces did not significantly change between the beginning and end parts of the task though TD children did look slightly more at emotional faces during the last quarter of the task than the first quarter (this difference was not statistically significant). This suggests a somewhat intact habituation response to neutral faces in children with ASD, in the absence of habituation or increased interest in response to emotional faces. This result does not fully support previous

eye-tracking studies observing impaired habituation in children with autism (35, 36); however, it does suggest that children with ASD may be impaired in their sensitivity to novelty.

Deficits in habituation and other attention processes, such as disengagement of attention, are now being studied as potential early markers that may contribute to an atypical developmental cascade resulting in socio-communicative impairments (21–24). According to previous studies and reviews, a primary impairment in attention disengagement could lead to a tendency to fixate on social stimuli early in life, decreased habituation preventing the maintenance of a homeostatic brain state leading to either hyperarousal or hypoarousal, and impaired attention shifting and novelty detection (23, 24). Trouble discriminating socially salient and non-salient stimuli could be the natural consequence, which in turn may contribute to impaired face processing (23). Social cues are then marked as unpleasant rather than rewarding, encouraging the avoidance of social stimuli, decreased social interest, and impaired joint attention and executive control (21–24). This also could lead to restricted and repetitive behaviors, as demonstrated in at-risk children with ASD as a strategy for coping with hyperarousal (21).

Further eye-tracking studies will be necessary to understanding the habituation response in young children with ASD, given the clinical heterogeneity in the ASD population (35) and the need to better understand attention processes that may precede decreased social orienting in at-risk ASD toddlers. Such behavioral markers could guide the development of new diagnostic tools and early interventions that target key behaviors. Hence, understanding the subtleties of altered attention processes in children with ASD could help determine their putative role in the core ASD features.

Limitations

The current study has some limitations. First, the sample size is quite small and, unfortunately, prevented us from separating the ASD group in subgroups based on clinical heterogeneity. The small sample size was due to the relatively long length of the task, and some participants dropped out. The children were excluded from the study because they did not complete enough of the task and did not differ in autism symptom severity from those who were included. However, we cannot guarantee that this did not bias our sample. Our small sample is also related to the fact that we applied very strict study inclusion criteria. Also, we defined habituation differently, by using the difference in time spent on faces during the first quarter of the task compared with the last quarter in order to observe changes over the course of the entire task. Given that the face identities changed between stimuli, the emotional face was not the only novel element, and the neutral face was not identical from trial to trial; however, given our choice of photos, the change in emotional expression was the most striking change.

CONCLUSION

In this eye-tracking study, we explored emotional and neutral face processing. Over the course of 32 stimulus repetitions, we observed the presence of the habituation response to social stimuli in a group of children with ASD aged 6 or younger. We found that children with ASD looked differently at emotional faces than TD children and that emotional faces were less interesting to our participants with ASD than predicted. We also observed a habituation process to neutral faces in children with ASD, in the absence of habituation to or increased interest in emotional faces throughout the task, suggesting a lack of sensitivity to changes in emotional expression. Further eye-tracking studies will be needed to explore attention to social stimuli and to better understand deficits in young children with autism, given the clinical heterogeneity of this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Research Committee, the Commission Centrale d'Ethique de Recherche (CCER) in Geneva, Switzerland. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MF, MS, and BG designed the study. MF and NK contributed to the clinical and eye-tracking data collection. AB analyzed the data and wrote the manuscript. MF, NK, BG, and MS contributed to the interpretation of the results and to the writing of the manuscript. All authors have approved the final manuscript.

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REFERENCES

1. APA. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. Washington, DC: American Psychiatric Pub (2013).
2. Franco F, Itakura S, Pomorska K, Abramowski A, Nikaido K, Dimitriou D. Can children with autism read emotions from the eyes? The eyes test revisited. *Res Dev Disabil*. (2014) 35:1015–26. doi: 10.1016/j.ridd.2014.01.037
3. Chita-Tegmark M. Social attention in ASD: a review and meta-analysis of eye-tracking studies. *Res Dev Disabil*. (2016) 48:79–93. doi: 10.1016/j.ridd.2015.10.011
4. Chevallier C, Kohls G, Troiani V, Brodkin ES, Schultz RT. The social motivation theory of autism. *Trends Cogn Sci*. (2012) 16:231–9. doi: 10.1016/j.tics.2012.02.007
5. Falck-Ytter T, Bölte S, Gredebäck G. Eye tracking in early autism research. *J Neurodev Disord*. (2013) 5:28. doi: 10.1186/1866-1955-5-28
6. Frazier TW, Klingemier EW, Beukemann M, Speer L, Markowitz L, Parikh S, et al. Development of an objective autism risk index using remote eye tracking. *J Am Acad Child Adolesc Psychiatry*. (2016) 55:301–9. doi: 10.1016/j.jaac.2016.01.011
7. Sasson NJ, Elison JT. Eye tracking young children with autism. *J Vis Exp*. (2012) 61:3675. doi: 10.3791/3675
8. Franchini M, Wood de Wilde H, Glaser B, Gentaz E, Eliez S, Schaer M. Brief report: a preference for biological motion predicts a reduction in symptom severity 1 year later in preschoolers with autism spectrum disorders. *Front Psychiatry*. (2016) 7:143. doi: 10.3389/fpsyt.2016.00143
9. Chawarska K, Shic F. Looking but not seeing: atypical visual scanning and recognition of faces in 2 and 4-year-old children with autism spectrum disorder. *J Autism Dev Disord*. (2009) 39:1663–72. doi: 10.1007/s10803-009-0803-7
10. Jones W, Carr K, Klin A. Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-old toddlers with autism spectrum disorder. *Arch Gen Psychiatry*. (2008) 65:946–54. doi: 10.1001/archpsyc.65.8.946
11. Klin A, Jones W, Schultz R, Volkmar F, Cohen D. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Arch Gen Psychiatry*. (2002) 59:809–16. doi: 10.1001/archpsyc.59.9.809
12. Chawarska K, Macari S, Shic F. Decreased spontaneous attention to social scenes in 6-month-old infants later diagnosed with autism spectrum disorders. *Biol Psychiatry*. (2013) 74:195–203. doi: 10.1016/j.biopsych.2012.11.022
13. Jones W, Klin A. Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. *Nature*. (2013) 504:427–31. doi: 10.1038/nature12715
14. Young GS, Merin N, Rogers SJ, Ozonoff S. Gaze behavior and affect at 6 months: predicting clinical outcomes and language development in typically developing infants and infants at risk for autism. *Dev Sci*. (2009) 12:798–814. doi: 10.1111/j.1467-7687.2009.00833.x
15. Chawarska K, Macari S, Shic F. Context modulates attention to social scenes in toddlers with autism. *J Child Psychol Psychiatry Allied Discip*. (2012) 53:903–13. doi: 10.1111/j.1469-7610.2012.02538.x
16. Black MH, Chen NTM, Iyer KK, Lipp OV, Bölte S, Falkmer M, et al. Mechanisms of facial emotion recognition in autism spectrum disorders: insights from eye tracking and electroencephalography. *Neurosci Biobehav Rev*. (2017) 80:488–515. doi: 10.1016/j.neubiorev.2017.06.016
17. Walsh JA, Creighton SE, Rutherford MD. Emotion perception or social cognitive complexity: what drives face processing deficits in autism spectrum disorder? *J Autism Dev Disord*. (2016) 46:615–23. doi: 10.1007/s10803-015-2606-3
18. Xavier J, Vignaud V, Ruggiero R, Bodeau N, Cohen D, Chaby L. A multidimensional approach to the study of emotion recognition in autism spectrum disorders. *Front Psychol*. (2015) 6:1954. doi: 10.3389/fpsyg.2015.01954
19. Jones CRG, Pickles A, Falcaro M, Marsden AJS, Happé F, Scott SK, et al. A multimodal approach to emotion recognition ability in autism spectrum disorders. *J Child Psychol Psychiatry Allied Discip*. (2011) 52:275–285. doi: 10.1111/j.1469-7610.2010.02328.x
20. Lerner MD, McPartland JC, Morris JP. Multimodal emotion processing in autism spectrum disorders: an event-related potential study. *Dev Cogn Neurosci*. (2013) 3:11–21. doi: 10.1016/j.dcn.2012.08.005
21. Baranek GT, Woynaroski TG, Nowell S, Turner-Brown L, DuBay M, Crais ER, et al. Cascading effects of attention disengagement and sensory seeking on social symptoms in a community sample of infants at-risk for a future diagnosis of autism spectrum disorder. *Dev Cogn Neurosci*. (2017) 29:30–40. doi: 10.1016/j.dcn.2017.08.006
22. Green SA, Hernandez L, Tottenham N, Krasileva K, Bookheimer SY, Dapretto M. Neurobiology of sensory overresponsivity in youth with autism spectrum disorders. *JAMA Psychiatry*. (2015) 72:778–86. doi: 10.1001/jamapsychiatry.2015.0737
23. Kaartinen M, Puura K, Himanen S-L, Nevalainen J, Hietanen JK. Autonomic arousal response habituation to social stimuli among children with Asd. *J Autism Dev Disord*. (2016) 46:3688–99. doi: 10.1007/s10803-016-2908-0
24. Keehn B, Müller R-A, Townsend J. Atypical attentional networks and the emergence of autism. *Neurosci Biobehav Rev*. (2013) 37:164–83. doi: 10.1016/j.neubiorev.2012.11.014
25. Elsabbagh M, Fernandes J, Webb SJ, Dawson G, Charman T, Johnson MH, et al. Disengagement of visual attention in infancy is associated with emerging autism in toddlerhood. *Biol Psychiatry*. (2013) 74:189–94. doi: 10.1016/j.biopsych.2012.11.030
26. Kleberg JL, Thorup E, Falck-Ytter T. Reduced visual disengagement but intact phasic alerting in young children with autism. *Autism Res*. (2017) 10:539–45. doi: 10.1002/aur.1675
27. Landry R, Bryson SE. Impaired disengagement of attention in young children with autism. *J Child Psychol Psychiatry Allied Discip*. (2004) 45:1115–22. doi: 10.1111/j.1469-7610.2004.00304.x
28. Sacrey L-AR, Armstrong VL, Bryson SE, Zwaigenbaum L. Impairments to visual disengagement in autism spectrum disorder: a review of experimental studies from infancy to adulthood. *Neurosci Biobehav Rev*. (2014) 47:559–77. doi: 10.1016/j.neubiorev.2014.10.011
29. Schmid S, Wilson DA, Rankin CH. Habituation mechanisms and their importance for cognitive function. *Front Integr Neurosci*. (2015) 8:97. doi: 10.3389/fnint.2014.00097
30. Grill-Spector K, Henson R, Martin A. Repetition and the brain: neural models of stimulus-specific effects. *Trends Cogn Sci*. (2006) 10:14–23. doi: 10.1016/j.tics.2005.11.006
31. Ewbank Michael P, Henson RN, Rowe JB, Stoyanova RS, Calder AJ. Different neural mechanisms within occipitotemporal cortex underlie repetition suppression across same and different-size faces. *Cereb Cortex*. (2013) 23:1073–84. doi: 10.1093/cercor/bhs070
32. Ewbank MP, Pell PJ, Powell TE, von dem Hagen EAH, Baron-Cohen S, Calder AJ. Repetition suppression and memory for faces is reduced in adults with autism spectrum conditions. *Cereb Cortex*. (2017) 27:92–103. doi: 10.1093/cercor/bhw373
33. Kleinhans NM, Johnson LC, Richards T, Mahurin R, Greenson J, Dawson G, et al. Reduced neural habituation in the amygdala and social impairments in autism spectrum disorders. *Am J Psychiatry*. (2009) 166:467–75. doi: 10.1176/appi.ajp.2008.07101681
34. Swartz JR, Wiggins JL, Carrasco M, Lord C, Monk CS. Amygdala habituation and prefrontal functional connectivity in youth with autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry*. (2013) 52:84–93. doi: 10.1016/j.jaac.2012.10.012
35. Vivanti G, Hocking DR, Fanning PAJ, Uljarevic M, Postorino V, Mazzone L, et al. Attention to novelty versus repetition: contrasting habituation profiles in Autism and Williams syndrome. *Dev Cogn Neurosci*. (2017) 29:54–60. doi: 10.1016/j.dcn.2017.01.006
36. Webb SJ, Jones EJH, Merkle K, Namkung J, Toth K, Greenson J, et al. Toddlers with elevated autism symptoms show slowed habituation to faces. *Child Neuropsychol*. (2010) 16:255–78. doi: 10.1080/09297041003601454
37. Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. Behavioral manifestations of autism in the first year of life. *Int J Dev Neurosci*. (2005) 23:143–52. doi: 10.1016/j.ijdevneu.2004.05.001
38. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord*. (2000) 30:205–23. doi: 10.1023/A:1005592401947

39. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop SL. *Autism Diagnostic Observation Schedule (ADOS-2)*. 2nd ed. Los Angeles, CA: Western Psychological Services (2012).
40. Gotham K, Pickles A, Lord C. Standardizing ADOS scores for a measure of severity in autism spectrum disorders. *J Autism DevDisord*. (2009) 39:693–705. doi: 10.1007/s10803-008-0674-3
41. Robain F, Franchini M, Kojovic N, Wood de Wilde H, Schaer M. Predictors of treatment outcome in preschoolers with autism spectrum disorder: an observational study in the greater Geneva Area, Switzerland. *J Autism Dev Disord*. (2020) 50:3815–30. doi: 10.1007/s10803-020-04430-6
42. Kojovic N, Ben Hadid L, Franchini M, Schaer M. Sensory processing issues and their association with social difficulties in children with autism spectrum disorders. *J Clin Med*. (2019) 8:1508. doi: 10.3390/jcm8101508
43. Howlin P, Savage S, Moss P, Tempier A, Rutter M. Cognitive and language skills in adults with autism: a 40-year follow-up. *J Child Psychol Psychiatry*. (2014) 55:49–58. doi: 10.1111/jcpp.12115
44. Park SE, Demakis GJ. Wechsler preschool and primary scale of intelligence. In Zeigler-Hill V, Shackelford TK, editors. *Encyclopedia of Personality and Individual Differences*. Cham: Springer International Publishing (2017). p. 1–4.
45. Mullen EM. *Mullen Scales of Early Learning Manual*. Circle Pines, MN: American Guidance Service Inc. (1995).
46. Schopler E, Lansing M, Reichler R, Marcus L. *Psychoeducational Profile: Third edition (PEP-3)*. Austin, TX: Pro-Ed (2005).
47. Langner O, Dotsch R, Bijlstra G, Wigboldus D, Hawk S, van Knippenberg A. Presentation and validation of the Radboud Face Database. *Cogn Emotion*. (2010) 24:1377–88. doi: 10.1080/02699930903485076
48. Olsen A. *The Tobii I-VT Fixation Filter*. (2012). Available online at: https://stemedhub.org/resources/2173/download/Tobii_WhitePaper_TobiiIVTFixationFilter.pdf (accessed August 20, 2020).
49. Falck-Ytter T, von Hofsten C. How special is social looking in ASD: a review. *Prog Brain Res*. (2011) 189:209–22. doi: 10.1016/B978-0-444-53884-0.00026-9
50. Kwon M-K, Moore A, Barnes CC, Cha D, Pierce K. Typical levels of eye-region fixation in toddlers with autism spectrum disorder across multiple contexts. *J Am Acad Child Adolesc Psychiatry*. (2019) 58:1004–15. doi: 10.1016/j.jaac.2018.12.011
51. Leung RC, Pang EW, Brian JA, Taylor MJ. Happy and angry faces elicit atypical neural activation in children with autism spectrum disorder. *Biol Psychiatry*. (2019) 4:1021–30. doi: 10.1016/j.bpsc.2019.03.013
52. Tsang V. Eye-tracking study on facial emotion recognition tasks in individuals with high-functioning autism spectrum disorders. *Autism*. (2018) 22:161–70. doi: 10.1177/1362361316667830
53. Van der Donck S, Dzhelyova M, Vettori S, Mahdi SS, Claes P, Steyaert J, et al. Rapid neural categorization of angry and fearful faces is specifically impaired in boys with autism spectrum disorder. *J Child Psychol Psychiatry Allied Discip*. (2020) 61:1019–29. doi: 10.1111/jcpp.13201
54. Aguillon-Hernandez N, Mofid Y, Latinus M, Roché L, Bufo MA, Lemaire M, et al. The pupil: a window on social automatic processing in autism spectrum disorder children. *J Child Psychol Psychiatry Allied Discip*. (2019) 61:768–78. doi: 10.1111/jcpp.13170

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PERSPECTIVE
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Pattern Unifies Autism

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Autism is a highly heterogeneous condition, genetically and phenotypically. This diversity of causation and presentation has impeded its definition, recognition, assessment, and treatment. Current diagnostic criteria for autism involve two domains, restricted interests and repetitive behavior (RRBs) and social deficits, whose relationship remains unclear. I suggest that the large suite of traits associated with autism can be usefully conceptualized under the single rubric of "pattern," a term that connects autism with basic brain and cognitive functions and structures its phenotypes within a single theoretical framework. Autism thus involves increases and enhancements to pattern perception, pattern recognition, pattern maintenance, pattern generation, pattern processing, and pattern seeking. RRBs result from increased and imbalanced pattern-related perception and cognition, and social alterations result in part from the usual lack of clear pattern in social interactions, combined with the interference of RRBs with social development. This framework has strong implications for assessment of social and non-social autism-related traits, personalized therapy, and priorities for research.

Keywords: autism, repetitive behavior, systemizing, social cognition, pattern, psychosis

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INTRODUCTION

The development of assessment tools and therapies for autism requires increased understanding of its nature and causes, as a disorder and in each affected individual. Kanner (1) considered autism as a syndrome, that can be defined as a constellation of phenotypic traits and differences from typical individuals, that show some tendency to be found together within individuals, or that when found together cause psychological differences or problems. Each individual diagnosed with autism thus exhibits some subset of its many associated traits, each to some degree.

The constellation of autistic traits is divided by DSM5 into two domains, (a) social cognition, communication and behavior and (b) restricted interests and repetitive behaviors (RRBs). RRBs include stereotyped or repetitive actions, ritualized behavior, extreme adherence to routines, insistence on sameness, restricted interests, and alterations in reactivity to, and interest in, sensory stimuli. Under the DSM5 rubric, diagnoses of autism are categorical, and continuous variation in its constituent pheotypes is accounted for using estimates of severity. However, the relative roles of categorical and continuous variation in characterizing autism remain matters of intense inquiry (2–4).

The two domains of sociality and RRBs are weakly to moderately associated with one another (5, 6), and the causes of their connections remain unclear. Links between RRBs and sociality may thus involve common causes of both, one causing the other, reciprocal causation, or little to no causation at all. Developing and testing theory for the relationship of RRBs with sociality is important for understanding autism. Such theory must, moreover,

be developed in the context of what adaptive phenotypes have become altered in autism to become problematic (7). The adaptive significance of social behavior and communication are evident, given that humans exhibit large, diverse brain regions subserving social cognition and tend to be highly socially interactive. By contrast, determining what adaptive traits have changed to generate RRBs, which include a tremendous diversity of phenotypes from self-stimulation, to stereotypy, to narrow interests in parts of objects or STEM disciplines and to savant skills, is more challenging. Is there any conceptual umbrella that can help to unify the diverse non-social, as well as social, phenotypes of autism, in the context of alterations to adaptive cognitive phenotypes?

At its most basic level, the function of the brain is to perceive and recognize patterns, transform them into information held in neuronal systems, process the information, and, when motivated to do so, act upon it in coherent ways (8, 9). Pattern perception, recognition, maintenance, processing, seeking, and generation thus represent the simplest and most general of neurological and cognitive functions, which in humans have evolved extreme complexity via expansion and specialization of neural subsystems.

In this short Perspective article, I propose, evaluate and apply the hypothesis that the dimensions of the concept of pattern can unify diverse autism phenotypes, across developmental, neurological, and psychological levels of analysis. This article thus presents the core of a unified framework for understanding autism in this way, set in the context of relevant previous theory.

I first describe what is meant here by pattern, and how this concept relates to previous theory for autism. Second, I explain a set of seven major dimensions of autism that can be conceptualized in terms of pattern and non-pattern, and provide evidence for the meaningfulness of each. Finally, I discuss implications for assessment of social and non-social cognition in autism, as well as for therapies and research.

PATTERN

Pattern is defined here as spatially or temporally repeated configuration, with recurring, ordered, or otherwise predictable characteristics, and discernable interrelationships of components. This conceptualization of pattern is closely allied to the presence of information, which can be considered from a variety of perspectives including sensory input, entropy, and predictability. Pattern connects especially directly with intelligence, which centrally involves the generation and inference of informational patterns. In this context, convergent evidence from previous work (7) indicates that autism can be characterized as a "disorder of high intelligence," whereby it involves especially-high levels of the genetic, neurological and psychological components of intelligence, but also imbalances between its components, that mediate the development and expression of autistic phenotypes. Pattern is more general than intelligence, because it encompasses a broader array of perceptual, cognitive, and behavioral phenomena.

The concept of pattern is related to the concept of systemizing as developed by Baron-Cohen (10). Systemizing has been defined as the drive to observe, analyze or construct rule-based systems that function in an "if-then" manner, and it is clearly elevated in individuals with autism (10). As such, systemizing naturally encompasses aspects of pattern seeking, pattern processing, and pattern recognition, but not pattern perception, pattern maintenance, or pattern generation. It thus does not, in a clear or direct way, help to explicate the presence and forms of many important autism-related traits, including stereotypies, insistence on sameness, self-stimulation, lining up of objects, highly-fixated interests, or exceptional memory, realistic art or musical skills in savants. Given its "if-then," rule-based structure, systemizing may, most generally, be considered as one component of high, human-evolved intelligence that is elevated in autism, leading to a cognitive imbalance characteristic of this condition.

Pattern Perception

Pattern perception is based upon sensory perception. Sensory perception, measured as sensory reactivity or acuity, is often increased in autism, across different modalities; however, reactivity can also be decreased, leading to reduced stimulus responsiveness (11, 12). Several influential theories of autism, "enhanced perceptual function" theory (13) and the "intense world" theory (14), explain how increases in perceptual functions in autism can lead to some of its central phenotypes. As described in accounts from persons with autism (15), increased sensory sensitivity and acuity commonly result in sensory overload: too much incoming unpatterned and unfiltered information. Sensory overload is dealt with in several ways by individuals with autism: (1) reducing perception of sensory input as much as possible, resulting in sensory "hypo-reactivity" from an observer's perspective, or (2) self-stimulation or other simple repetitive behavior, or insistence on sameness, [e.g., (16, 17)] to calm the autonomic system by self-generating regularity; or (3) increases in focused attention on particular patterned stimuli, which leads to blocking out of other sensory inputs [e.g., (18, 19)]. Liss et al. (20) reported, for example, that about 40% of a large sample of autistic subjects showed a clear profile of high sensory sensitivity coupled with highly over-focused attention. Taken together, these findings can help to explain the apparently-paradoxical observations of especially high as well as low sensory sensitivities in autism, in the context of a pattern-based perspective.

Given that one of the primary functions of the brain is to extract information from sensory stimuli (8), enhanced sensory acuity, and increased attention to detail, may also increase the potential to obtain information from the world regarding patterns and thus may facilitate systemizing as well as high intelligence (7, 21). Sensory sensitivity, however, shows no evidence of association with systemizing among children with or without autism, but instead demonstreates a negative correlation with empathizing (22), suggesting that it may interfere with the acquisition of social abilities. By contrast, high sensory acuity has been positively associated with measures of intelligence across many studies tracing back to Galton and Spearman [reviewed in (7)]. The reasons for these associations remain unclear, but they strongly support the hypothesis that autism encompasses

correlates, and imbalances, of high intelligence and highly-patterned perception and cognition.

Pattern Recognition

Pattern recognition involves finding a particular visual-spatial pattern in a broader scene (as in the embedded figures test, EFT), and inferring what pattern comes next in a series of systematically changing visual forms (as in Raven's Progressive Matrices, RPM). Individuals with autism tend to show absolutely or relatively enhanced abilities in both of these tests, compared with control individuals, as well as in other tests and metrics of pattern recognition such as visual search [e.g., (23); reviewed in (7)]. Performance on both the EFT and RPM is positively correlated with general intelligence, and indeed the RPM serves as a metric of fluid intelligence (ability to think logically, identify patterns, and solve problems independently of acquired knowledge), which is enhanced in autism relative to crystallized intelligence (ability to solve problems using acquired knowledge) (24, 25). The recognition of repeating patterns in stimuli has also been proposed as a primary basis for forms of talent and savantism in autism, such as calendar calculating, mathematics and other specialized skills (21, 26).

Might enhanced pattern recognition be causally linked to RRBs, or sociality, in autism? Better performance on the EFT has traditionally been considered to reflect "weak central coherence," which can be construed as a local pattern processing bias and relative inability to see the "big picture" (27). It can also be seen to indicate high sensory acuity combined with stronger attentional focus and working memory, both of which are associated with high intelligence (7). In principle, local processing biases and sharper attentional focus can synergistically contribute to intense, narrow interests as found in some RRBs, because higher-level structures ("wholes"), which are not necessarily repeated, are not perceived (27, 28). As such, a focus on pattern can also help to explain increased local compared to global information processing in autism, as a cognitive imbalance with both benefits and costs in different psychological contexts.

Pattern Maintenance

Insistence on sameness represents a uniquely autistic trait. This phenotype can be described in terms of the temporal maintenance of current patterns in the environment. Insistence on sameness and associated ritualistic behaviors are developmentally typical for children aged about 2–4 years [see (29)], but in autism they extend into much later ages. The intensity and developmental persistence of insistence on sameness appear to be mediated by some combination of high sensory sensitivities and high attention to details in the environment, as evidence by high reactivity on ERP oddball tasks of novelty detection [e.g., (30)], higher mismatch negativity (31), and reduced levels of inattentional blindness (32). Individuals with autism also tend to score lower than controls on the temperament trait of novelty-seeking (33). Finally, pattern maintenance in autism may also encompass overselective attention (18, 34), which serves to actively maintain sameness. Pattern maintenance can thus describe a range of autism-related traits, especially ones that are difficult to explain from other theoretical perspectives.

Pattern Generation

Pattern generation in its overt form represents repetitive, stereotypic behaviors and self stimulation. These behaviors are postulated to help individuals with autism to cope with strong and uncontrolled, unpredictable sensory inputs, and accompanying stress, by producing a pattern that can mask or override them, or calm the autonomic nervous system [e.g., (17)], as noted above. Pattern generation may also be covert and cognitive, whereby individuals with autism engage in repetitive thought patterns, reflected for example in the recent finding of higher organizational activity in the default mode, the brain system that underlies stimulus-independent thought, in autistic individuals (35).

The nature of pattern generation is notably associated with overall intelligence in individuals with autism, in that stereotyped behaviors such as motor mannerisms are found more commonly in autistic individuals of lower intelligence, while more-complex ritualized behaviors are more characteristic of autistic individuals with higher intelligence (36). This variation appears to reflect the complexity of neurologically-based patterns that can be sustained under different levels of general intelligence, and different levels of its imbalance in components, such as sensory acuity in relation to capacity for logic and self-regulated executive functions.

Pattern Seeking

Pattern seeking involves cognitive drive to find and confirm patterns in the external environment. This phenomenon is closely allied to systemizing, though it also involves higher explanatory drive in non-social problem-solving in autism (37), and higher, albeit imbalanced, intelligence (7), given that systemizing is not positively associated with intelligence [e.g., (38)]. Enhanced pattern seeking in autism is also manifest in, for example: (a) pursuits in highly-organized collecting and related aspects of systemizing and (b) the associations of the autism spectrum with interests and skills in STEM disciplines [e.g., (10, 39)]. Pattern seeking and autism in the context of STEM disciplines are also closely related to high intelligence, and imbalances in intelligence, given the especially high intelligence reported among individuals in these disciplines [see (7)].

Pattern Processing

Pattern processing is logical, organized transformation of patterned information that involves problem solving, decoding, or other mental manipulation of cause-effect relationships. Evidence for enhancement of this cognitive domain in autism includes (a) hyperlexic decoding of written words and other examples of veridical mapping (40), (b) a more deliberative than intuitive cognitive style, by the cognitive reflections test or jumping to conclusions protocols (41, 42), (c) increased logical consistency (43, 44), (d) less influence from prior beliefs and experiences in conditional reasoning tasks (45), (e) better syllogistic reasoning skills (46), and (f) enhanced performance in the Iowa Gambling Task compared to controls (47). Pattern processing also represents a core component of intelligence and

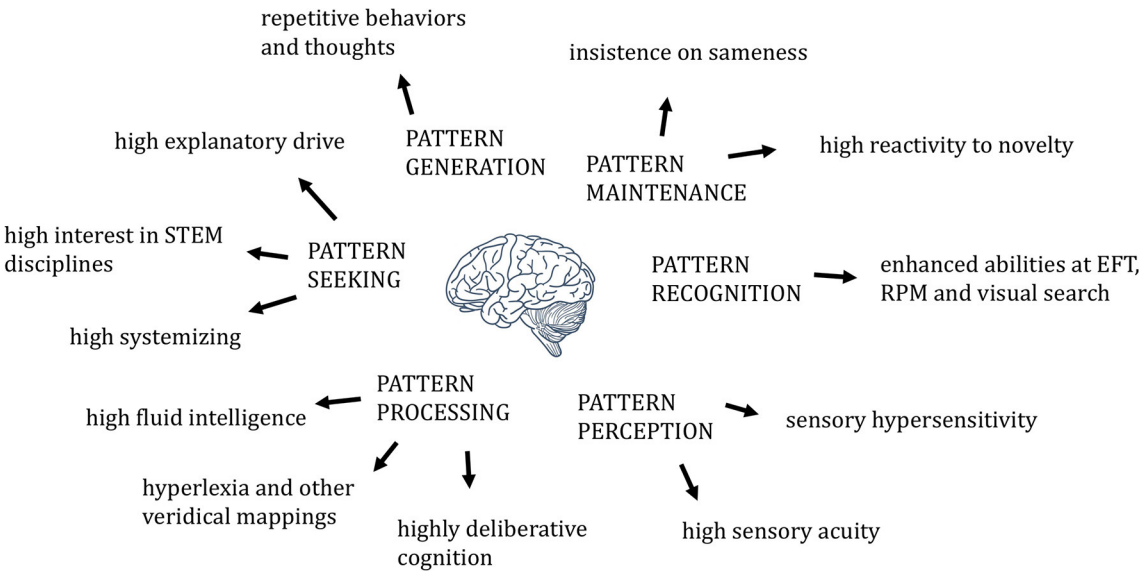

FIGURE 1 | The six non-social dimensions of pattern, in relation to relevant autism-associated phenotypes.

the task-positive network, that mediates between information input and decision-making (7).

The six non-social dimensions of pattern in autism described above are related to one another in their links with neural-system models of intelligence, especially the Parietal-Frontal Integration Theory (P-FIT) [see (7)]. Thus, pattern perception and generation are associated with Sensory Processing in the P-FIT model, pattern recognition and maintenance are associated with Abstraction and Generalization of sensory information in the model, and pattern seeking and processing are associated with Hypothesis Testing and Decision Making. These connections provide a hypothesis for an explicit neural basis to pattern in autism, grounded in the sequential processes by which the human brain takes in, processes, and acts upon information.

Non-pattern Avoidance

The considerations described above show that virtually all non-social autism-related traits can be conceptualized in terms of relative increases and imbalances in pattern perception, recognition, maintenance, generation, seeking, and processing. A simple corollary of these observation is that non-pattern should be avoided. Social interaction and cognition exhibit low levels of predictable pattern because they result, in large part, from idiosyncracies in the minds of others. These are intrinsically not computable or generalizable except in weakly-probablistic ways, being dependent on emotions that may not even be perceived by the actors themselves. These considerations do not deny the existence of social patterns, but note that they involve brain systems that are temporally incompatible with non-social ones (48) as well as being less predictable.

How, then, might RRBs and patterned cognition be related to sociality? A suite of evidence indicates that social skills, empathizing, or verbal skills are inversely related to (a) sensory sensitivity (22), (b) visual spatial abilities (49), (c) systemizing (50), (d) EFT scores (51–53), (e) RPM scores (54), (f) visual search skills (55, 56), and (g) mathematical ability (57). These findings suggest that pattern-related cognition, as a phenotype that is broadly and deeply increased or enhanced in autism, may pre-empt, preclude or trade off with phenotypes that are absent or reduced: social skills and interests. For assessment and therapy, the important questions to address involves if and how this occurs, and what to do about it.

DISCUSSION

The human brain is an engine for pattern perception, recognition, maintenance, generation, seeking, and processing. Brains of individuals with autism show evidence of increases or enhancements in each of these processes (**Figure 1**), though only in some subset of the six for any given individual with autistic traits. Such imbalances may, like imbalances in components of intelligence more generally (7), favor the development of what we call autism.

The usefulness of the pattern-centric framework for autism described in this Perspective is conceptual unity, which provides guidance toward ways to better study its causes, ways to better assess individuals with autistic traits, and ways to develop better treatments. A focus on the domains of pattern also connects more directly with specific neurological structures and functions than do other conceptual models [e.g., (7)], and can thus help to encompass the wide heterogeneity among autistic individuals. For example, convergent evidence suggests that autism is associated with increased hippocampus-mediated pattern separation, which may help to explain aspects of sensory

sensitivity and pattern recognition ability, with direct impacts on regulation of social-emotional behavior in some autistic individuals (58–60).

The main upshot of these inferences is that for individuals with autism, social cognition cannot be thoroughly or properly assessed without consideration of the structure of non-social cognition. Thus, far, such assessment is mainly limited to analysis of sensory symptoms, stereotypies, and systemizing, without a coherent analytic framework for linking them to other traits, to each other, or to social and typical cognition. In principle, the non-social, pattern-related phenotypes of autism should connect with the social ones, through pre-emption, biasing, tradeoffs, and other forms of association.

Under the framework described here, and given some understanding of how the domains of pattern are altered in individuals with autism, therapies can develop in one of two main ways: (a) patterning of sociality and (b) socializing of patterns.

Patterning of sociality involves attempts to make social interactions more understandable and predictable, by treating other individuals as pattern-driven beings. This approach can be called "systemizing" of sociality (61), whereby animate beings are "deanimated" into causal, if-then patterns as best possible. This is an intellectual, reverse-engineering process, and is thus only likely to work well in individuals with autism of relatively high general intelligence.

Socializing of patterns involves working from inanimate to animate, via the incorporation of metarepresentation, imagination and novelty into the highly-patterned cognition elements of individuals with autism [e.g., (62)]. "Things" are thus transformed into forms and components of "people." This approach involves the overlay of imaginative non-pattern onto patterned elements of cognition and behavior, to move them in the direction of typicality and toward completion of typical development (29). Given the extensive evidence of opposite cognitive phenotypes in autism compared to psychosis and schizophrenia (63), this direction is also the direction of non-pathological positive schizotypy, which can provide guidance as to what specific traits to encourage, such as imagination, animation, novelty-seeking, and openness. The nature of such therapies should take account of the non-social, patterned cognitive system of each particular individual with autism, to understand how they fit with the domains of pattern described above.

Kanner (1) discussed non-social autistic traits in great detail, and intimated their links with extreme autistic aloneness. However, he never mentioned social deficits *per se*, which appear to be the main emphasis of autism research at present. A return to focus on pattern and non-social cognition in autism, in the context of their links to sociality, should lead to useful insights.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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REFERENCES

1. Kanner L. Autistic disturbances of affective contact. *Nerv. Child.* (1943) 2:217–50.
2. Xavier J, Bursztejn C, Stiskin R, Canitano R, Cohen D. Autism spectrum disorders: a developmental and dimensional approach toward a tailored therapeutic program. *Res. Autism Spectr. Disord.* (2015) 18:21–33. doi: 10.1016/j.rasd.2015.06.011
3. Lai MC, Lombardo MV, Chakrabarti B, Baron-Cohen S. Subgrouping the autism "Spectrum": reflections on DSM-5. *PLoS Biol.* (2013) 11:e1001544. doi: 10.1371/journal.pbio.1001544
4. Mottron L, Bzdok D. Autism spectrum heterogeneity: fact or artifact? *Mol. Psychiatry.* (2020) 25:3178–85. doi: 10.1038/s41380-020-0748-y
5. Mandy WP, Skuse DH. Research review: what is the association between the social-communication element of autism and repetitive interests, behaviours and activities? *J. Child Psychol. Psychiatry.* (2008) 49:795–808. doi: 10.1111/j.1469-7610.2008.01911.x
6. Robinson EB, Koenen KC, McCormick MC, Munir K, Hallett V, Happé F, et al. A multivariate twin study of autistic traits in 12-year-olds: testing the fractionable autism triad hypothesis. *Behav. Genet.* (2012) 42:245–55. doi: 10.1007/s10519-011-9500-3
7. Crespi BJ. Autism as a disorder of high intelligence. *Front. Neurosci.* (2016) 10:300. doi: 10.3389/fnins.2016.00300
8. Kurzweil R. *How to Create a Mind: The Secret of Human Thought Revealed*. London: Penguin. (2013). p. 352.
9. Mattson MP. Superior pattern processing is the essence of the evolved human brain. *Front. Neurosci.* (2014) 8:265. doi: 10.3389/fnins.2014.00265
10. Baron-Cohen S. Autism and the empathizing-systemizing (ES) theory. In: Zelazo PD, Chandler M, Crone E, editors. *Developmental Social Cognitive Neuroscience*. London: Psychology Press (2016). p. 139–52.
11. Baron-Cohen S, Lombardo MV. Autism and talent: the cognitive and neural basis of systemizing. *Dialog. Clin. Neurosci.* (2017) 19:345. doi: 10.31887/DCNS.2017.19.4/sbaroncohen
12. Robertson CE, Baron-Cohen S. Sensory perception in autism. *Nat. Rev. Neurosci.* (2017) 18:671. doi: 10.1038/nrn.2017.112
13. Mottron L, Dawson M, Soulieres I, Hubert B, Burack J. Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *J. Autism Dev. Disord.* (2006) 36:27–43. doi: 10.1007/s10803-005-0040-7
14. Markram K, Markram H. The intense world theory–a unifying theory of the neurobiology of autism. *Front. Hum. Neurosci.* (2010) 4:224. doi: 10.3389/fnhum.2010.00224
15. Chamak B, Bonniau B, Jaunay E, Cohen D. What can we learn about autism from autistic persons? *Psychother. Psychosom.* (2008) 77:271–79. doi: 10.1159/000140086
16. Black KR, Stevenson RA, Segers M, Ncube BL, Sun SZ, Philipp-Muller A, et al. Linking anxiety and insistence on sameness in autistic children: the role of sensory hypersensitivity. *J. Autism Dev. Disord.* (2017) 47:2459–70. doi: 10.1007/s10803-017-3161-x

17. Hirstein W, Iversen P, Ramachandran VS. Autonomic responses of autistic children to people and objects. *Proc. R. Soc. Lond. B Biol. Sci.* (2001) 268:1883–8. doi: 10.1098/rspb.2001.1724
18. Ploog BO. Stimulus overselectivity four decades later: a review of the literature and its implications for current research in autism spectrum disorder. *J. Autism Dev. Disord.* (2010) 40:1332–49. doi: 10.1007/s10803-010-0990-2
19. Baranek GT, Little LM, Parham LD, Ausderau KK, Sabatos-DeVito MG. Sensory features in autism spectrum disorders. In: Volkmar FR, Paul R, Rogers SJ, Pelphrey KA, editors. *Handbook of Autism and Pervasive Developmental Disorders, Volume 1: Diagnosis, Development, and Brain Mechanisms*. *4th ed*. New York, NY: Wiley (2014). p. 378–408.
20. Liss M, Saulnier C, Fein D, Kinsbourne M. Sensory and attention abnormalities in autistic spectrum disorders. *Autism*. (2006) 10:155–72. doi: 10.1177/1362361306062021
21. Baron-Cohen S, Ashwin E, Ashwin C, Tavassoli T, Chakrabarti B. Talent in autism: hyper-systemizing, hyper-attention to detail and sensory hypersensitivity. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* (2009) 364:1377–83. doi: 10.1098/rstb.2008.0337
22. Tavassoli T, Miller LJ, Schoen SA, Brout JJ, Sullivan J, Baron-Cohen S. Sensory reactivity, empathizing and systemizing in autism spectrum conditions and sensory processing disorder. *Dev. Cogn. Neurosci.* (2018) 29:72–7. doi: 10.1016/j.dcn.2017.05.005
23. Gliga T, Bedford R, Charman T, Johnson MH, Baron-Cohen S, Bolton P, et al. Enhanced visual search in infancy predicts emerging autism symptoms. *Curr. Biol.* (2015) 25:1727–30. doi: 10.1016/j.cub.2015.05.011
24. Dawson M, Soulières I, Gernsbacher MA, Mottron L. The level and nature of autistic intelligence. *Psychol. Sci.* (2007) 18:657–62. doi: 10.1111/j.1467-9280.2007.01954.x
25. Hayashi M, Kato M, Igarashi K, Kashima H. Superior fluid intelligence in children with Asperger's disorder. *Brain Cogn.* (2008) 66:306–10. doi: 10.1016/j.bandc.2007.09.008
26. Mottron L, Dawson M, Soulières I. Enhanced perception in savant syndrome: patterns, structure and creativity. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* (2009) 364:1385–91. doi: 10.1098/rstb.2008.0333
27. Happé F. The weak central coherence account of autism. In: Volkmar FR, Paul R, Klin A, Cohen D, editors. *Handbook of Autism and Pervasive Developmental Disorders, Volume 1: Diagnosis, Development, and Brain Mechanisms*. 3rd ed. New York, NY: Wiley (2005). p. 640–9. doi: 10.1002/9780470939345.ch24
28. Crespi BJ. The psychiatry of imagination. In: Abraham A, editor. *The Cambridge Handbook of the Imagination*. Cambridge: Cambridge University Press (2020). doi: 10.1017/9781108580298.045
29. Crespi B. Developmental heterochrony and the evolution of autistic perception, cognition and behavior. *BMC Med.* (2013) 11:119. doi: 10.1186/1741-7015-11-119
30. Gomot M, Belmonte MK, Bullmore ET, Bernard FA, Baron-Cohen S. Brain hyper-reactivity to auditory novel targets in children with high-functioning autism. *Brain*. (2008) 131:2479–88. doi: 10.1093/brain/awn172
31. Orekhova EV, Stroganova TA. Arousal and attention re-orienting in autism spectrum disorders: evidence from auditory event-related potentials. *Front. Hum. Neurosci.* (2014) 8:34. doi: 10.3389/fnhum.2014.00034
32. Swettenham J, Remington A, Murphy P, Feuerstein M, Grim K, Lavie N. Seeing the unseen: autism involves reduced susceptibility to inattentional blindness. *Neuropsychology.* (2014) 28:563. doi: 10.1037/neu0000042
33. Anckarsäter H, Stahlberg O, Larson T, Hakansson C, Jutblad SB, Niklasson L, et al. The impact of ADHD and autism spectrum disorders on temperament, character, and personality development. *Am. J. Psychiatry*. (2006) 163:1239–44. doi: 10.1176/ajp.2006.163.7.1239
34. Reed P, McCarthy J. Cross-modal attention-switching is impaired in autism spectrum disorders. *J. Autism Dev. Disord.* (2012) 42:947–53. doi: 10.1007/s10803-011-1324-8
35. Pérez Velázquez JL, Galán RF. Information gain in the brain's resting state: a new perspective on autism. *Front. Neuroinform*. (2013) 7:37. doi: 10.3389/fninf.2013.00037
36. Richler J, Bishop SL, Kleinke JR, Lord C. Restricted and repetitive behaviors in young children with autism spectrum disorders. *J. Autism Dev. Disord.* (2007) 37:73–85. doi: 10.1007/s10803-006-0332-6
37. Rutherford MD, Subiaul F. Children with autism spectrum disorder have an exceptional explanatory drive. *Autism*. (2016) 20:744–53. doi: 10.1177/1362361315605973
38. Ling J, Burton TC, Salt JL, Muncer SJ. Psychometric analysis of the systemising quotient (SQ) scale. *Br. J. Psychol.* (2009) 100:539–52. doi: 10.1348/000712608X368261
39. Wei X, Jennifer WY, Shattuck P, McCracken M, Blackorby J. Science, technology, engineering, and mathematics (STEM) participation among college students with an autism spectrum disorder. *J. Autism Dev. Disord.* (2013) 43:1539–46. doi: 10.1007/s10803-012-1700-z
40. Mottron L, Bouvet L, Bonnel A, Samson F, Burack JA, Dawson M, Heaton P. Veridical mapping in the development of exceptional autistic abilities. *Neurosci. Biobehav. Rev.* (2013) 37:209–28. doi: 10.1016/j.neubiorev.2012.11.016
41. Brosnan M, Chapman E, Ashwin C. Adolescents with autism spectrum disorder show a circumspect reasoning bias rather than 'jumping-to-conclusions'. *J. Autism Dev. Disord.* (2014) 44:513–20. doi: 10.1007/s10803-013-1897-5
42. Brosnan M, Lewton M, Ashwin C. Reasoning on the autism spectrum: a dual process theory account. *J. Autism Dev. Disord.* (2016) 46:2115–25. doi: 10.1007/s10803-016-2742-4
43. De Martino B, Harrison NA, Knafo S, Bird G, Dolan RJ. Explaining enhanced logical consistency during decision making in autism. *J. Neurosci.* (2008) 28:10746–50. doi: 10.1523/JNEUROSCI.2895-08.2008
44. Farmer GD, Baron-Cohen S, Skylark WJ. People with autism spectrum conditions make more consistent decisions. *Psychol. Sci.* (2017) 28:1067–76. doi: 10.1177/0956797617694867
45. McKenzie R, Evans JSB, Handley SJ. Conditional reasoning in autism: activation and integration of knowledge and belief. *Dev. Psychol.* (2010) 46:391. doi: 10.1037/a0017412
46. Lewton M, Ashwin C, Brosnan M. Syllogistic reasoning reveals reduced bias in people with higher autistic-like traits from the general population. *Autism*. (2019) 23:1311–21. doi: 10.1177/1362361318808779
47. South M, Chamberlain PD, Wigham S, Newton T, Le Couteur A, McConachie H, et al. Enhanced decision making and risk avoidance in high-functioning autism spectrum disorder. *Neuropsychology*. (2014) 28:222. doi: 10.1037/neu0000016
48. Jack AI, Dawson AJ, Begany KL, Leckie RL, Barry KP, Ciccia AH, et al. fMRI reveals reciprocal inhibition between social and physical cognitive domains. *NeuroImage.* (2013) 66:385–401. doi: 10.1016/j.neuroimage.2012.10.061
49. Johnson W, Bouchard TJ Jr. Sex differences in mental abilities: *g* masks the dimensions on which they lie. *Intelligence*. (2007) 35:23–39. doi: 10.1016/j.intell.2006.03.012
50. Nettle D. Empathizing and systemizing: what are they, and what do they contribute to our understanding of psychological sex differences? *Br. J. Psychol.* (2007) 98:237–55. doi: 10.1348/000712606X117612
51. Baron-Cohen S, Hammer J. Parents of children with asperger syndrome: what is the cognitive phenotype? *J. Cogn. Neurosci.* (1997) 9:548–54. doi: 10.1162/jocn.1997.9.4.548
52. Pellicano E, Maybery M, Durkin K, Maley A. Multiple cognitive capabilities/deficits in children with an autism spectrum disorder: "weak" central coherence and its relationship to theory of mind and executive control. *Dev. Psychopathol.* (2006) 18:77–98. doi: 10.1017/S0954579406060056
53. Russell-Smith SN, Maybery MT, Bayliss DM, Sng AA. Support for a link between the local processing bias and social deficits in autism: an investigation of embedded figures test performance in non-clinical individuals. *J. Autism Dev. Disord.* (2012) 42:2420–30. doi: 10.1007/s10803-012-1506-z
54. Fugard AJB, Stewart ME, Stenning K. Visual/verbal-analytic reasoning bias as a function of self-reported autistic-like traits: a study of typically developing individuals solving Raven's advanced progressive matrices. *Autism*. (2011) 15:327–40. doi: 10.1177/1362361310371798
55. Joseph RM, Keehn B, Connolly C, Wolfe JM, Horowitz TS. Why is visual search superior in autism spectrum disorder? *Dev. Sci.* (2009) 12:1083–96. doi: 10.1111/j.1467-7687.2009.00855.x
56. Keehn B, Shih P, Brenner LA, Townsend J, Müller RA. Functional connectivity for an "island of sparing" in autism spectrum disorder: an fMRI study

of visual search. *Hum. Brain Mapp.* (2013) 34:2524–37. doi: 10.1002/hbm.22084
57. Escovar E, Rosenberg-Lee M, Uddin LQ, Menon V. The empathizing-systemizing theory, social abilities, and mathematical achievement in children. *Sci. Rep.* (2016) 6:23011. 10.1038/srep23011
58. Sahay A, Wilson DA, Hen R. Pattern separation: a common function for new neurons in hippocampus and olfactory bulb. *Neuron.* (2011) 70:582–8. doi: 10.1016/j.neuron.2011.05.012
59. South M, Stephenson KG, Nielson CA, Maisel M, Top DN, Kirwan CB. Overactive pattern separation memory associated with negative emotionality in adults diagnosed with autism spectrum disorder. *J. Autism Dev. Disord.* (2015) 45:3458–67. doi: 10.1007/s10803-015-2547-x
60. Benevento M, Oomen CA, Horner AE, Amiri H, Jacobs T, Pauwels C, et al. Haploinsufficiency of EHMT1 improves pattern separation and increases hippocampal cell proliferation. *Sci. Rep.* (2017) 7:1–11. doi: 10.1038/srep40284
61. Golan O, Baron-Cohen S. Systemizing empathy: teaching adults with Asperger syndrome or high-functioning autism to recognize complex emotions using interactive multimedia. *Dev. Psychopathol.* (2006) 18:591–617. doi: 10.1017/S0954579406060305
62. Woodard CR, Chung J, Korn M. A pilot study of the meta-play method: a novel play intervention for toddlers with autism. *J. Autism Dev. Disord.* (2014) 1:3. doi: 10.7243/2054-992X-1-3
63. Crespi B, Badcock C. Psychosis and autism as diametrical disorders of the social brain. *Behav. Brain Sci.* (2008) 31:241–60. doi: 10.1017/S0140525X08004214

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Reduced Inter-hemispheric Resting State Functional Connectivity and Its Association With Social Deficits in Autism

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Autism spectrum disorder (ASD) is an early onset developmental disorder which persists throughout life and is increasing in prevalence over the last few decades. Given its early onset and variable cognitive and emotional functional impairments, it is generally challenging to assess ASD individuals using task-based behavioral and functional MRI paradigms. Consequently, resting state functional MRI (rs-fMRI) has become a key approach for examining ASD-associated neural alterations and revealed functional alterations in large-scale brain networks relative to typically developing (TD) individuals, particularly those involved in social-cognitive and affective processes. Recent progress suggests that alterations in inter-hemispheric resting state functional connectivity (rsFC) between regions in the 2 brain hemispheres, particularly homotopic ones, may be of great importance. Here we have reviewed neuroimaging studies examining inter-hemispheric rsFC abnormities in ASD and its associations with symptom severity. As an index of inter-hemispheric functional connectivity, we have additionally reviewed previous studies on corpus callosum (CC) volumetric and fiber changes in ASD. There are converging findings on reduced inter-hemispheric (including homotopic) rsFC in large-scale brain networks particularly in posterior hubs of the default mode network, reduced volumes in the anterior and posterior CC, and on decreased FA and increased MD or RD across CC subregions. Associations between the strength of inter-hemispheric rsFC and social impairments in ASD together with their classification performance in distinguishing ASD subjects from TD controls across ages suggest that the strength of inter-hemispheric rsFC may be a more promising biomarker for assisting in ASD diagnosis than abnormalities in either brain wide rsFC or brain structure.

Keywords: autism spectrum disorder, resting state, inter-hemispheric functional connectivity, homotopic connectivity, corpus callosum, social deficits, biomarker

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INTRODUCTION

Autism spectrum disorder (ASD) is an early onset developmental disorder which persists throughout life and has an increasing prevalence rate over the last decades, with a general average of around 1% of the population being affected (1). Although symptoms of ASD are highly heterogeneous, the disorder is generally characterized by deficits mainly in social

communication/interaction, restricted interests, and repetitive behaviors (2). Task-based behavioral and neuroimaging studies have further shown specific behavioral deficits and corresponding neural dysfunctions in ASD primarily in social-cognitive and affective domains, such as facial emotion recognition (3–5), eye contact avoidance (6–8), and social interest (9, 10).

However, given the early onset of the disorder and general cognitive deficits in ASD, assessment of ASD individuals, particularly young children, by means of task-based behavioral and fMRI paradigms is challenging. Consequently, resting state fMRI (rs-fMRI) has been proposed as a promising approach for examining ASD-associated alterations. Rs-fMRI assesses subjects in the absence of a specific task and thus allows comparisons across different studies and data acquisition sites. Previous rs-fMRI studies have reported functional abnormalities in large-scale brain networks in ASD relative to typically developing (TD) individuals (11–14), particularly in brain networks involved in social-cognitive and affective processes (15–17). Importantly, rs-fMRI measurement across different sites and research groups allows the collection of large sample sizes and data sharing initiatives, such as the Autism Brain Imaging Data Exchange (ABIDE) databases (ABIDE-I and -II), although it should be acknowledged that these span wide age ranges and are restricted to individuals with high-functioning ASD. As a result of increased statistical power using these large databases, previous studies have demonstrated more consistent and reproducible patterns of alterations in resting state functional connectivity (rsFC) in ASD populations (11, 18, 19).

It has been shown that functional connectivity alterations in psychiatric disorders are mainly contributed by counterpart regions in the opposite hemisphere (20). This is also the case in ASD where rsFC alterations are primarily contributed by inter-hemispheric connectivity between regions in the 2 hemispheres (11, 21), and homotopic ones (between identical regions in the 2 hemispheres) may be of particular importance (19, 22, 23). The aims of the present review are to detail findings from neuroimaging studies directly examining interhemispheric rsFC abnormalities in ASD (see **Table 1**), particularly the homotopic ones together with their associations with symptom severity, and studies investigating structural changes in the corpus callosum (CC) in ASD (see **Table 2** for volumetric studies and **Table 3** for diffusion-weighted imaging (DWI) studies), which is also an important index of interhemispheric functional connectivity. We also discussed their functional significance and whether they can be used as promising biomarkers for future clinical application.

INTER-HEMISPHERIC rsFC ABNORMALITIES IN ASD

Based on the cortical underconnectivity theory, aberrant rsFC patterns of ASD can be characterized by local over-connectivity but long-distance under-connectivity (13, 71, 72). As a typical long-distance connection, inter-hemispheric rsFC reflects the correlation of fMRI BOLD signal time series between brain regions belonging to the 2 brain hemispheres and can be used as an important index for delineating inter-hemispheric synchronization abnormalities in spontaneous neural activity in ASD. Support for the functional importance of inter-hemispheric connections comes from studies on agenesis or sections of CC. The CC is the major white-matter tract between the left and right hemispheres and plays a crucial role in the maintenance of interhemispheric functional communications (73). Individuals with congenital callosal agenesis have been reported to exhibit ASD-like symptoms such as deficits in language comprehension, theory of mind and social reasoning (74) and strongly elevated autistic traits as measured by the Autism Spectrum Quotient (75). Reduced inter-hemispheric rsFC in brain regions of the default mode network (DMN) and salience network have also been found in callosal dysgenesis subjects (76), although interestingly this was not found to influence the qualitative organization pattern of the rsFC (76). However, another study has reported an intact pattern of inter-hemispheric rsFC in callosal dysgenesis individuals using region of interest (ROI) and independent component analysis-based approaches (77). This inconsistency could be due to the occurrence of a remarkable plasticity compensating for the disconnection, as revealed by an animal callosotomy study reporting that a restoration of inter-hemispheric rsFC occurred from 7 to 28 days post-callosotomy but only when the callosotomy was partial and not when it was total (78). The human callosal dysgenesis studies reporting normal interhemispheric rsFC would similarly have been partial. Furthermore, another gene knockdown study in rodents has further emphasized the importance of inter-hemispheric connectivity in ASD symptomatology, such that permanent deficits in callosal projections and associated inter-hemispheric connections caused by downregulation of Wnt signaling induced ASD-like impairments, including social interaction deficits and repetitive motor behavior (79). Overall these studies both emphasize the importance of inter-hemispheric connections in the context of normal social functioning and autism and that under normal circumstances these functional connections can be restored to a large extent even when the CC does not develop fully or is partially disconnected.

Based on a voxel-based whole brain analysis, Cheng et al. (11) revealed that the majority of altered rsFC occur between regions from the opposite hemispheres using the ABIDE database, and more specifically that reduced rsFC is found mainly between brain regions implicated in face expression processing, theory of mind and self-other distinction. Also using the ABIDE database, another voxel-based study using a graph theory analysis approach specifically examined inter- and intra-hemispheric rsFC in ASD subjects and reported that they had reduced inter and intra-hemispheric functional connectivity strength in regions of the DMN and the visual system relative to TD subjects (21). Note that significant correlations were only observed between symptom severity, as measured by the restricted and repetitive behavior subscale of the Autism Diagnostic Observation Schedule (ADOS), and the density of inter- but not intra-hemispheric FC in the posterior cingulate cortex (PCC) and precuneus which both represent core nodes of the posterior DMN. Using only data from children included in the ABIDE database, a more recent study using a sliding-window analysis has shown increased inter- and intra-hemispheric

TABLE 1 | Overview of the studies examining alterations in interhemispheric (homotopic) functional connectivity in ASD patients.

References	Autism					Control					Method	Conclusion
	N (F)	Age	VIQ	PIQ	FIQ	*N* (F)	Age	VIQ	PIQ	FIQ		
Anderson et al. (22)	53 (0)	22.40 (7.20)	101.30 (21.10)	101.30 (16.50)	/	39 (0)	21.10 (6.50)	116.00 (14.80)	114.20 (13.90)	/	Voxel-Based whole brain	↓*
Cheng et al. (11)	418 (51)	17.17 (7.97)	104.50 (15.87)	105.30 (15.17)	105.7 (14.16)	509 (85)	16.40 (7.08)	111.10 (12.84)	107.24 (12.56)	110.62 (11.93)	Voxel-Based whole brain	↓
Dickinson et al. (24)	59 (13)	5.79 (2.01)	68.96 (34.35)	74.67 (33.82)	/	39 (13)	5.96 (2.22)	121.12 (19.42)	112.55 (12.07)	/	EEG coherence analysis	↓
Dickinson et al. (25)	35 (9)	12/24 months	/	/	/	20 (11)	12/24 months	/	/	/	EEG coherence analysis	↓
Di Martino et al. (19)	360 (0)	16.30 (7.00)	105.00 (16.00)	106.00 (15.00)	105.00 (16.00)	403 (0)	16.30 (7.00)	111.00 (13.00)	108.00 (12.00)	111.00 (11.00)	Voxel-Based whole brain	↓*
Dinstein et al. (26)	29 (/)	29 months (/)	/	/	/	30 (/)	28 months (/)	/	/	/	ROI analysis	↓*
Guo et al. (27)	105 (0)	10.15 (1.26)	/	/	110.53 (17.42)	102 (0)	10.02 (1.38)	/	/	113.78 (11.98)	Sliding-Window FC analysis	↓
Hahamy et al. (28)	68 (6)	26.6 (1.87)	105.79 (7.28)	108.42 (6.35)	107.76 (7.56)	73 (14)	25.82 (2.02)	113.27 (2.95)	111.67 (2.62)	114.14 (2.48)	Voxel-Based whole brain	↓ and ↑*
Keehn et al. (29)	27 (/)	3/6/9/12 months	/	/	/	37 (/)	3/6/9/12 months	/	/	/	fNIRS ROI analysis	↓
King et al. (30)	579 (373)	15.1 (6.9)	105.70 (17.93)	105.18 (17.06)	106.05 (16.79)	823 (463)	15.1 (6.8)	113.85 (13.48)	109.43 (13.64)	113.03 (12.53)	ROI analysis	↓*
Lazarev et al. (31)	14 (0)	9.70 (2.20)	91.00 (27.50)	94.30 (20.40)	91.40 (22.80)	19 (0)	10.10 (3.46)	/	/	/	EEG coherence analysis	↓
Lee et al. (21)	458 (54)	16.2 (7.4)	/	/	106.0 (16.3)	517 (90)	16.50 (7.30)		/	111.20 (12.40)	Voxel-Based whole brain	↓
Li et al. (23)	409 (47)	17.42 (8.56)	105.20 (18.10)	106.27 (16.81)	106.72 (16.65)	455 (72)	17.35 (7.76)	111.48 (13.53)	108.17 (13.46)	111.45 (12.55)	Voxel-Based whole brain	↓*
Yao et al. (32)	146 (25)	8.48 (1.07)	107.80 (19.37)	107.27 (20.15)	106.03 (19.40)	175 (47)	8.62 (0.84)	115.09 (15.89)	109.35 (15.40)	114.43 (13.40)	Voxel-Based whole brain	↓*
Zhu et al. (33)	10 (0)	9.00 (1.30)	/	/	/	10 (0)	8.90 (1.40)	/	/	/	fNIRS ROI analysis	↓

*For age and IQs, mean and standard deviation are reported. N (F): Number of subjects and female subjects; VIQ, Verbal IQ; PIQ, Performance IQ; FIQ, Full IQ; EEG, electroencephalographic; ICA, Independent component analysis; ↑ or ↓, Increased or decreased rsFC in autism subjects compared to typically developing subjects; *Homotopic functional connections.*

dynamic FC variability in the medial pre-frontal cortex and the anterior cingulate cortex but decreased inter- and intra-hemispheric dynamic FC variability in the fusiform gyrus and the inferior temporal gyrus (ITG) in ASD relative to TD children (27). Furthermore, again only aberrant temporal variability of the inter- but not intra-hemispheric FC was associated with ADS symptom load, specifically social communication deficits as measured by the ADOS communication subscale. Overall, these findings tend to indicate that, although inter- and intra-hemispheric rsFC both show abnormities in ASD, the inter-hemispheric ones may be of greater clinical relevance.

Given that atypical developmental trajectories of functional and structural organization in these brain networks have also been demonstrated by longitudinal studies (72, 80, 81), attention should also be paid to the neurodevelopmental trajectories of inter-hemispheric functional connectivity, but current studies on this are very limited. Using functional near infrared spectroscopy (fNIRS), a longitudinal study on infants with a high risk of ASD in the first year of life has demonstrated that while they show an increase in both the inter- and intra-hemispheric connectivity in temporal and inferior frontal cortex at the age of 3 months, they exhibit a pattern of decreased functional connectivity at the age of 12 months (29). Another fNIRS study using similar regions of interest reported that this pattern of decreased inter-hemispheric functional connectivity was maintained in older children (mean age $= 9.0 \pm 1.3$) (33), although no longitudinal study to date has specifically investigated the developmental trajectories of interhemispheric rsFC for children between the ages of 1 to 9 years of age. A recent study using electroencephalographic (EEG) measurement on alpha phase coherence has also revealed reduced inter-hemispheric connectivity in the temporal cortex in ASD children (mean age $= 5.79 \pm 2.01$) (24). A similar pattern of reduced inter-hemispheric connection has also been found between temporal and parietal cortex in tuberous sclerosis complex infants who later developed ASD, which becomes to be most robust at 24 months (25), although the comorbidities of tuberous sclerosis complex and ASD have to be kept in mind when interpreting these findings. Finally, another EEG

TABLE 2 | Overview of the studies examining alterations in corpus callosum volume in ASD patients.

References	Autism					Control					Method	Conclusion
	N (F)	Age	VIQ	PIQ	FIQ	*N* (F)	Age	VIQ	PIQ	FIQ		
Anderson et al. (22)	53 (0)	22.40 (7.20)	101.30 (21.10)	101.30 (16.50)	/	39 (0)	21.10 (6.50)	116.00 (14.80)	114.20 (13.90)	/	SBM	↓
Chung et al. (34)	16 (0)	16.10 (4.50)	/	/	/	12 (0)	17.10 (2.80)	/	/	/	VBM	↓
Egaas et al. (35)	51 (6)	15.50 (10.0)	<70:16; ≥70:31	/	/	51 (6)	15.50 (9.90)	/	/	/	TMA	↓
Elia et al. (36)	22 (0)	10.92 (4.02)	/	/	/	11 (0)	10.86 (2.85)	/	/	/	TMA	N.S.
Frizer et al. (37)	253 (27)	14.58 (6.00)	/	/	/	250 (53)	14.41 (5.31)	/	/	/	Meta	↓
Gaffney et al. (38)	13 (3)	11.30 (4.70)	/	/	84.9 (26.7)	35 (14)	12.00 (5.20)	/	/	/	TMA	N.S.
Haar et al. (39)	295 (0)	16.89 (8.10)	/	/	106.16 (17.16)	295 (0)	16.72 (7.55)	/	/	111.21 (12.15)	SBM	↓
Hardan et al. (40)	22 (0)	22.40 (10.10)	103.00 (16.40)	97.50 (12.60)	100.40 (14.70)	22 (0)	22.40 (10.00)	100.50 (14.70)	99.60 (12.50)	100.50 (14.20)	TMA	↓
Lefebvre et al. (41)	328 (38)	16.60 (8–39)	103.00 (18.00)	106.00 (17.00)	105.00 (17.00)	366 (62)	17.00 (8–40)	111.00 (13.00)	107.00 (13.00)	111.00 (12.00)	SBM	N.S.
Li et al. (23)	409 (47)	17.42 (8.56)	105.20 (18.10)	106.27 (16.81)	106.72 (16.65)	455 (72)	17.35 (7.76)	111.48 (13.53)	108.17 (13.46)	111.45 (12.55)	VBM	↓
Manes et al. (42)	27 (5)	14.35 (6.80)	/	/	/	17 (6)	11.85 (5.00)	/	/	/	TMA	↓
Piven et al. (43)	35 (9)	18.00 (4.50)	/	91.00 (19.80)	/	36 (16)	20.20 (3.80)	/	102.10 (12.80)	/	TMA	↓
Rice et al. (44)	12 (0)	12.42 (4.32)	106.00 (33.01)	107.83 (17.66)	107.33 (26.06)	8 (0)	12.50 (3.46)	123.25 (10.90)	120.38 (10.08)	124.00 (11.28)	TMA	N.S.
Sui et al. (45)	16 (0)	21.38 (2.39)	/	/	108.88 (17.39)	17 (0)	21.71 (2.14)	/	/	116.65 (11.98)	DKI	↓
Vidal et al. (46)	24 (0)	10.00 (3.30)	92.90 (13.30)	99.10 (14.00)	95.90 (11.50)	26 (0)	11.00 (2.50)	105.40 (11.20)	104.10 (14.00)	104.80 (11.70)	TMA	↓
Waiter et al. (47)	15 (0)	15.20 (2.20)	100.60 (24.20)	99.40 (19.50)	100.50 (22.40)	16 (0)	15.50 (1.60)	101.30 (21.10)	98.80 (13.90)	99.70 (18.30)	VBM	↓
Wolff et al. (48)	57 (10)	6.60 (0.7)	/	/	79.80 (17.60)	108 (42)	6.70 (0.7)	/	/	110.90 (16.00)	Fourier contour model	↑
		12.90 (0.8)	/	/			12.70 (0.7)	/	/			↑
		24.80 (1.2)	/	/			24.70 (0.8)	/	/			N.S.
Yao et al. (32)	146 (25)	8.48 (1.07)	107.80 (19.37)	107.27 (20.15)	106.03 (19.40)	175 (47)	8.62 (0.84)	115.09 (15.89)	109.35 (15.40)	114.43 (13.40)	VBM	N.S.

For age and IQs, mean and standard deviation are reported. N (F): Number of subjects and female subjects; VIQ, Verbal IQ; PIQ, Performance IQ; FIQ, Full IQ; SBM, Surface-based morphometric analysis; TMA, Traditional morphometric analysis; VBM, Voxel-based morphometric analysis; DKI, diffusional kurtosis imaging; ↑ or ↓, Increased or decreased corpus callosum volume in autism subjects compared to typically developing subjects; N.S, No significant group difference.

study with intermittent photic stimulation on an older sample size (mean age = 9.7 ± 2.2) revealed a more general decrease in inter-hemispheric coherent connections of the 20 highest connections at all the beta frequencies corresponding to photic stimulation (31).

ALTERED HOMOTOPIC INTER-HEMISPHERIC rsFC IN ASD

Homotopic inter-hemispheric rsFC is a component part of overall interhemispheric rsFC and is an important measure reflecting activity synchronization between homotopic regions of the 2 hemispheres (82, 83). Homotopic FC can be measured using voxel-mirrored connectivity analysis on the correlation of fMRI BOLD signal time series between each voxel in 1 hemisphere and its mirrored counterpart in the other side (82). Homotopic inter-hemispheric rsFC abnormalities have been found in a number of psychiatric disorders including schizophrenia (84), major depression (85), substance dependence (86), and even Parkinson's disease (87).

In the first study examining homotopic inter-hemispheric rsFC changes in ASD, a moderate sample size (53 high-functioning ASD males vs. 39 TD controls) was used and found decreased homotopic rsFC between the bilateral sensorimotor cortex, anterior insula, and superior parietal lobule in ASD

TABLE 3 | Overview of the diffusion-weighted imaging studies examining corpus callosum abnormities in ASD patients.

References	Autism					Control					Method	Conclusion			
	N (F)	Age	VIQ	PIQ	FIQ	*N* (F)	Age	VIQ	PIQ	FIQ		FA	MD	RD	AD
Alexander et al. (49)	43 (0)	16.23 (6.70)	/	107.49 (13.04)	/	34 (0)	16.44 (5.97)	/	112.79 (12.08)	/	ROI	↓	↑	↑	N.S.
Ameis et al. (50)	71 (15)	11.40 (3.40)	/	/	95.0 (19.7)	62 (25)	10.80 (2.80)	/	/	112.5 (17.1)	TBSS	↓	N.S.	N.S.	N.S.
Aoki et al. (51)	567 (81)	14.23 (/)	/	/	106.42 (/)	482 (116)	15.47 (/)	/	/	111.94 (/)	Meta	↓	↑	/	/
Aoki et al. (52)	69 (7)	8.90 (1.70)	108 (16)	110 (19)	109 (17)	50 (12)	9.40 (1.50)	114 (15)	114 (14)	114 (13)	TBSS	↓	↑	↑	↑
Barnea-Goraly et al. (53)	7 (0)	14.60 (3.40)	84 (17)	121.5 (8)	101 (12.2)	9 (0)	13.40 (2.80)	105.2 (11.4)	107 (10)	107 (8.5)	Voxel based whole brain	↓	/	/	/
Barnea-Goraly et al. (54)	13 (2)	10.50 (2.00)	/	/	85.9 (17.4)	11 (2)	9.60 (2.10)	/	/	119.9 (13.3)	TBSS	↓	/	N.S.	↓
Bashat et al. (55)	17 (/)	1.8–3.3	/	/	/	41 (18)	0.25–23	/	/	/	ROI	↑	/	/	/
Brito et al. (56)	8 (0)	9.53 (1.83)	/	/	/	8 (0)	9.57 (1.36)	/	/	/	ROI	↓	/	/	/
Di et al. (57)	297 (28)	22.40 (/)	/	/	107.87 (/)	302 (30)	22.2 (/)	/	/	112.50 (/)	Meta	↓	/	/	/
Groen et al. (58)	17 (3)	14.40 (1.60)	97 (19)	100 (15)	98 (18)	25 (3)	15.50 (1.80)	105 (10)	105 (11)	105 (9)	Voxel based whole brain	↓	↑	/	/
Hong et al. (59)	18 (0)	8.69 (2.18)	/	/	105.22 (21.12)	16 (0)	9.81 (1.91)	/	/	106.13 (20.13)	ROI	N.S.	/	/	/
Keller et al. (60)	34 (0)	18.90 (7.30)	/	/	102.0 (14.8)	31 (0)	18.90 (6.20)	/	/	109.5 (9.0)	Voxel based whole brain	↓	/	/	/
Kumar et al. (61)	32 (3)	5.00 (/)	/	/	/	16 (4)	5.50 (/)	/	/	/	TBSS	↓	/	/	/
Nickel et al. (62)	30 (11)	35.40 (9.07)	/	/	124.5 (12.26)	30 (11)	35.53 (8.30)	/	/	123.63 (13.80)	Voxel based whole brain	↓	N.S.	/	/
Noriuchi et al. (63)	7 (1)	13.96 (2.68)	93.7 (7.41)	93.14 (8.07)	92.71 (6.68)	7 (1)	13.36 (2.74)	/	/	116.43 (9.50)	Voxel based whole brain	↓	/	/	/
Shukla et al. (64)	26 (2)	12.70 (0.60)	105.6 (3.6)	109.5 (3.3)	/	24 (1)	13.00 (0.60)	108.2 (2.6)	110.3 (2.5)	/	ROI	↓	↑	↑	N.S
Shukla et al. (65)	26 (1)	12.80 (0.60)	104.3 (3.4)	108.8 (3.3)	/	24 (1)	13.00 (0.60)	108.2 (2.6)	110.3 (2.5)	/	TBSS	↓	↑	↑	N.S.
Thomas et al. (66)	12 (0)	28.50 (9.70)	105.08 (10.09)	107.25 (13.9)	106.92 (10.47)	18(0)	22.40 (4.10)	109.8 (12.54)	111 (10.03)	111.6 (9.91)	ROI	N.S.	/	/	/
Travers et al. (67)	100 (0)	18.30 (8.50)	96.3 (21.1)	102.6 (17.9)	100.1 (17.6)	56 (0)	18.90 (7.80)	114.7 (13.2)	116.3 (14.8)	118.2 (13.2)	ROI	↓	↑	↑	↑
Vogan et al. (68)	61 (10)	10.90 (2.00)	/	/	102.2 (14.9)	69 (18)	11.10 (2.40)	/	/	112.7 (11.6)	TBSS	↓	N.S.	N.S.	↓
Walker et al. (69)	39 (11)	4.63 (1.76)	/	/	/	39 (13)	4.74 (1.76)	/	/	/	TBSS	↓	↑	↑	↑
Weinstein et al. (70)	22 (/)	3.20 (1.10)	/	/	/	32 (/)	3.40 (1.30)	/	/	/	TBSS	↑	N.S.	↓	N.S.

For age and IQs, mean and standard deviation are reported. N (F): Number of subjects and female subjects; VIQ, Verbal IQ; PIQ, Performance IQ; FIQ, Full IQ; TBSS, Tract based spatial statistics; ROI, Region of interest; FA, Fractional anisotropy; MD, Mean diffusivity; RD, Radial diffusivity; AD, Axial diffusivity; ↑ or ↓, Increased or decreased in autism subjects compared to typically developing subjects; N.S, No significant group difference.

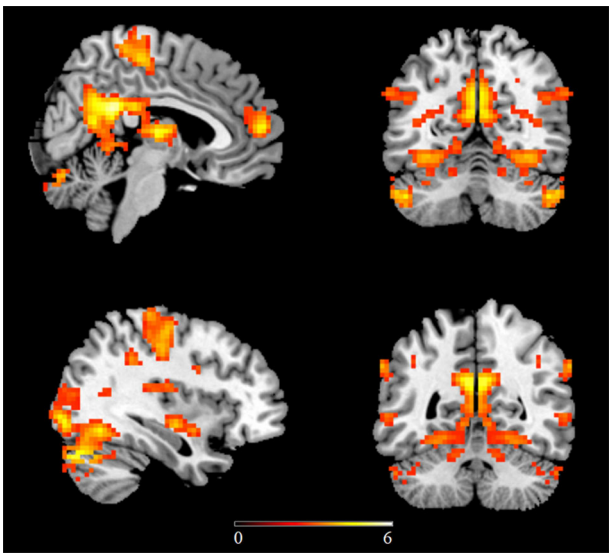

FIGURE 1 | Regions showing decreased homotopic inter-hemispheric functional connectivity in ASD relative to matched typically developing controls using the ABIDE database. Statistic maps were displayed with a $p < 0.05$ FDR corrected threshold. Color bar indicates *t* values of the statistical map. This figure is adapted from Li et al. (23).

subjects compared to TD controls (22). A further ROI-based study has also revealed decreased homotopic inter-hemispheric rsFC between the superior temporal gyrus (STG) and inferior frontal gyrus (IFG) in naturally sleeping toddlers with autism relative to TD controls (29 ASD vs. 30 controls), with homotopic connectivity strengths of the IFG being negatively correlated with social and communication impairments, as measured by ADOS (26). However, while decreased homotopic connectivity was found in the lateral occipital cortex and the postcentral gyrus in ASD, Hahamy et al. (28) additionally demonstrated increased homotopic inter-hemispheric rsFC in the ITG and the middle frontal gyrus in ASD using a moderate sample size (68 ASD males vs. 73 TD controls) consisting of subjects from selective sites in ABIDE-I. This study has further revealed significantly greater individual topographical distortions in the homotopic rsFC patterns in ASD relative to TD controls (28). More robust findings have subsequently come from studies using larger numbers of subjects from the ABIDE database. In the first study using the ABIDE database, reduced homotopic inter-hemispheric rsFC has also been found in regions including the PCC, insula, and thalamus (19). In a further study which included gender as an additional covariate, Li et al. (23) carried out a voxel-based whole brain analysis on differences in homotopic inter-hemispheric rsFC in ASD subjects and further examined associations between homotopic rsFC and symptom severity. Results showed decreased homotopic rsFC of regions in large-scale brain networks including the DMN, salience network, mirror neuron/motor systems, and auditory and visual systems in ASD adolescents and adults (**Figure 1**), with homotopic rsFC in the PCC, insula and STG showing significant associations with social impairments as measured by ADOS. A more recent follow-up study using independent data from children in ABIDE I and ABIDE II databases and the same analysis approach has revealed consistent patterns of reduced homotopic inter-hemispheric rsFC in ASD children between the ages of 5 and 10 years old, suggesting that the homotopic alterations can occur at an early age and remain stable in contrast to other dysregulations which vary across developmental periods. Moreover, this study has also demonstrated significant associations between ASD symptom severity and homotopic inter-hemispheric rsFC changes in regions of the DMN (the PCC and the precuneus) and the visual processing networks (inferior and middle temporal gyri and inferior occipital gyrus) (32). Atypical developmental trajectories of homotopic rsFC and its association with symptom severity have also been reported in ASD (88). Note that although a recent study specifically examining reproducibility across sites has also demonstrated overall decreased homotopic inter-hemispheric rsFC in ASD using the whole ABIDE datasets, as consistently observed in most of the previous studies, the decreased homotopic rsFC pattern was not generally reproducible across sites (30), which could be due to decreased statistical power as a result of smaller sample sizes when individual sites were examined separately.

INTERHEMISPHERIC rsFC—A MORE PROMISING BIOMARKER FOR ASD?

In both seed-based and voxel-based rsFC analyses, altered rsFC in the DMN, particularly the PCC, is one of the most replicated findings in ASD samples (12, 13, 19, 89–92). As we outlined above, this is also the case for interhemispheric rsFC, particularly the homotopic connections (19, 21, 23, 32). Interestingly, the PCC and precuneus of the DMN, the STG, and the insula which exhibited associations between their interhemispheric rsFC (including the homotopic ones) and symptom severity in ASD, are all regions strongly involved in social and affective processing (21, 23, 32). These associations have been demonstrated only for the inter-hemispheric (including the homotopic) rsFC alterations but not for the intra-hemispheric ones (21, 23, 27). Furthermore, based on inter-hemispheric, but not only the homotopic rsFC changes, pattern classification analysis achieved an average accuracy of 88.70% for distinguishing ASD subjects from TD controls across sites (23), which is slightly higher than a previous study (82.87%) using the same pattern classification approach based on whole brain-wide rsFC changes (namely more features) (11), although there is no direct statistical comparison. These findings together suggest that brain regions implicated in processing of social and affective domains maybe of greater clinical relevance. Note that although alterations in homotopic inter-hemispheric rsFC have also been found in other disorders such as schizophrenia (84), major depression (85), substance dependence (86), and Parkinson's disease (87), a consistent pattern of decreased homotopic interhemispheric rsFC has only been found in ASD in most of the previous studies across children, adolescents and adults. In other developmental disorders, increased rather than decreased homotopic rsFC has

been observed in children with attention-deficit hyperactivity disorder (93) and both increased and decreased homotopic rsFC have been reported in children with Tourette's syndrome (94). Thus, although decreased inter-hemispheric rsFC may not be a biomarker specific for ASD, it may still be a promising biomarker for ASD diagnosis although probably in conjunction with other measures.

CORPUS CALLOSUM AND INTER-HEMISPHERIC rsFC IN ASD

As the major white-matter tract between the 2 brain hemispheres, CC serves as a bridge for interhemispheric functional communications. In ASD, CC volume has been proposed as an important index of interhemispheric functional connectivity (37, 46). Early findings on CC volume mainly utilize the traditional morphometric method based on the Witelson partition [**Figure 2**; (95)]. While these studies have consistently demonstrated an overall reduction of CC volume in ASD subjects with and without intellectual disability (35, 42, 43, 96), evidence on the main contributing subregions for such a global reduction effect has tended to be inconsistent with some studies showing significant decreased volume in the anterior subregions (40) and others reporting decreases in posterior part (35, 43) or the CC body (42), although subjects examined in these studies vary across young children, adolescents and adults (from 3 to 42 years old) and across high and low functioning ASD. Vidal et al. (46) further confirmed a global reduction in CC volume and the anterior part of the CC using traditional morphometric methods and found regional reduction in both the anterior (genu) and posterior (splenium) part of the CC using computational mapping methods, reflecting an impact of analysis methods on revealing which specific CC subregions exhibit alterations in ASD. Based on a voxel-based morphometric (VBM) whole brain analysis, a volume reduction has only been found in the posterior CC in ASD [splenium and isthmus; Waiter et al. (47)]. Another VBM study that specifically focused on the CC, has also revealed reduced volume in the posterior (splenium) and additionally in the anterior part (genu and rostrum) of the CC (34). Thus, the regionally restricted (ROI) approach in the latter study may be of greater sensitivity compared to analyses corrected at the whole brain used in the former one. A volume reduction in the anterior and posterior regions of the CC in ASD has also been confirmed by a VBM analysis in a more recent study using the ABIDE database, in which gender, age, IQ, and total brain volume were controlled as potential confounding variables (23). However, using a surface-based approach, Haar et al. (39) did not observe any significant changes in global CC volume in ASD using the ABIDE database, whereas they did find decreased volume in the central part of CC with a small effect size after segmenting the CC into 5 equal parts. Morphometric CC changes in the middle (midbody) and posterior (isthmus and splenium) part have also been confirmed by a diffusional kurtosis imaging study examining axonal density and caliber (45). Finally, another study using the ABIDE database, found no significant CC volume changes based on a more complex model-based

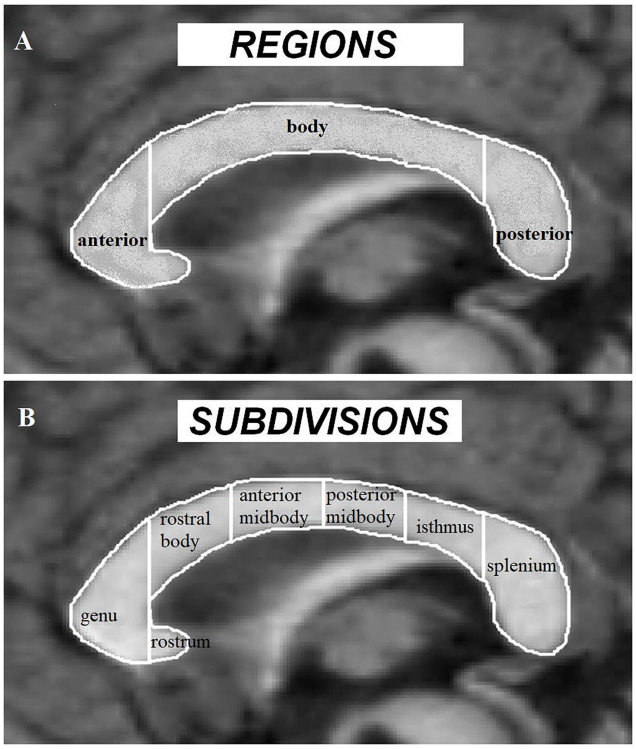

FIGURE 2 | Corpus callosum regions **(A)** and Witelson subdivisions **(B)** adapted from Frazier and Hardan (37).

analysis method but that CC scaled non-linearly with brain volume, as reflected by large brains having a proportionally smaller CC (41). Meta-analysis studies can provide us with more comprehensive and robust insight on ASD-associated CC changes. In one meta-analytic study ASD individuals were reported to exhibit a general CC volume reduction with the reduction magnitude decreasing from the anterior to posterior part (37). A subsequent meta-analysis has also suggested a group difference in CC volume between the ASD and the TD control groups, but this effect was highly underpowered due to the small sample sizes used in the included studies (41).

In addition, diffusion-weighted imaging (DWI) studies have also revealed CC abnormalities in ASD, as reflected by a general pattern of reduced fractional anisotropy (FA) and concomitantly increased mean diffusivity (MD) or radial diffusivity (RD) in ASD compared to TD controls. This pattern has been found not only in the total CC or across all subregions including the anterior (genu), body, and posterior (splenium) part of CC (49, 52, 58, 64, 65, 67–69), but also in specific CC subregions such as in the genu and body (49, 53, 62), the genu/rostral body (56, 63), the posterior midbody and isthmus (60), and the splenium of CC (50, 57) in high/low-functioning ASD individuals across different age ranges, including children, adolescents, and adults. This has also been confirmed by a diffusion tensor imaging meta-analysis study (51). While having confirmed this pattern of FA changes in ASD children, Barnea-Goraly et al. (54) further revealed that this pattern was shared between ASD children and their unaffected

siblings, indicating that FA changes may represent a neural marker reflecting an increased genetic risk or generally increased vulnerability for ASD. Of note very young children with ASD exhibit a different pattern of alterations, such that increased FA in genu and splenium of CC have been found in ASD children aging from 1.8 to 3.3 (55) and an increase in FA but a decrease in RD in the genu and midbody of CC have been found in a slightly older sample (mean age 3.2 ± 1.1) with no changes in MD (70). Moreover, another study did not detect FA changes in adults with ASD (66). Thus, apart from these latter findings the majority of studies converge on a decrease in FA but an increase in MD and RD of CC in ASD. A longitudinal study has further revealed an atypical developmental trajectory of FA of the genu and body of CC before the age of 10 in ASD (67). In contrast, examination of axial diffusivity (AD) revealed somewhat inconsistent results in ASD, with some studies demonstrating significantly higher AD (52) or lower AD either across all 3 subregions (68) or specifically in the body or genu of CC (54, 64) in ASD and others reporting no significant AD differences (49, 70). With respect to associations between diffusion tensor imaging alterations and ASD symptom severity, FA in CC has been found to be negatively correlated with social impairment in ASD as measured by the Social Responsiveness Scale completed by Parents (SRS-P), while alterations in MD and RD have been found to be positively correlated with SRS-P scores (52). In contrast, no significant correlations between FA and diffusivity indices and symptom severity as measured by ADOS have been observed (49, 54, 68). In addition to lower FA and higher diffusivity (as measured by apparent diffusion coefficient), longer fiber length, higher fiber density but a lower fiber number of CC have been reported in ASD children (59, 61), with the fiber number in the anterior CC being negatively correlated with scores on the Childhood Autism Rating Scale (59).

Given that both interhemispheric rsFC and CC volumes exhibit a decreased pattern in ASD individuals, there are also a few studies which have investigated possible relationships between these 2 measures. An absence of significant correlations between the homotopic interhemispheric rsFC and CC volumes has been reported both in a study based on a moderate sample size (53 ASD vs. 39 TDs) (22) and in another larger one using the ABIDE database (23). However, no studies to date have explored the associations between overall interhemispheric rsFC (i.e., not only the homotopic ones) and either CC volumes or DWI indices. Pattern classification analyses based on anatomical abnormalities including variations in CC volumes have reported relatively low classification accuracies of <60% using the ABIDE database (39), which is much lower than pattern classification accuracy based on interhemispheric rsFC changes (23), indicating that anatomical abnormalities measured by conventional MRI protocols are probably too coarse to be a sensitive and robust diagnostic biomarker.

Taken together, although there are some studies which have found no significant CC volume or DWI indices changes in ASD patients (36, 38, 44, 66, 70), the majority of studies have provided converging evidence for decreased CC volumes and FA but increased MD or RD in ASD, particularly those studies based on the traditional morphometric, VBM and DWI methods, although findings on the involvement of specific CC subregions have been less consistent. The heterogeneity of findings on CC volume and DWI indices could be due to differences in sample size, age range, gender, and subject phenotypes [e.g., with and without intellectual disability/high vs. low functioning; cf., (36, 38, 44, 51, 57)]. Differences in analytical approaches and whether potential confounding covariates (e.g., age, gender, IQ, and total brain volume) are well-controlled may also have contributed to these inconsistencies [cf., (34, 40, 43)]. Furthermore, in a longitudinal study of infants (6–24 months), in which subjects were much younger than in all of the studies reviewed above, increased CC area and thickness, particularly robust in the anterior CC, have been found for ASD infants at 6 and 12 months and associated with repetitive behaviors shown at the age of 24 months (48). Similarly, different patterns of FA and RD of CC have been found in very young children with ASD as reviewed above (55, 70). Thus, the developmental trajectory of CC, similar to the aberrant developmental trajectory of the homotopic rsFC (88), should be taken into consideration when interpreting these findings.

CONCLUSION AND FUTURE DIRECTIONS

In summary, we have reviewed the literature on inter-hemispheric rsFC and structural CC changes in ASD. While evidence on these differences are heterogeneous, due undoubtedly to some extent to variations in sample size, age range, gender, subject phenotypes and even whether potential confounding covariates are well-controlled, there are nevertheless converging findings on reduced interhemispheric (including homotopic) rsFC in large-scale brain networks particularly in the posterior hubs in the DMN, on reduced volumes in the anterior and posterior CC, and on decreased FA and increased MD or RD across CC subregions. Correlations between the inter-hemispheric rsFC changes and symptom severity in social impairments and the superior classification performance in distinguishing ASD subjects from TD controls based on the interhemispheric rsFC changes together suggest that inter-hemispheric rsFC changes, a typical form of long-distance connection, may be a more promising biomarker for ASD diagnosis than whole brain wide rsFC and structural abnormalities. Future studies will also need to focus on investigating whether these biomarkers can be applied to other novel samples with a high generalizability if we are to progress toward the ultimate goal of such biomarkers having utility at an individual as opposed to a group level. Additionally, the specificity of interhemispheric rsFC changes in ASD compared with other childhood disorders needs to be more fully established.

More future studies are also required using different multimodal brain imaging and behavioral approaches to better establish the functional consequences of dysfunctional inter-hemispheric connectivity in ASD. Furthermore, given evidence in both humans and animal models for considerably potential for functional recovery in interhemispheric rsFC following CC damage or impaired development it will be important to establish

if this could be exploited therapeutically. In addition, based on previous finding that the development or microstructure of CC can be modulated by factors such as sex hormones (97, 98), age (99), prenatal inflammation (100) and mutation of specific genes (101, 102), future studies should aim at disentangling the potential contributions of these factors to CC alterations in ASD.

There has also been considerable interest in identifying sub-types in ASD, as in other disorders, and moving forward it will clearly be important to do this either based on brain- or behavioral-based subtyping. Previous research on brain-based biomarkers has also been focused almost exclusively on high functioning ASD and on adolescents and adults and therefore there is an urgent need for more studies and hopefully databases which include low-functioning individuals and particularly young children where early diagnosis and therapeutic interventions are potentially of greatest importance. Finally, to make findings across studies and databases more comparable and reproducible, it is also important for future studies follow standardized data processing procedures with potential confounding covariates being well-controlled [cf., (103, 104)].

AUTHOR CONTRIBUTIONS

All authors contributed to the information and ideas presented in the review and writing of the manuscript.

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REFERENCES

1. Fombonne E. The rising prevalence of autism. *J Child Psychol Psychiatry*. (2018) 59:717–20. doi: 10.1111/jcpp.12941
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Washington, DC: APA (2013). doi: 10.1176/appi.books.9780890425596
3. Fedor J, Lynn A, Foran W, DiCicco-Bloom J, Luna B, O'Hearn K. Patterns of fixation during face recognition: differences in autism across age. *Autism*. (2018) 22:866–80. doi: 10.1177/1362361317714989
4. Joseph RM, Tanaka J. Holistic and part-based face recognition in children with autism. *J Child Psychol Psychiatry*. (2003) 44:529–42. doi: 10.1111/1469-7610.00142
5. Wang AT, Dapretto M, Hariri AR, Sigman M, Bookheimer SY. Neural correlates of facial affect processing in children and adolescents with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry*. (2004) 43:481–90. doi: 10.1097/00004583-200404000-00015
6. Madipakkam AR, Rothkirch M, Dziobek I, Sterzer P. Unconscious avoidance of eye contact in autism spectrum disorder. *Sci Rep*. (2017) 7:13378. doi: 10.1038/s41598-017-13945-5
7. Senju A, Johnson MH. Atypical eye contact in autism: models, mechanisms and development. *Neurosci Biobehav Rev*. (2009) 33:1204–14. doi: 10.1016/j.neubiorev.2009.06.001
8. von dem Hagen EA, Stoyanova RS, Rowe JB, Baron-Cohen S, Calder AJ. Direct gaze elicits atypical activation of the theory-of-mind network in autism spectrum conditions. *Cereb Cortex*. (2014) 24:1485–92. doi: 10.1093/cercor/bht003
9. Chevallier C, Grèzes J, Molesworth C, Berthoz S, Happé F. Brief report: selective social anhedonia in high functioning autism. *J Autism Dev Disord*. (2012) 42:1504–9. doi: 10.1007/s10803-011-1364-0
10. Morrison KE, Pinkham AE, Penn DL, Kelsven S, Ludwig K, Sasson NJ. Distinct profiles of social skill in adults with autism spectrum disorder and schizophrenia. *Autism Res*. (2017) 10:878–87. doi: 10.1002/aur.1734
11. Cheng W, Rolls ET, Gu G, Zhang J, Feng J. Autism: reduced connectivity between cortical areas involved in face expression, theory of mind and the sense of self. *Brain*. (2015) 138:1382–93. doi: 10.1093/brain/awv051
12. Hull JV, Jacokes ZJ, Torgerson CM, Irimia A, van Horn JD. Resting-state functional connectivity in autism spectrum disorders: a review. *Front Psychiatry*. (2017) 7:205. doi: 10.3389/fpsyt.2016.00205
13. Lau W, Leung MK, Lau B. Resting-state abnormalities in autism spectrum disorders: a meta-analysis. *Sci Rep*. (2019) 9:3892. doi: 10.1038/s41598-019-40427-7
14. Rane P, Cochran D, Hodge SM, Haselgrove C, Kennedy DN, Frazier JA. Connectivity in autism: a review of MRI connectivity studies. *Harv Rev Psychiatry*. (2015) 23:223–44. doi: 10.1097/HRP.0000000000000072
15. Fishman I, Keown CL, Lincoln AJ, Pineda JA, Müller RA. Atypical cross talk between mentalizing and mirror neuron networks in autism spectrum disorder. *JAMA Psychiatry*. (2014) 71:751–60. doi: 10.1001/jamapsychiatry.2014.83
16. Funakoshi Y, Harada M, Otsuka H, Mori K, Ito H, Iwanaga T. Default mode network abnormalities in children with autism spectrum disorder detected by resting-state functional magnetic resonance imaging. *J Med Invest*. (2016) 63:204–8. doi: 10.2152/jmi.63.204
17. Monk CS, Peltier SJ, Wiggins JL, Weng SJ, Carrasco M, Risi S, et al. Abnormalities of intrinsic functional connectivity in autism spectrum disorders. *Neuroimage*. (2009) 47:764–72. doi: 10.1016/j.neuroimage.2009.04.069
18. Holiga Š, Hip JF, Chatham CH, Garces P, Spooren W, D'Ardhuy XL, et al. Patients with autism spectrum disorders display reproducible functional connectivity alterations. *Sci Transl Med*. (2019) 11:eaat9223. doi: 10.1126/scitranslmed.aat9223
19. Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, et al. The autism brain imaging data exchange: towards large-scale evaluation of the intrinsic brain architecture in autism. *Mol Psychiatry*. (2014) 19:659–67. doi: 10.1038/mp.2013.78
20. Zhang J, Kendrick KM, Lu G, Feng J. The fault lies on the other side: altered brain functional connectivity in psychiatric disorders is mainly caused by counterpart regions in the opposite hemisphere. *Cereb Cortex*. (2015) 25:3475–86. doi: 10.1093/cercor/bhu173
21. Lee JM, Kyeong S, Kim E, Cheon KA. Abnormalities of inter- and intra-hemispheric functional connectivity in autism spectrum disorders: a study using the autism brain imaging data exchange database. *Front Neurosci*. (2016) 10:191. doi: 10.3389/fnins.2016.00191
22. Anderson JS, Druzgal TJ, Froehlich A, DuBray MB, Lange N, Alexander AL, et al. Decreased interhemispheric functional connectivity in autism. *Cereb Cortex*. (2011) 21:1134–46. doi: 10.1093/cercor/bhq190
23. Li Q, Becker B, Jiang X, Zhao Z, Zhang Q, Yao S, et al. Decreased interhemispheric functional connectivity rather than corpus callosum volume as a potential biomarker for autism spectrum disorder. *Cortex*. (2019) 119:258–66. doi: 10.1016/j.cortex.2019.05.003
24. Dickinson A, DiStefano C, Lin YY, Scheffler AW, Senturk D, Jeste SS. Interhemispheric alpha-band hypoconnectivity in children with autism spectrum disorder. *Behav Brain Res*. (2018) 348:227–34. doi: 10.1016/j.bbr.2018.04.026
25. Dickinson A, Varcin KJ, Sahin M, Nelson III CA, Jeste SS. Early patterns of functional brain development associated with autism spectrum

disorder in tuberous sclerosis complex. *Autism Res*. (2019) 12:1758–73. doi: 10.1002/aur.2193
26. Dinstein I, Pierce K, Eyler L, Solso S, Malach R, Behrmann M, et al. Disrupted neural synchronization in toddlers with autism. *Neuron*. (2011) 70:1218–25. doi: 10.1016/j.neuron.2011.04.018
27. Guo X, Duan X, Chen H, He C, Xiao J, Han S, et al. Altered inter- and intrahemispheric functional connectivity dynamics in autistic children. *Hum Brain Mapp*. (2020) 41:419–28. doi: 10.1002/hbm.24812
28. Hahamy A, Behrmann M, Malach R. The idiosyncratic brain: distortion of spontaneous connectivity patterns in autism spectrum disorder. *Nat Neurosci*. (2015) 18:302. doi: 10.1038/nn.3919
29. Keehn B, Wagner J, Tager-Flusberg H, Nelson CA. Functional connectivity in the first year of life in infants at-risk for autism: a preliminary near-infrared spectroscopy study. *Front Hum Neurosci*. (2013) 7:444. doi: 10.3389/fnhum.2013.00444
30. King JB, Prigge M, King CK, Morgan J, Weathersby F, Fox JC, et al. Generalizability and reproducibility of functional connectivity in autism. *Mol Autism*. (2019) 10:27. doi: 10.1186/s13229-019-0273-5
31. Lazarev VV, Pontes A, Mitrofanov AA, deAzevedo LC. Reduced interhemispheric connectivity in childhood autism detected by electroencephalographic photic driving coherence. *J Autism Dev Disord*. (2013) 45:537–47. doi: 10.1007/s10803-013-1959-8
32. Yao S, Zhou M, Zhang Y, Zhang Q, Zhao Z, Jiang X, et al. Decreased homotopic interhemispheric functional connectivity in children with autism spectrum disorder. *bioRxiv*. (2020). doi: 10.1101/2020.11.08.373126
33. Zhu H, Fan Y, Guo H, Huang D, He S. Reduced interhemispheric functional connectivity of children with autism spectrum disorder: evidence from functional near infrared spectroscopy studies. *Biomed Opt Express*. (2014) 5:1262–74. doi: 10.1364/BOE.5.001262
34. Chung MK, Dalton KM, Alexander AL, Davidson RJ. Less white matter concentration in autism: 2D voxel-based morphometry. *Neuroimage*. (2004) 23:242–51. doi: 10.1016/j.neuroimage.2004.04.037
35. Egaas B, Courchesne E, Saitoh O. Reduced size of corpus callosum in autism. *Arch Neurol*. (1995) 52:794–801. doi: 10.1001/archneur.1995.00540320070014
36. Elia M, Ferri R, Musumeci SA, Panerai S, Bottitta M, Scuderi C. Clinical correlates of brain morphometric features of subjects with low-functioning autistic disorder. *J Child Neurol*. (2000) 15:504–8. doi: 10.1177/088307380001500802
37. Frazier, TW, Hardan, AY. A meta-analysis of the corpus callosum in autism. *Biol psychiatry*. (2009) 66:935–41. doi: 10.1016/j.biopsych.2009.07.022
38. Gaffney GR, Kuperman S, Tsai LY, Minchin S, Hassanein KM. Midsagittal magnetic resonance imaging of autism. *Br J Psychiatry*. (1987) 151:831–3. doi: 10.1192/bjp.151.6.831
39. Haar S, Berman S, Behrmann M, Dinstein I. Anatomical abnormalities in autism. *Cereb Cortex*. (2016) 26:1440–52. doi: 10.1093/cercor/bhu242
40. Hardan AY, Minshew NJ, Keshavan MS. Corpus callosum size in autism. *Neurology*. (2000) 55:1033–6. doi: 10.1212/WNL.55.7.1033
41. Lefebvre A, Beggiato A, Bourgeron T, Toro R. Neuroanatomical diversity of corpus callosum and brain volume in autism: meta-analysis, analysis of the autism brain imaging data exchange project, and simulation. *Biol Psychiatry*. (2015) 78:126–34. doi: 10.1016/j.biopsych.2015.02.010
42. Manes F, Piven J, Vrancic D, Nanclares V, Plebst C, Starkstein SE. An MRI study of the corpus callosum and cerebellum in mentally retarded autistic individuals. *J Neuropsychiatry Clin Neurosci*. (1999) 11:470–4. doi: 10.1176/jnp.11.4.470
43. Piven J, Bailey J, Ranson BJ, Arndt S. An MRI study of the corpus callosum in autism. *Am J Psychiatry*. (1997) 154:1051–6. doi: 10.1176/ajp.154.8.1051
44. Rice SA, Bigler ED, Cleavinger HB, Tate DF, Sayer J, McMahon W, et al. Macrocephaly, corpus callosum morphology, and autism. *J Child Neurol*. (2005) 20:34–41. doi: 10.1177/08830738050200010601
45. Sui YV, Donaldson J, Miles L, Babb JS, Castellanos FX, Lazar M. Diffusional kurtosis imaging of the corpus callosum in autism. *Mol Autism*. (2018) 9:62. doi: 10.1186/s13229-018-0245-1
46. Vidal CN, Nicolson R, DeVito TJ, Hayashi KM, Geaga JA, Drost DJ, et al. Mapping corpus callosum deficits in autism: an index of aberrant cortical connectivity. *Biol Psychiatry*. (2006) 60:218–25. doi: 10.1016/j.biopsych.2005.11.011
47. Waiter GD, Williams JH, Murray AD, Gilchrist A, Perrett DI, Whiten A. Structural white matter deficits in high-functioning individuals with autistic spectrum disorder: a voxel-based investigation. *Neuroimage*. (2005) 24:455–61. doi: 10.1016/j.neuroimage.2004.08.049
48. Wolff JJ, Gerig G, Lewis JD, Soda T, Styner MA, Vachet C, et al. Altered corpus callosum morphology associated with autism over the first 2 years of life. *Brain*. (2015) 138:2046–58. doi: 10.1093/brain/awv118
49. Alexander AL, Lee JE, Lazar M, Boudos R, DuBray MB, Oakes TR, et al. Diffusion tensor imaging of the corpus callosum in Autism. *Neuroimage*. (2007) 34:61–73. doi: 10.1016/j.neuroimage.2006.08.032
50. Ameis SH, Lerch JP, Taylor MJ, Lee W, Viviano JD, Pipitone J, et al. A diffusion tensor imaging study in children with ADHD, autism spectrum disorder, OCD, and matched controls: distinct and non-distinct white matter disruption and dimensional brain-behavior relationships. *Am J Psychiatry*. (2016) 173:1213–22. doi: 10.1176/appi.ajp.2016.15111435
51. Aoki Y, Abe O, Nippashi Y, Yamasue H. Comparison of white matter integrity between autism spectrum disorder subjects and typically developing individuals: a meta-analysis of diffusion tensor imaging tractography studies. *Mol Autism*. (2013) 4:25. doi: 10.1186/2040-2392-4-25
52. Aoki Y, Yoncheva YN, Chen B, Nath T, Sharp D, Lazar M, et al. Association of white matter structure with autism spectrum disorder and attention-deficit/hyperactivity disorder. *JAMA Psychiatry*. (2017) 74:1120–8. doi: 10.1001/jamapsychiatry.2017.2573
53. Barnea-Goraly N, Kwon H, Menon V, Eliez S, Lotspeich L, Reiss AL. White matter structure in autism: preliminary evidence from diffusion tensor imaging. *Biol Psychiatry*. (2004) 55:323–6. doi: 10.1016/j.biopsych.2003.10.022
54. Barnea-Goraly N, Lotspeich LJ, Reiss AL. Similar white matter aberrations in children with autism and their unaffected siblings: a diffusion tensor imaging study using tract-based spatial statistics. *Arch Gen Psychiatry*. (2010) 67:1052–60. doi: 10.1001/archgenpsychiatry.2010.123
55. Bashat DB, Kronfeld-Duenias V, Zachor DA, Ekstein PM, Hendler T, Tarrasch R, et al. Accelerated maturation of white matter in young children with autism: a high b value DWI study. *Neuroimage*. (2007) 37:40–7. doi: 10.1016/j.neuroimage.2007.04.060
56. Brito AR, Vasconcelos MM, Domingues RC, Hygino da Cruz Jr LC, Rodrigues LDS, Gasparetto EL, et al. Diffusion tensor imaging findings in school-aged autistic children. *J Neuroimaging*. (2009) 19:337–43. doi: 10.1111/j.1552-6569.2009.00366.x
57. Di X, Azeez A, Li X, Haque E, Biswal BB. Disrupted focal white matter integrity in autism spectrum disorder: A voxel-based meta-analysis of diffusion tensor imaging studies. *Prog Neuropsychopharmacol Biol Psychiatry*. (2018) 82:242–8. doi: 10.1016/j.pnpbp.2017.11.007
58. Groen WB, Buitelaar JK, Van Der Gaag RJ, Zwiers MP. Pervasive microstructural abnormalities in autism: a DTI study. *J Psychiatry Neurosci*. (2011) 36:32. doi: 10.1503/jpn.090100
59. Hong S, Ke X, Tang T, Hang Y, Chu K, Huang H, et al. Detecting abnormalities of corpus callosum connectivity in autism using magnetic resonance imaging and diffusion tensor tractography. *Psychiatry Res*. (2011) 194:333–9. doi: 10.1016/j.pscychresns.2011.03.009
60. Keller TA, Kana RK, Just MA. A developmental study of the structural integrity of white matter in autism. *Neuroreport*. (2007) 18:23–7. doi: 10.1097/01.wnr.0000239965.21685.99
61. Kumar A, Sundaram SK, Sivaswamy L, Behen ME, Makki MI, Ager J, et al. Alterations in frontal lobe tracts and corpus callosum in young children with autism spectrum disorder. *Cereb Cortex*. (2010) 20:2103–13. doi: 10.1093/cercor/bhp278
62. Nickel K, Tebartz van Elst L, Perlov E, Endres D, Müller GT, Riedel A, et al. Altered white matter integrity in adults with autism spectrum disorder and an IQ > 100: a diffusion tensor imaging study. *Acta Psychiatr Scand*. (2017) 135:573–83. doi: 10.1111/acps.12731
63. Noriuchi M, Kikuchi Y, Yoshiura T, Kira R, Shigeto H, Hara T, et al. Altered white matter fractional anisotropy and social impairment in children with autism spectrum disorder. *Brain Res*. (2010) 1362:141–9. doi: 10.1016/j.brainres.2010.09.051
64. Shukla DK, Keehn B, Lincoln AJ, Müller RA. White matter compromise of callosal and subcortical fiber tracts in children with autism spectrum

disorder: a diffusion tensor imaging study. *J Am Acad Child Adolesc Psychiatry*. (2010) 49:1269–78. doi: 10.1016/j.jaac.2010.08.018
65. Shukla DK, Keehn B, Müller RA. Tract-specific analyses of diffusion tensor imaging show widespread white matter compromise in autism spectrum disorder. *J Child Psychol Psychiatry*. (2011) 52:286–95. doi: 10.1111/j.1469-7610.2010.02342.x
66. Thomas C, Humphreys K, Jung KJ, Minshew N, Behrmann M. The anatomy of the callosal and visual-association pathways in high-functioning autism: a DTI tractography study. *Cortex*. (2011) 47:863–73. doi: 10.1016/j.cortex.2010.07.006
67. Travers BG, Tromp DP, Adluru N, Lange N, Destiche D, Ennis C, et al. Atypical development of white matter microstructure of the corpus callosum in males with autism: a longitudinal investigation. *Mol Autism*. (2015) 6:15. 10.1186/s13229-015-0001-8. doi: 10.1186/s13229-015-0001-8
68. Vogan VM, Morgan BR, Leung RC, Anagnostou E, Doyle-Thomas K, Taylor MJ. Widespread white matter differences in children and adolescents with autism spectrum disorder. *J Autism Dev Disord*. (2016) 46:2138–47. doi: 10.1007/s10803-016-2744-2
69. Walker L, Gozzi M, Lenroot R, Thurm A, Behseta B, Swedo S, et al. Diffusion tensor imaging in young children with autism: biological effects and potential confounds. *Biol Psychiatry*. (2012) 72:1043–51. doi: 10.1016/j.biopsych.2012.08.001
70. Weinstein M, Ben-Sira L, Levy Y, Zachor DA, Itzhak EB, Artzi M, et al. Abnormal white matter integrity in young children with autism. *Hum Brain Mapp*. (2011) 32:534–43. doi: 10.1002/hbm.21042
71. Courchesne E, Pierce K. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Curr Opin Neurobiol*. (2005) 15:225–30. doi: 10.1016/j.conb.2005.03.001
72. Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. *Curr Opin Neurobiol*. (2007) 17:103–11. doi: 10.1016/j.conb.2007.01.009
73. Roland JL, Snyder AZ, Hacker CD, Mitra A, Shimony JS, Limbrick DD, et al. On the role of the corpus callosum in interhemispheric functional connectivity in humans. *Proc Natl Acad Sci USA*. (2017) 114:13278–83. doi: 10.1073/pnas.1707050114
74. Paul LK, Corsello C, Kennedy DP, Adolphs R. Agenesis of the corpus callosum and autism: a comprehensive comparison. *Brain*. (2014) 137:1813–29. doi: 10.1093/brain/awu070
75. Lau YC, Hinkley LB, Bukshpun P, Strominger ZA, Wakahiro ML, Baron-Cohen S, et al. Autism traits in individuals with agenesis of the corpus callosum. *J Autism Dev Disord*. (2013) 43:1106–18. doi: 10.1007/s10803-012-1653-2
76. Owen JP, Li YO, Yang FG, Shetty C, Bukshpun P, Vora S, et al. Resting-state networks and the functional connectome of the human brain in agenesis of the corpus callosum. *Brain Connect*. (2013) 3:547–62. doi: 10.1089/brain.2013.0175
77. Tyszka JM, Kennedy DP, Adolphs R, Paul LK. Intact bilateral resting-state networks in the absence of the corpus callosum. *J Neurosci*. (2011) 31:15154–62. doi: 10.1523/JNEUROSCI.1453-11.2011
78. Zhou IY, Liang YX, Chan RW, Gao PP, Cheng JS, Hu Y, et al. Brain resting-state functional MRI connectivity: morphological foundation and plasticity. *Neuroimage*. (2014) 84:1–10. doi: 10.1016/j.neuroimage.2013.08.037
79. Bocchi R, Egervari K, Carol-Perdiguer L, Viale B, Quairiaux C, De Roo M, et al. Perturbed Wnt signaling leads to neuronal migration delay, altered interhemispheric connections and impaired social behavior. *Nat Commun*. (2017) 8:1158. doi: 10.1038/s41467-017-01046-w
80. Ecker C, Bookheimer SY, Murphy DGM. Neuroimaging in autism spectrum disorder: brain structure and function across the lifespan. *Lancet Neurol*. (2015) 14:1121–34. doi: 10.1016/S1474-4422(15)00050-2
81. Piven J, Elison JT, Zylka MJ. Toward a conceptual framework for early brain and behavior development in autism. *Mol Psychiatry*. (2017) 22:1385–94. doi: 10.1038/mp.2017.131
82. Zuo XN, Kelly C, Di Martino A, Mennes M, Margulies DS, Bangaru S, et al. Growing together and growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. *J Neurosci*. (2010) 30:15034–43. doi: 10.1523/JNEUROSCI.2612-10.2010
83. Stark DE, Marguiles DS, Shehzad ZE, Reiss P, Clare Kelly AMC, Milham MP. Regional variation in interhemispheric coordination of intrinsic hemodynamic fluctuations. *J Neurosci*. (2008) 28:13754–64. doi: 10.1523/JNEUROSCI.4544-08.2008
84. Li HJ, Xu Y, Zhang KR, Hoptman MJ, Zuo XN. Homotopic connectivity in drug-naïve, first-episode, early-onset schizophrenia. *J Child Psychol Psychiatry*. (2015) 56:432–43. doi: 10.1111/jcpp.12307
85. Wang L, Li K, Zhang QE, Zeng YW, Jin Z, Dai WJ, et al. Interhemispheric functional connectivity and its relationships with clinical characteristics in major depressive disorder: a resting state fMRI study. *PLoS ONE*. (2013) 8:e60191. doi: 10.1371/journal.pone.0060191
86. Kelly C, Zuo XN, Gotimer K, Cox CL, Lynch L, Brock D, et al. Reduced interhemispheric resting state functional connectivity in cocaine addiction. *Biol Psychiatry*. (2011) 69:684–92. doi: 10.1016/j.biopsych.2010.11.022
87. Hu X, Zhang J, Jiang X, Zhou C, Wei L, Yin X, et al. Decreased interhemispheric functional connectivity in subtypes of Parkinson's disease. *J Neurol*. (2015) 262:760–7. doi: 10.1007/s00415-014-7627-x
88. Kozhemiako N, Vakorin V, Nunes AS, Iarocci G, Ribary U, Doesburg SM. Extreme male developmental trajectories of homotopic brain connectivity in autism. *Hum Brain Mapp*. (2019) 40:987–1000. doi: 10.1002/hbm.24427
89. Anderson JS, Nielsen JA, Froehlich AL, DuBray MB, Druzgal TJ, Cariello AN, et al. Functional connectivity magnetic resonance imaging classification of autism. *Brain*. (2011) 134:3742–54. doi: 10.1093/brain/awr263
90. Lau W, Leung MK, Zhang R. Hypofunctional connectivity between the posterior cingulate cortex and ventromedial prefrontal cortex in autism: Evidence from coordinate-based imaging meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. (2020) 103:109986. doi: 10.1016/j.pnpbp.2020.109986
91. Padmanabhan A, Lynch CJ, Schaer M, Menon V. The default mode in autism. *Biol Psychiatry*. (2017) 2:476–86. doi: 10.1016/j.bpsc.2017.04.004
92. Weng SJ, Wiggins JL, Peltier SJ, Carrasco M, Risi S, Lord C, et al. Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders. *Brain Res*. (2010) 1313:202–14. doi: 10.1016/j.brainres.2009.11.057
93. Jiang K, Yi Y, Li L, Li H, Shen H, Zhao F, et al. Functional network connectivity changes in children with attention-deficit hyperactivity disorder: a resting-state fMRI study. *Int J Dev Neurosci*. (2019) 78:1–6. doi: 10.1016/j.ijdevneu.2019.07.003
94. Liao W, Yu Y, Miao HH, Feng YX, Ji GJ, Feng JH. Inter-hemispheric intrinsic connectivity as a Neuromarker for the diagnosis of boys with Tourette syndrome. *Mol Neurobiol*. (2017) 54:2781–9. doi: 10.1007/s12035-016-9863-9
95. Witelson SF. Hand and sex differences in the isthmus and genu of the human corpus callosum: a postmortem morphological study. *Brain*. (1989) 112:799–835. doi: 10.1093/brain/112.3.799
96. Bauman ML, Kemper TL. *The Neurobiology of Autism*. Baltimore, MD: Johns Hopkins University Press (1994).
97. van Hemmen J, Saris IM, Cohen-Kettenis, PT, Veltman, DJ, Pouwels PJW, Bakker, J. Sex differences in white matter microstructure in the human brain predominantly reflect differences in sex hormone exposure. *Cereb Cortex*. (2017) 27:2994–001. doi: 10.1093/cercor/bhw156
98. Patel R, Moore S, Crawford DK, Hannsun G, Sasidhar MV, Tan K, et al. Attenuation of corpus callosum axon myelination and remyelination in the absence of circulating sex hormones. *Brain Pathol*. (2013) 23:462–75. doi: 10.1111/bpa.12029
99. Vannucci RC, Barron TF, Vannucci SJ. Development of the corpus callosum: an MRI study. *Dev Neurosci*. (2017) 39:97–106. doi: 10.1159/000453031
100. Pont-Lezica L, Beumer W, Colasse S, Drexhage H, Versnel M, Bessis A. Microglia shape corpus callosum axon tract fasciculation: functional impact of prenatal inflammation. *Eur J Neurosci*. (2014) 39:1551–7. doi: 10.1111/ejn.12508
101. Howard HC, Mount DB, Rochefort D, Byun N, Dupré N, Lu J, et al. The K-Cl cotransporter KCC3 is mutant in a severe peripheral neuropathy associated with agenesis of the corpus callosum. *Nat Genet*. (2002) 32:384–92. doi: 10.1038/ng1002

102. Qiu M, Anderson S, Chen S, Meneses JJ, Hevner R, Kuwana E, et al. Mutation of the Emx-1 homeobox gene disrupts the corpus callosum. *Dev Biol.* (1996) 178:174–8. doi: 10.1006/dbio.1996.0207
103. Di Martino A, O'connor D, Chen B, Alaerts K, Anderson JS, Assaf M, et al. Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. *Sci Data*. (2017) 4:1–15. doi: 10.1038/sdata.2017.10
104. Yan CG, Craddock RC, Zuo XN, Zang YF, Milham MP. Standardizing the intrinsic brain: towards robust measurement of inter-individual variation in 1000 functional connectomes. *Neuroimage*. (2013) 80:246–62. doi: 10.1016/j.neuroimage.2013.04.081

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Social Attention Deficits in Children With Autism Spectrum Disorder: Task Dependence of Objects vs. Faces Observation Bias

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Social attention deficits represent a central impairment of patients suffering from autism spectrum disorder (ASD), but the nature of such deficits remains controversial. We compared visual attention regarding social (faces) vs. non-social stimuli (objects), in an ecological diagnostic context, in 46 children and adolescents divided in two groups: ASD ($N = 23$) and typical neurodevelopment (TD) ($N = 23$), matched for chronological age and intellectual performance. Eye-tracking measures of visual scanning, while exploring and describing scenes from three different tasks from the Autism Diagnostic Observation Schedule (ADOS), were analyzed: "Description of a Picture," "Cartoons," and "Telling a Story from a Book." Our analyses revealed a three-way interaction between Group, Task, and Social vs. Object Stimuli. We found a striking main effect of group and a task dependence of attentional allocation: while the TD attended first and longer to faces, ASD participants became similar to TD when they were asked to look at pictures while telling a story. Our results suggest that social attention allocation is task dependent, raising the question whether spontaneous attention deficits can be rescued by guiding goal-directed actions.

Keywords: autism spectrum disorder, social attention, eye-tracking, attentional bias, autism diagnostic observation schedule

INTRODUCTION

Autism spectrum disorder (ASD) is an early-onset neurodevelopmental disorder marked by the specificity of significant impairments in social interaction and communication, restricted interests, and the presence of repetitive and stereotyped behaviors (1). Social deficits in other domains include deviations in basic attentional processes, impairments in attention to faces or social stimuli across the lifespan, as well as attention during social exchanges; for a review, see (2–5).

The ability to direct the attention to social stimuli is present and evident in typically developing children from early infancy onwards (6–8). The attention to faces serves as a window into individuals' emotional and intentional states, providing critical information for social, cognitive, and communicative development and functioning (9–14). It has been hypothesized that deficits in social attention present in ASD, such as reduced attention to social stimuli as a whole or atypical allocation of attention to social stimuli, are the cause of a compromised social functioning. Such deficits might lead to reduced social processing, loss of information necessary for the development of adaptive social functioning (15, 16), and difficulties in the interpretation of emotional information (17, 18).

Eye-tracking studies in ASD showed a correlation between reduced attention to social stimuli and behavioral measures (19–22). Klin et al. (21) showed, early on, that adolescents with ASD spent significantly less time attending to people when watching a segment of a movie and more time attending to the objects and the background of the scene. Deficits in social attention were thereafter replicated: (i) when looking at pictures of social scenes, participants with ASD spent less time attending to faces (23); (ii) ASD children showed no difference in the time looking at people or objects, unlike in typical neurodevelopment (TD) (24); and (iii) ASD attended less to the activities of others and focused more on the background objects (22).

Atypical imbalance in the attention for social (e.g., videos of playing children) vs. non-social stimuli (repeated geometrical patterns) in ASD was reported in a large-cohort study (25). A meta-analysis on gaze patterns (26) suggested the presence in ASD of a problem in selecting socially relevant vs. irrelevant information.

Other studies, however, do not confirm this hypothesis. Kemner et al. (27) found that the fixation times on face drawings embedded in an assortment of distractors of both children with ASD and TD were similar. Parish-Morris et al. (28) found that ASD and TD children and adolescents did not differ in the attention toward movies of faces as opposed to objects. In a study focused on magic, Kuhn et al. (29) found that ASD individuals were more susceptible to magic tricks, relying on sensitivity to social cues, than TD controls, contrary to their expectation. They found no between-group differences in fixation time on the magician's face and eyes. These studies suggest that the type of context and task may be relevant to disclose differences in social attentional allocation.

Several studies with infants suggest that innate or early-emerging attentional biases for faces or complex social scenes may be intact within the first months of life in infants who later develop ASD (30, 31) in line with negative results from behavioral studies in early infancy (32).

Other important aspect to consider in the study of social attention with eye tracking in ASD is the ecological and task relevance of the stimuli. Static stimuli have been associated with no group differences, which might indicate that they are not optimally sensitive. Adding to this information, it has been suggested that scenes depicting ecological social interactions are the ones that evoke robust social responses (33–35).

So far, no consensus has been reached on whether social attention is fundamentally reduced or absent in individuals with ASD. We hypothesize that the role of type of stimuli and task is critical. This may explain why a large number of studies show significantly diminished attention to social information in ASD compared to TD controls (21–23, 36–39), while many others show no differences (27–29, 40–44). Given this discrepancy, it is important to understand whether the putative social attention deficits are task and stimuli dependent.

We previously showed that task and context are determinant for perceptual performance in ASD, only showing coherence loss in task conditions favoring local attentional analysis (45). The same might hold for the attentional bias that characterizes this population. In this study, we extended this prior work by comparing attention allocation to social vs. non-social stimuli in three tasks in ASD and TD children and adolescents. We used a paradigm based on stimuli from the Autism Diagnostic Observation Schedule (ADOS) (46), a diagnostic tool that we used as a routine in the diagnostic procedure, to try to see if it can discriminate between ASD and TD children in what concerns to visual social attention and corroborate the attentional bias claim. We hypothesized that ASD children differ from TD children in visual attention to social stimuli and, in particular, demonstrate less looking toward faces than TD children.

METHODS

Participants

The study comprised two groups of participants: the experimental, composed by individuals with ASD without intellectual disability (1), and the control, composed by individuals with typical neurodevelopment (TD). A total of 46 children and adolescents were enrolled in the study: 23 for the ASD group (22 male, 1 female; mean age = 13 years and 1 month, minimum age = 8 years and 10 months, maximum age = 17 years and 4 months) and 23 for the control group (21 Male, 2 female; mean age = 13 years and 5 months, minimum age = 8 years and 5 months, maximum age = 17 years and 8 months). Sample sizes were based on previously established effect sizes from other studies using eye tracking (23). Groups were matched by chronological age, gender, and performance intelligence quotient (PIQ) (47). Analyses were conducted to ensure that participants were matched with respect to chronological age, gender, handedness, and PIQ in both groups (T-test, $p > 0.05$). Further group characterization details can be found in **Table 1**.

ASD participants were recruited from a sample from the Neurodevelopmental and Autism Unit, Child Developmental Center, Pediatric Hospital, Centro Hospitalar e Universitário

Abbreviations: ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; AFD, Average Fixation Duration; ANOVA, analysis of variance; AOI, area of interest; ASD, autism spectrum disorder; CHUC, Centro Hospitalar E Universitário De Coimbra; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; DT%, Dwell Time Percentage; ET, Entry Time; FFD, First Fixation Duration; FSIQ, Full-Scale Intelligence Quotient; FT%, Fixation Time Percentage; IQ, Intelligence Quotient; MANOVA, multivariate analysis of variance; NDT%, Net Dwell Time Percentage; NormD, Normalized Dwell; PIQ, Performance IQ; SD, standard deviation; TD, typical neurodevelopment.

TABLE 1 | Characterization of the clinical and control groups.

	ASD	TD	
	Mean (SE)	**Mean (SE)**	***T* tests**
N	23	23	
Gender (M/F)	22/1	21/2	$p > 0.05$
CA (months)	156.8 (4.9)	160.5 (6.4)	$p > 0.05$
FSIQ	99.2 (3.0)	124.8 (4.1)	
VIQ	96.3 (2.7)	123.9 (4.1)	
PIQ	104.0 (3.2)	112.1 (3.6)	$p > 0.05$
ADI-R RSI	15.7 (1.1)	–	
ADI-R L/C	9.4 (0.8)	–	
ADI-R RB/I	5.1 (0.6)	–	
ADOS COM	4.6 (0.3)	–	
ADOS SI	8.0 (0.5)	–	
ADOS Total	12.6 (0.7)	–	

ASD, Autism Spectrum Disorder group; TD, typical neurodevelopment group; SE, standard error of the mean; M, male; F, female; CA, chronological age; FSIQ, Full-Scale Intelligence quotient (IQ); VIQ, Verbal IQ; PIQ, Performance IQ; ADI-R RSI, ADI-R Reciprocal Social Interactions; ADI-R L/C, Autism Diagnostic Interview–Revised Language/Communication; RB/I, ADI-R Repetitive Behaviors/Interests; ADOS COM, ADOS Communication; ADOS SI, ADOS Social Interaction. T-tests; p > 0.05.

de Coimbra, Portugal. ASD diagnosis was assigned on the basis of the gold standard instruments: parental or caregiver interview, Autism Diagnostic Interview–Revised (ADI-R) (48); direct structured proband assessment, ADOS (46); and clinical examination performed by an experienced neurodevelopmental pediatrician, based on the current diagnostic criteria for autism spectrum disorder from the Diagnostic and Statistical Manual of Mental Disorders 5, DSM-5 (1). All ASD patients had positive results in the ADI-R and ADOS for autism or ASD and met the criteria for ASD from the DSM-5. A comprehensive medical observation excluded associated medical condition such as epilepsy, neurocutaneous or other genetic syndromes, or other usual comorbidities in ASD samples. TD participants were recruited from local schools and from our volunteers' database.

The exclusion criteria for the children who participated in this study were evaluated through an extensive anamnesis carried out with the parents or caregivers. They included neurological, neurodevelopmental, and genetic diseases, brain lesions, sensory, auditory, motor deficits, and neurodevelopmental milestones. Additionally, the parents of TD participants completed the Social Communication Questionnaire and Social Responsiveness Scale to ensure the exclusion of ASD symptomatology. TD participants with history of ASD symptomatology, other neurodevelopmental and neurological disorders, as well as other diseases mentioned above were excluded.

Both groups underwent an exhaustive neuropsychological evaluation and an assessment of the IQ to exclude intellectual disabilities [all participants had a Full-Scale IQ (FSIQ) > 70]. To be included in this study, participants also had to be able to read, describe pictures, and also remain still during the task. This increased the age of the participants able to be included, despite the efforts to recruit younger subjects.

Apparatus

Eye movements were measured with a remote binocular eye tracking (SMI RED) system (SMI-SensoMotoric Instruments, Germany), with a sampling rate of 250 Hz. The tracker has a reported gaze position accuracy of 0.4° and a spatial resolution of 0.05. The participants sat ∼between 60 and 70 cm away from a 22-in flat screen with a resolution of 1,680 × 1,050 pixels. The system compensates for head movements within a 50 cm × 30 cm (at 65 cm distance), allowing the participants to look at the screen in a naturalistic manner. A 9-point calibration procedure with a fixation cross was performed before each task. The children were instructed to fixate on the cross. After the calibration, there was a validation trial to ensure the precision of the data collection. The calibration process was repeated when necessary until both eyes achieved good mapping on all nine test positions (tracking error smaller than 1° visual angle).

Visual Stimuli and Task

The experimental protocol was created and implemented through SensoMotoric Instruments Experiment Center Version 3.2 (SMI-SensoMotoric Instruments, Germany). It was composed of three types of tasks, which integrated visual stimuli adapted from the ADOS (46). The ADOS is a semistructured, examiner's dependent, tool to assess communication, social interaction, and imagination. It allows to diagnose autism spectrum disorder (ASD) across ages, neurodevelopmental levels, and language skills. The tasks from ADOS adapted were "Description of a Picture," "Cartoons," and "Telling a Story from a Book." In the "Description of a Picture" task, the participant was asked to look at a scene and tell what she/he sees. In the "Cartoons" and "Telling a story from a Book" tasks, they are asked to tell a story from the images that are presented one at a time as if they were really narrating a book. Therefore, they were instructed to tell the researcher when they want to move to the following page. In total, they were 25 visual stimuli, representing social scenes, displayed on a screen.

Participants were allowed to move forward to the next stimulus as soon as they had described what they were seeing and told the experimenter they wanted to move to the next picture. This choice was made instead of using a button to prevent subjects' fatigue, or boredom, and a subsequent attention decrease that may lead to just pressing the button without the description. To increase subjects' attention, involvement, and motivation, and to assure that the exploration of the image begins at the same point, between each image, a fixation cross was always presented. This fixation cross disappeared once the participant's gaze was detected to be within the embedded area of interest (AOI) in it. **Figure 1** illustrates the experimental procedure. There was no time constraint in each picture.

Eye Tracking Recordings and Analysis

Eye movement data were recorded with iViewX™ 2.7 and analyzed offline with BeGaze™ 3.7 software where different AOIs were defined in a semiautomatic procedure: "faces" and "objects" (**Figure 2**).

We considered the following gaze metrics (defined in accordance with the manual of the BeGaze™ 3.7 software):

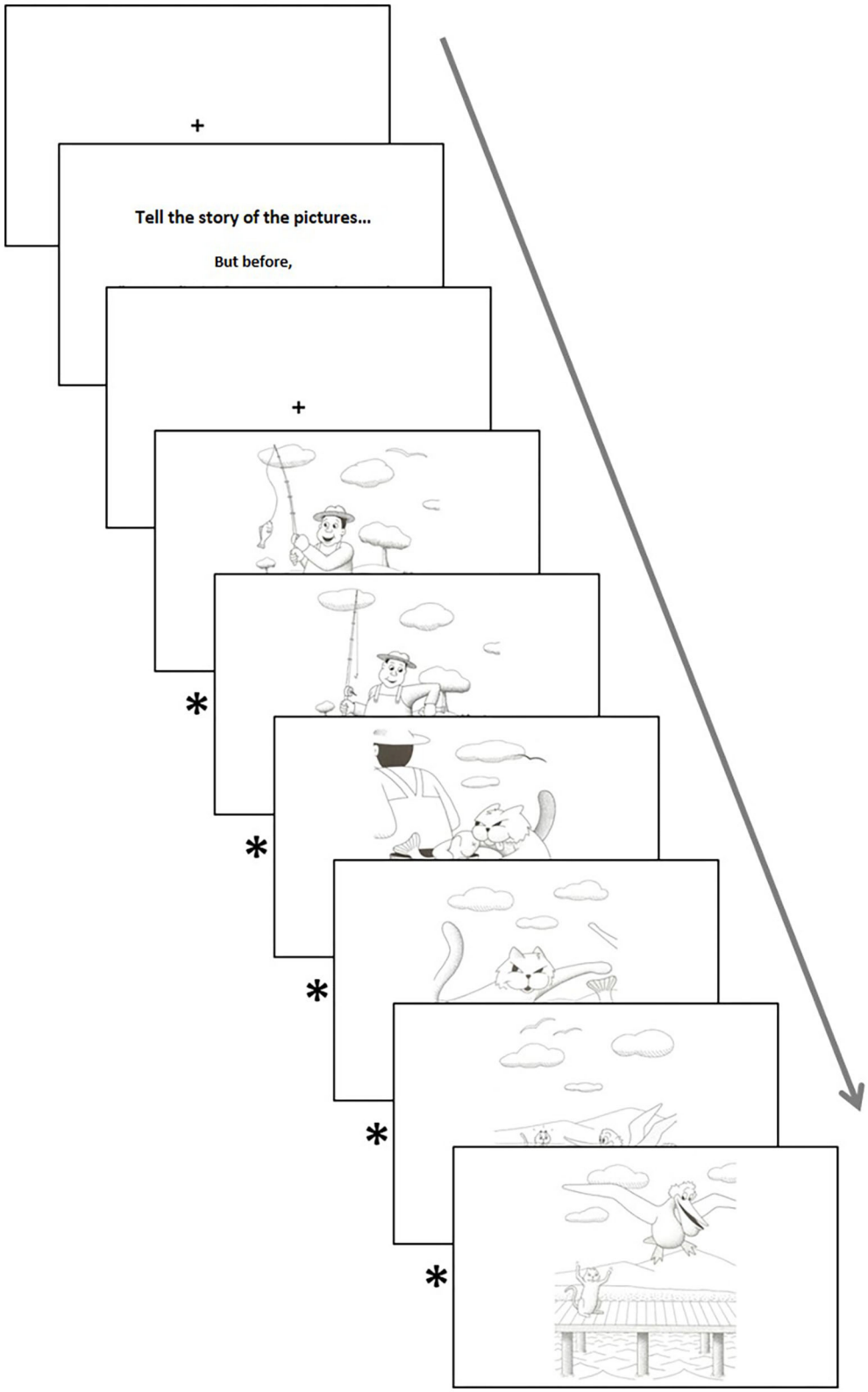

FIGURE 1 | Acquisition protocol of the task "Cartoons." *Between each image is always presented a fixation cross (signaled with an asterisk in the schematic representation of the task) to ensure that the exploration of the image begins at the same point.

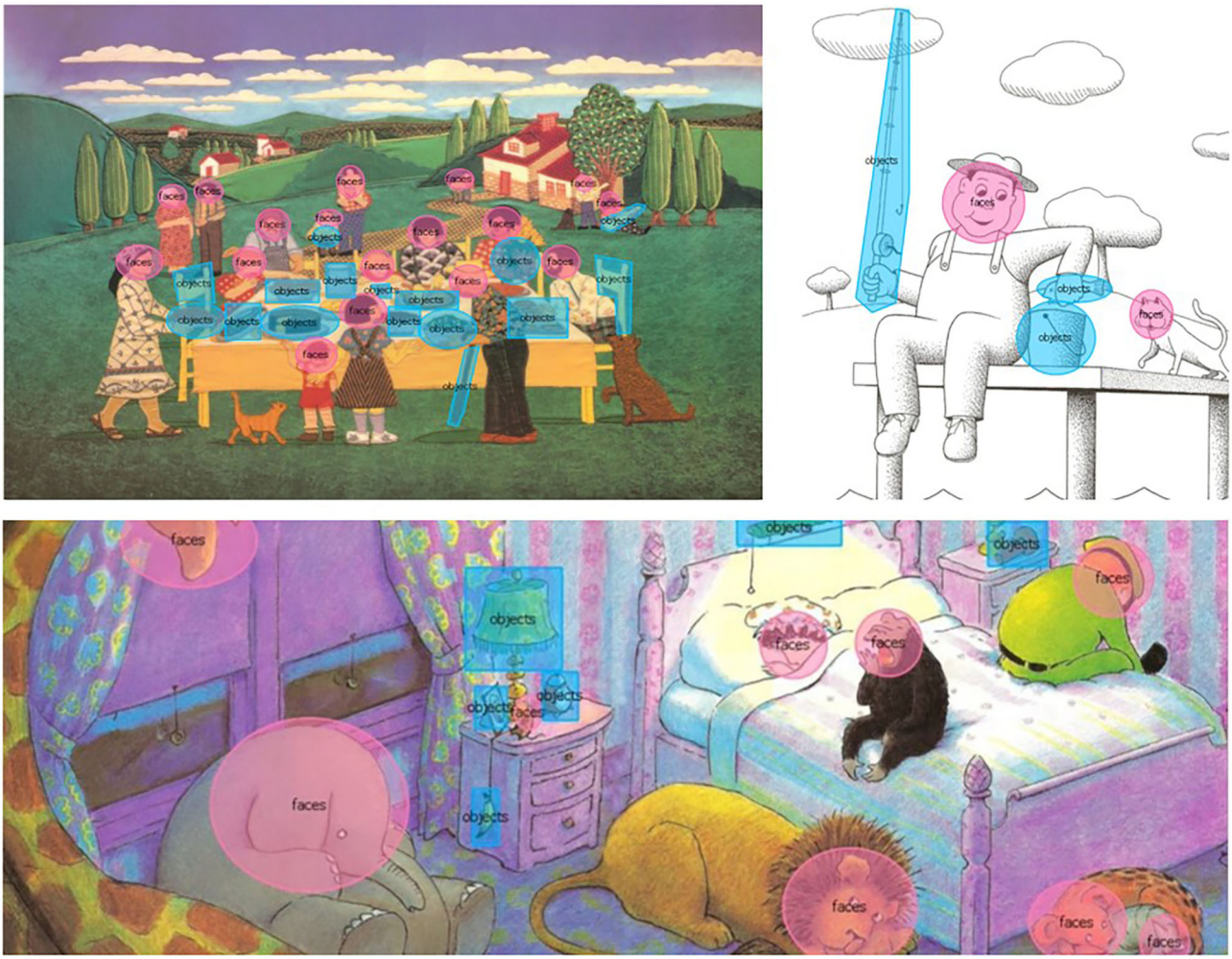

FIGURE 2 | Example of the different areas of interest defined.

Entry Time (ET), Dwell Time Percentage (DT%), Net Dwell Time Percentage (NDT%), Normalized Dwell (ms/coverage) (NormD), First Fixation Duration (FFD), Fixation Time Percentage (FT%), Average Fixation Duration (AFD), and Revisits. Entry Time expresses the average interval in milliseconds (ms) from the presentation of the visual stimuli (start of the trial) to the first gaze fixation on each area of interest (AOI). The Dwell Time Percentage (DT%) consists of the percentage of the sum of durations from all fixations and saccades (between the first and last fixations within the AOI) that hit the AOI (in ms), divided by the total stimulus duration. NDT% represents the percentage of the sum of sample durations for all gaze data samples that hit the AOI, divided by the total stimulus duration. NormD is the ratio between the DT and the AOI coverage, where coverage is the AOI size (measured in pixel) in comparison to stimulus size, thus representing a percentage of the number of pixel (px). It represents a more reliable measure to understand attention distribution patterns since it adjusts the duration that a subject spent to process an item relative to its surface in the display. FFD represents the duration (in ms) of the first fixation to hit the AOI. FT% consists of the percentage of the sum of the fixation durations inside the AOI, divided by the total stimulus duration. AFD is the total duration (ms) of all fixations divided by the number of fixations inside the AOI. A longer fixation duration is often associated with a deeper and more effortful cognitive processing. Revisits represent the number of time subjects visit an AOI.

Data Analysis and Statistics

Initially, we conducted a descriptive statistics analysis in order to characterize the sample.

Eye-position data were analyzed with a standard AOI approach. Eye-tracking data were preprocessed using the SMI software, BeGaze Version 3.7 (SMI-SensoMotoric Instruments, Germany), which uses a dispersion-based algorithm for detecting fixations. The minimum fixation duration was 80 ms, and the maximum dispersion value was 100 pixels. Different aspects of eye movements were assessed. We included seven dependent

variables in our eye-tracking analyses: ET, NDT%, NormD, FFD, FT%, AFD, and Revisits.

One participant in the TD group was excluded from analysis due to problems with eye-tracking data collection in tasks Picture and Book. In total, there were, therefore, valid data for 23 ASD and 22 TD participants in the Picture and Book Tasks and for 23 ASD and 23 TD participants in the Cartoons Task.

Multivariate analysis of variance (MANOVA) with a three-way interaction was used to evaluate differences in the eye-tracking measures by group, task, and AOI type (faces or objects). The goal of the three-way MANOVA was to understand if there was an interaction effect for group, AOI type, and task in the eye-tracking measures. Follow-up univariate three-way ANOVAs were run for each dependent variable. In the dependent variables with statistically significant interaction effects, simple two-way interactions and main effect of group were run. In the statistically significant main effect of group, pairwise comparisons were run with a Bonferroni adjustment applied. Effect sizes (partial η^2 for F statistics and Cohen's d for Bonferroni) are reported with p-values for significant main effects, interactions, and pairwise comparisons. Our MANOVA reached a power of 92%.

All statistical analysis was completed with the support of the version for Microsoft Windows® of the Statistical Package for Social Sciences, version 26 (SPSS®, Chicago, IL, USA). A significance level of 0.05 was adopted.

Ethics Statement

All the procedures in this study were reviewed and approved by the ethics committees from the Faculty of Medicine from University of Coimbra, Portugal (CE-11/2013) and the Centro Hospitalar e Universitário de Coimbra, Portugal (CHUC-102-13) and was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the parents/guardians of all participants. Children and adolescents also gave oral informed consent.

RESULTS

A three-way MANOVA was run with seven eye-tracking measures (ET, NDT%, NormD, FFD, FT%, AFD, and Revisits) as dependent variables and independent variables: Group (ASD and TD), Task (Picture, Cartoons, and Book), and AOI (faces and objects). There was a statistically significant three-way interaction between Group, Task, and AOI in all our dependent variables

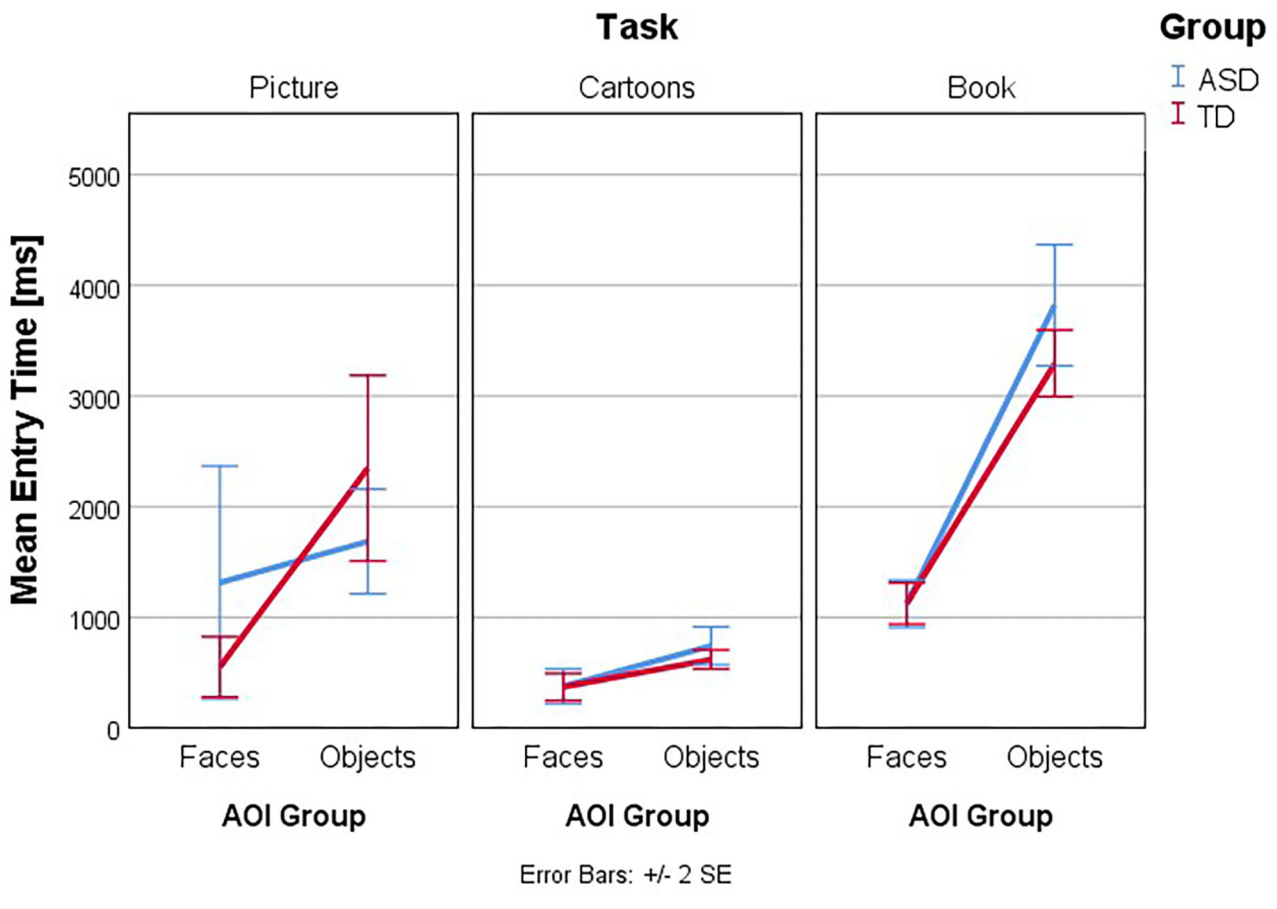

FIGURE 3 | Interaction effects between group, task, and type of AOI. Mean Entry Time (ms): interaction plot Group × Task × AOI. Mean Entry Time is shown for the AOI group Faces and Objects, plotted by Group (ASD and TD) in the three tasks. Lower numbers indicate the first AOI to have the first gaze fixation.

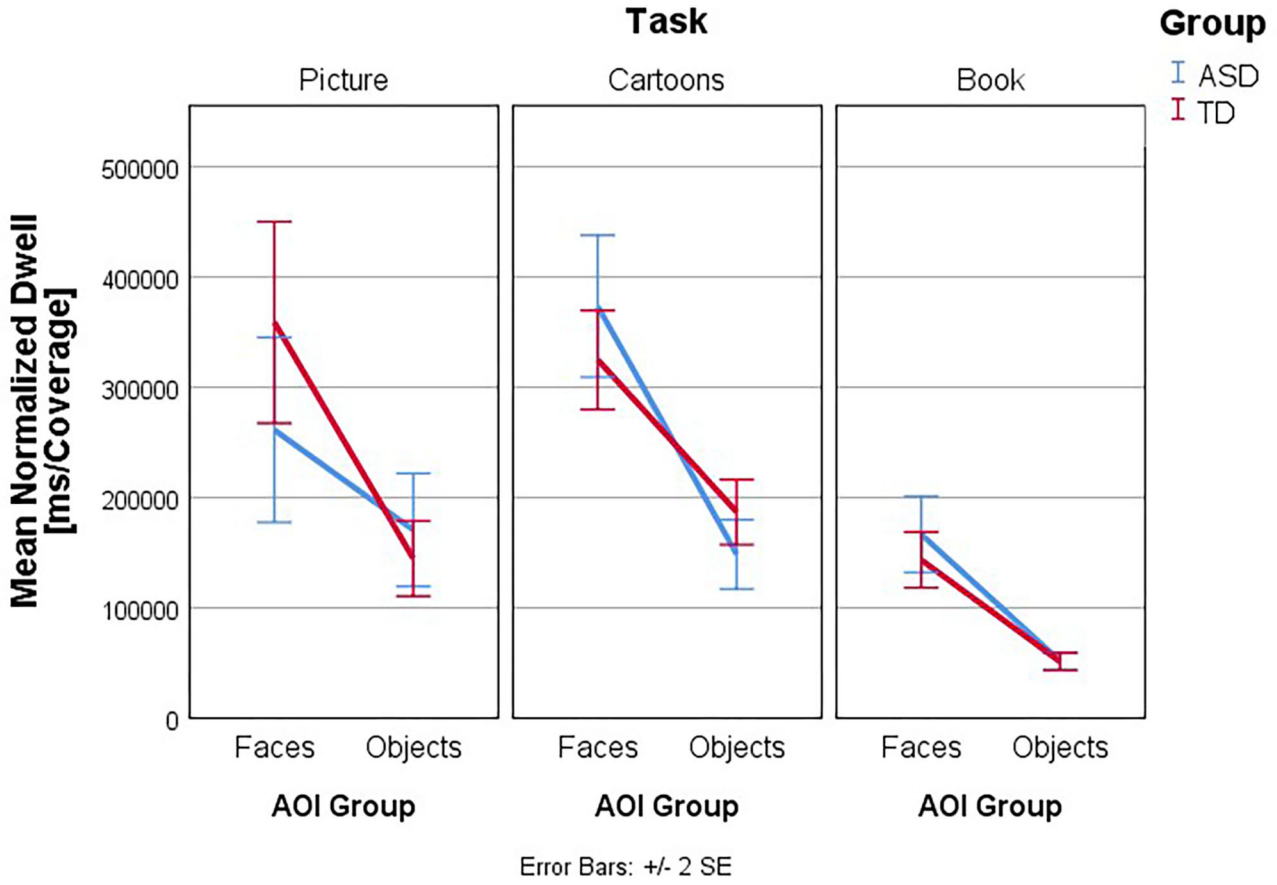

FIGURE 4 | Interaction effects between group, task, and type of AOI. Mean Normalized Dwell (ms/coverage): interaction plot Group × Task × AOI. Mean Normalized Dwell is shown for the AOI group Faces and Objects, plotted by Group (ASD and TD) in the three tasks. Higher numbers indicate more time spent within the AOI, normalized by the AOI size in comparison to stimulus size, thus more time the subject spent to process the stimuli.

together, Pillai's Trace = 0.092; $F_{(2, 260)} = 1.764$, $p = 0.041$, partial $\eta^2 = 0.046$.

Follow-up univariate three-way ANOVAs were run for each dependent variable. These showed a statistically significant three-way interaction effect between group, task, and AOI for ET [$F_{(2, 260)} = 4.763$, $p = 0.009$, partial $\eta^2 = 0.035$], NormD [$F_{(2, 260)} = 4.805$, $p = 0.009$, partial $\eta^2 = 0.036$], NDT% [$F_{(2, 260)} = 4.693$, $p = 0.010$, partial $\eta^2 = 0.035$], and FT% [$F_{(2, 260)} = 3.81$, $p = 0.023$, partial $\eta^2 = 0.029$] but not for FFD [$F_{(2, 260)} = 0.59$, $p = .556$, partial $\eta^2 = 0.005$], Revisits [$F_{(2, 260)} = 1.77$, $p = 0.172$, partial $\eta^2 = 0.013$] and AFD [$F_{(2, 260)} = 0.28$, $p = 0.756$, partial $\eta^2 = 0.002$]. The interaction effects of Group, Task, and AOI in ET and NDT% are illustrated in **Figures 3–6**.

Figures 3–6 present the interaction between Task and AOI at the different groups: ASD and TD. According to **Figures 3–6**. This interaction effect indicates that the relationship between task and AOI depends on the group.

For the dependent variables with the statistically significant three-way interaction effect between group, task, and AOI, we now present the simple two-way interactions, main effect of group and pairwise comparisons, where needed, separately. Pairwise comparisons are summarized in **Table 2**.

Entry Time

Follow-up univariate two-way ANOVAs were run for the dependent variable ET and the main effect of group considered. These showed a statistically significant simple two-way interaction between Group and AOI in the dependent variable Entry Time, for the Picture Task [$F_{(2, 260)} = 9.08$, $p = 0.003$, partial $\eta^2 = 0.034$] but not for the Cartoons [$F_{(2, 260)} = 0.07$, $p = 0.799$, partial $\eta^2 = 0.000$] and Book [$F_{(2, 260)} = 1.27$, $p = 0.262$, partial $\eta^2 = 0.005$] Tasks. As such, a simple main effect analysis was conducted for Picture Task, and we found a statistically significant main effect of Group in the dependent variable Entry Time, for the AOI Faces $F_{(2, 260)} = 5.194$, $p = 0.023$, partial $\eta^2 = 0.020$, and for the AOI Objects $F_{(2, 260)} = 3.93$, $p = 0.049$, partial $\eta^2 = 0.015$, in the Picture Task. Therefore, simple pairwise comparisons were run for the differences in mean ET score in the AOI Faces and AOI Objects between groups in the Picture Task, with a Bonferroni adjustment applied. In the Picture Task, in the AOI Faces, the mean ET in the ASD group was 1313.08 [standard deviation (SD) = 2526.63] and 551.51 (SD = 637.78) in the TD group, a statistically significant mean difference of 761.56, 95% CI (103.55, 1419.57), $p = 0.023$, $d = -0.41$. In the same task, in the AOI Objects, the mean Entry Time in

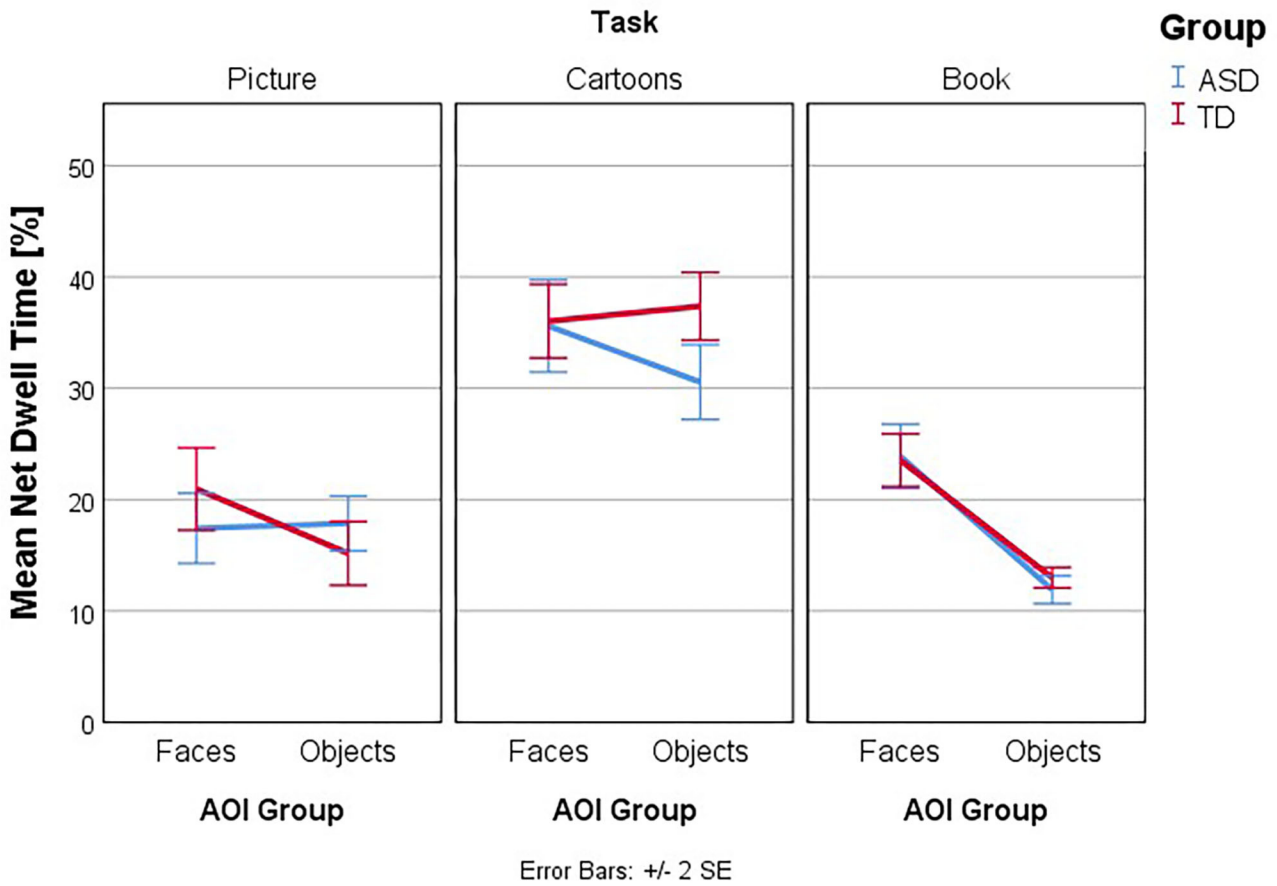

FIGURE 5 | Interaction effects between group, task, and type of AOI. Mean Net Dwell Time (%): interaction plot Group × Task × AOI. Mean Net Dwell Time (%) is shown for the AOI group Faces and Objects, plotted by Group (ASD and TD) in the three tasks. Higher numbers indicate more time spent within the AOI.

the ASD group was 1685.34 (SD = 1134.27) and 2347.37 (SD = 1967.34) in the TD group, a statistically significant mean difference of −662.038, 95% CI (−1320.05, −4.03), p = 0.049, d = 0.41.

Normalized Dwell

Follow-up univariate two-way ANOVAs were run for the dependent variable NormD and the main effect of group considered. These showed a statistically significant simple two-way interaction between Group and AOI in the dependent variable NormD, for the Picture task [$F_{(2, 260)}$ = 6.25, p = 0.013, partial η^2 = 0.023] but not for the Cartoons [$F_{(2, 260)}$ = 3.17, p = 0.076, partial η^2 = 0.012] and Book [$F_{(2, 260)}$ = 0.21, p = 0.647, partial η^2 = 0.001] Tasks. Afterwards, a simple main effect analysis was conducted for Picture Task, and we found a statistically significant main effect of Group in the dependent variable NormD, for the AOI Faces $F_{(2, 260)}$ = 7.79, p = 0.006, partial η^2 = 0.029. As such, simple pairwise comparisons were run for the differences in mean NormD score in the AOI Faces and AOI Objects between groups in the Picture Task, with a Bonferroni adjustment applied. In the AOI faces in the Picture Task, the mean NormD in the ASD group was 261306.24 (SD = 200946.01) and 358870.71 (SD = 214344.38) in the TD group, a statistically significant mean difference of −97564.48, 95% CI (−166398.89, −28730.07), p = 0.006, d = 0.47.

Net Dwell Time

Follow-up univariate two-way ANOVAs were run for the dependent variable NTD% and the main effect of group considered. These showed a statistically significant simple two-way interaction between Group and AOI in the dependent variable Net Dwell Time, for the task Picture $F_{(2, 260)}$ = 4.46, p = 0.036, partial η^2 = 0.017, and for the task Cartoons $F_{(2, 260)}$ = 4.80, p = 0.029, partial η^2 = 0.018 but not for the Book [$F_{(2, 260)}$ = 0.24, p = 0.625, partial η^2 = 0.001] Task. As such, a simple main effect analysis was conducted for Picture and Cartoons Tasks, and we found a statistically significant main effect of Group in the dependent variable Net Dwell Time, for the AOI Faces in the Cartoons Task $F_{(2, 260)}$ = 10.97, p = 0.001, partial η^2 = 0.040. Therefore, simple pairwise comparisons were run for the differences in mean NTD% score in the AOI Faces between groups in the Cartoons Task, with a Bonferroni adjustment applied. In the AOI objects in the Cartoons Task, the

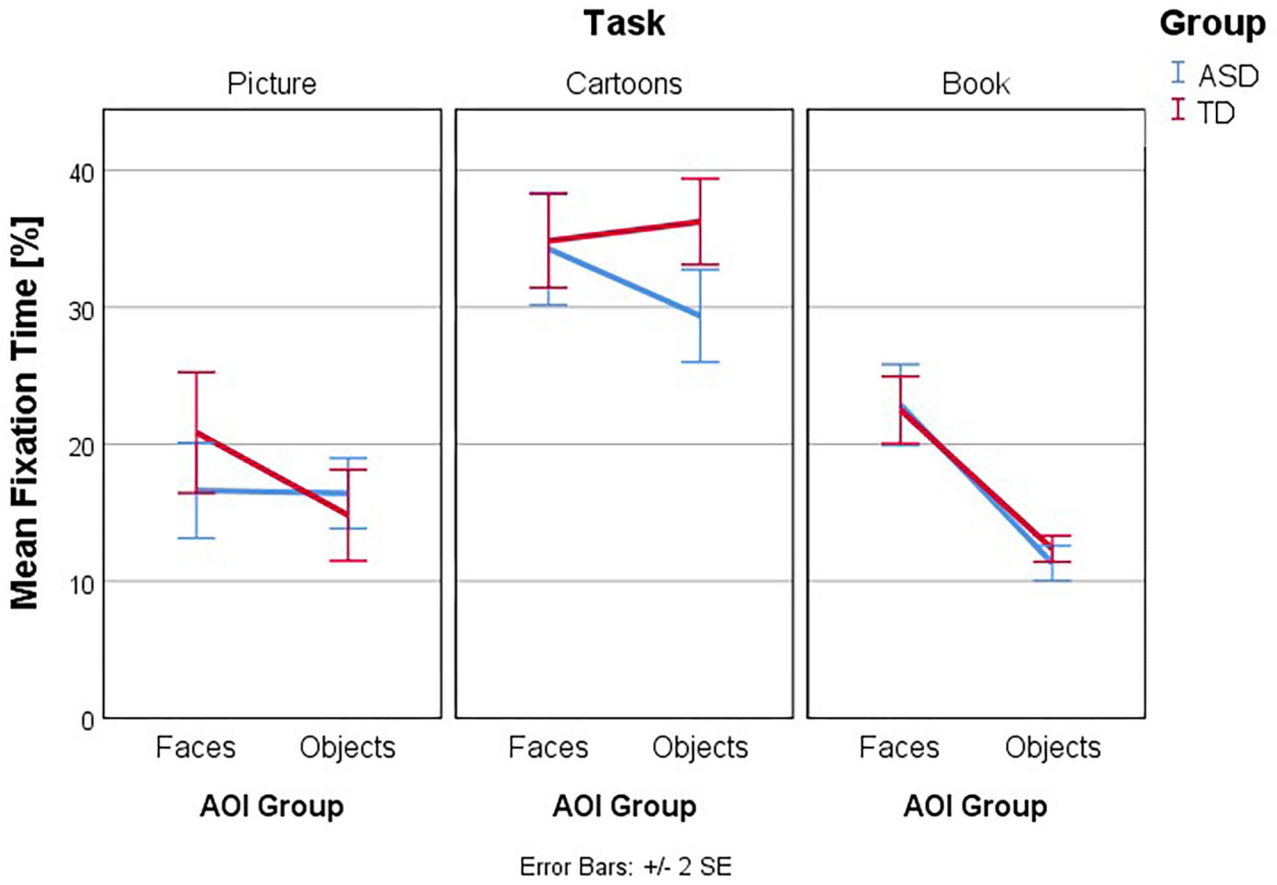

FIGURE 6 | Interaction effects between group, task, and type of AOI. Mean Fixation Time (%): interaction plot Group × Task × AOI. Mean Fixation Time is shown for the AOI group Faces and Objects, plotted by Group (ASD and TD) in the three tasks. Higher numbers indicate more time spent within the AOI.

mean Net Dwell Time in the ASD group was 30.55 ($SD = 8.06$) and 37.37 ($SD = 7.28$) in the TD group, a statistically significant mean difference of −6.82, 95% CI (−10.88, −2.77), $p = 0.001$, $d = 0.89$.

Fixation Time

Follow-up univariate two-way ANOVAs were run for the dependent variable FT% and the main effect of group considered. These showed a statistically significant simple two-way interaction between Group and AOI in the dependent variable FT%, for the task Cartoons [$F_{(2, 260)} = 4.15$, $p = 0.043$, partial $\eta^2 = 0.016$]. Afterwards, a simple main effect analysis was conducted for Cartoons Task, and we found a statistically significant main effect of Group in the dependent variable FT%, for the AOI Objects in the Cartoons Task $F_{(2, 260)} = 9.89$, $p = 0.002$, partial $\eta^2 = 0.037$. As such, simple pairwise comparisons were run for the differences in mean FT% score in the AOI Objects between groups in the Cartoons Task, with a Bonferroni adjustment applied. In the AOI objects in the Cartoons Task, the mean Fixation Time in the ASD group was 29.36 ($SD = 8.09$) and 36.24 ($SD = 7.52$) in the TD group, a statistically significant mean difference of −6.88, 95% CI (−11.18, −2.57), $p = 0.002$, $d = 0.88$.

DISCUSSION

We studied social attention deficits in ASD and focused, in particular, on face stimuli, in the clinical context of different tasks of ADOS. For that purpose, we used eye-tracking methodology to compare the task dependence of visual attention to social stimuli (faces) vs. nonsocial stimuli (objects) in two matched groups of children and adolescents with ASD or TD.

We found significant interaction effects (between group, task, and type of AOI), when the participants are requested to perform spontaneous and simple descriptions of a picture or even a set of cartoons. When scenarios implied generating a goal-oriented narrative in the task, the pattern of attentional allocation in ASD subjects was normalized. In other words, it became similar to controls when children have to create a more complex story, such as the story of a book, doing an enforced narrative description. The absence of interaction effects in that case corroborates similar visual search patterns in TD children. The "Description of a Picture task," despite being a painting and not a real picture, is the one depicting a more ecological social interaction: a table surrounded by people interacting while having a lunch party, playing guitar, and talking to each other. Our findings thereby provide a framework that reconciles previous literature. Scenes

TABLE 2 | The comparison of the mean ± SD of the eye-tracking measures between ASD ($n = 23$) and TD ($n = 23$).

			ASD	TD	*Statistics*	
Eye-tracking measures	**Task**	**AOI**	**Mean ± SD**	**Mean ± SD**	***p***	***d***
Entry time (ms)	Picture	Faces	1313.07 ± 2526.63	551.51 ± 637.78	0.023*	−0.413
		Objects	1685.33 ± 1134.27	2347.37 ± 1967.34	0.049*	0.412
	Cartoons	Faces	375.59 ± 375.76	370.32 ± 291.46	0.987	−0.016
		Objects	742.39 ± 410.65	617.82 ± 207.70	0.706	−0.383
	Book	Faces	1120.47 ± 514.29	1124.77 ± 439.73	0.99	0.009
		Objects	3821.01 ± 1311.36	3293.79 ± 708.56	0.116	−0.497
Normalized dwell (ms/coverage)	Picture	Faces	261306.23 ± 200946.10	358870.71 ± 214344.38	0.006*	0.47
		Objects	170705.95 ± 122808.11	144670.91 ± 79,944.23	0.457	−0.251
	Cartoons	Faces	373543.36 ± 154277.07	324851.21 ± 107742.37	0.160	−0.366
		Objects	148538.82 ± 75339.15	186859.44 ± 70924.83	0.269	0.524
	Book	Faces	166567.76 ± 82569.63	143424.55 ± 59218.12	0.509	−0.321
		Objects	51705.32 ± 19204.18	51205.75 ± 18,307.33	0.989	−0.027
Net dwell time (%)	Picture	Faces	17.42 ± 7.55	20.95 ± 8.66	0.091	0.435
		Objects	17.86 ± 5.90	15.16 ± 6.70	0.197	−0.428
	Cartoons	Faces	35.59 ± 9.93	36.03 ± 7.95	0.832	0.049
		Objects	30.55 ± 8.06	37.37 ± 7.28	0.001*	0.888
	Book	Faces	23.89 ± 6.93	23.53 ± 5.54	0.861	−0.057
		Objects	11.90 ± 3.00	12.98 ± 2.17	0.605	0.411
Fixation time (%)	Picture	Faces	16.62 ± 8.36	20.84 ± 10.35	0.057	0.449
		Objects	16.41 ± 6.16	14.80 ± 7.78	0.469	−0.229
	Cartoons	Faces	34.26 ± 9.85	34.84 ± 8.18	0.792	0.064
		Objects	29.36 ± 8.09	36.24 ± 7.52	0.002*	0.881
	Book	Faces	22.87 ± 7.07	22.50 ± 5.75	0.867	−0.057
		Objects	11.30 ± 3.06	12.35 ± 2.25	0.636	0.390

*Pairwise comparisons with a Bonferroni adjustment: significance levels and effect-sizes; *p < 0.05. All comparisons signaled with * are significant. Effect sizes were computed using Cohen's d.*

depicting ecological social interactions have been associated to better evoke robust social responses (33, 34). Currently, a methodological approach, denominated cognitive ethology, also focused on ecological validity. It advocates that one's research approach should begin at the level of the phenomenon of interest and to systematically move toward a simplified and abstract level but also doing the inverse approach, reinforcing the idea of analyzing a continuum (49, 50). In our study, we presented three different tasks, with large clinical relevance (used in ADOS) with a growing level of abstract social scenes (from the representation of the social gathering around the table, to the interaction of cartoons in the story of the book).

As predicted, we found that TD children looked first to faces and during a longer period of time in the socially rich and familiar context of a gathering of people around a table ("Description of a Picture task"). The ASD children did not show a differential pattern, between faces and objects. In other words, under these conditions interaction effects are triggered: the ASD group tends to have a similar pattern of visual search in what concerns to attention to social and non-social stimuli, that is, faces and objects, while the TD group looks first at faces and for a longer period of time, which corroborates the hypothesis that ASD participants are less attentive to faces (21–23, 36–39).

On the other hand, our study corroborates that children and adolescents with and without ASD show remarkably similar visual search patterns in their initial eye gaze to faces (51). However, in our study, participants are not instructed to specifically look at faces, which adds meaning and ecological importance to the result. In fact, the participants only had to describe what they were seeing, and therefore, the visual search pattern is natural and more spontaneous.

Overall, our results seem to provide a unifying view of previous research. The TD group always presented a lower ET to the AOI faces than objects, looking at the faces first, when exploring visually the images, also spending more time looking at social stimuli. This visual search pattern is absent in the ASD group. In fact, although children with ASD look at the faces first (lower ET in the AOI faces, than in the AOI objects), there are no statistical differences in the Cartoons and Book tasks (the ones that guide a goal oriented narrative), when compared with TD.

Taken together, our results point to the fact that social attention allocation patterns in ASD population are strongly task dependent, which extends our previous work in other cognitive domains (45). Accordingly, the task not requiring an explicit goal-oriented narrative yields the greatest differences. This raises the question whether spontaneous attention deficits can be

rescued by guiding goal-directed actions (40). These results are relevant for the selection of interventional strategies and in ASD children, since it stresses the importance of goal-oriented actions, which are the foundations of the structured teaching.

ASD and TD groups analyze social and non-social content differently. However, when they have to do a narrative, visual behavior tends to normalize (that is, ASD has similar visual patterns as TD), which suggests that the narrative is used as guidance.

Entry time is an eye-tracking measure that characterizes rapid events, and it is in this measure that there are more differences between ASD and TD, which can be interpreted as the best measures to distinguish the groups.

In the present study, there are some limitations to consider. Inclusion of younger children and subjects with intellectual disability was difficult because most of them were not able to make a good calibration and were therefore excluded. Our experimental design did not explicitly account for low-level saliency. However, we believe that, in accordance with previous studies, gaze behavior is better predicted by the social features than by low-level saliency alone (52–54).

In the current analysis, we focused on attention to the faces and objects in the pictures from the different tasks of ADOS (a well-validated but examiner's dependent diagnosis tool for ASD) thereby trying to provide a complementary quantitative information of potential value in clinical practice to distinguish between ASD children without intellectual disability and TD. Although precise, the sensitivity of eye-tracking as a diagnostic tool remains uncertain. Here, we provide evidence for task dependence, with patterns "normalizing" when a narrative is required. With this strategy, we hope to provide a tool that may help improve the course of ASD diagnostic evaluation, especially in subjects with ASD without intellectual disability, where the differential diagnosis with a typical neurodevelopment is often very difficult.

In conclusion, eye-tracking measures of visual scanning, while exploring and describing activities from the ADOS, in particular, "Description of a Picture," can discriminate between ASD and TD groups. Individuals with ASD allocated their attention to faces and objects in a similar way, while individuals from the TD group attend first and more time to faces. However, when ASD children are asked to look at pictures, organize the thought, and tell a story, they attend to the same stimuli and have a similar pattern of visual search as the TD group, which raises interesting insights on the origin of this "normalization." Accordingly, when goal-directed actions, in this case, an enforced narrative description, are required, visual search patterns in ASD tend to resemble TD and therefore "normalize" as compared to spontaneous attention. These findings are of potential relevance to training strategies, by providing clues on learning adaptive attentional deployment. In addition, they stress the importance from a diagnostic perspective point of view of observation and classification of spontaneous behavior. Future work should confirm the value of this tool to help differential diagnosis especially in difficult cases with other neurodevelopmental disorders or typical development.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

All procedures in this study were reviewed and approved by the ethics committees from the Faculty of Medicine from University of Coimbra, Portugal (CE-11/2013) and the Centro Hospitalar e Universitário de Coimbra, Portugal (CHUC-102-13) and was conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the parents/guardians of all participants. Children and adolescents also gave oral informed consent.

AUTHOR CONTRIBUTIONS

SM, GO, and MC-B: conceived and designed the study. SM: performed the study and wrote the original manuscript. SM, CC, DS, and FD: contributed with data collection. SM and JC: analyzed the data. GO and MC-B: supervision. JC, GO, and MC-B: reviewed and edited the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing (2013). doi: 10.1176/appi.books.9780890425596
2. Chita-Tegmark M. Social attention in ASD: a review and meta-analysis of eye-tracking studies. *Res Dev Disabil.* (2016) 48:79–93. doi: 10.1016/j.ridd.2015.10.011
3. Chita-Tegmark M. Attention allocation in ASD: a review and meta-analysis of eye-tracking studies. *Rev J Autism Dev Disord.* (2016) 3:209–23. doi: 10.1007/s40489-016-0077-x

4. Falck-Ytter T, Bölte S, Gredebäck G. Eye tracking in early autism research. *J Neurodev Disord.* (2013) 5:28. doi: 10.1186/1866-1955-5-28
5. Guillon Q, Hadjikhani N, Baduel S, Rogé B. Visual social attention in autism spectrum disorder: insights from eye tracking studies. *Neurosci Biobehav Rev.* (2014) 42:279–97. doi: 10.1016/j.neubiorev.2014.03.013
6. Gliga T, Csibra G. Seeing the face through the eyes: a developmental perspective on face expertise. In: von Hofsten C, Rosander K, editors. *Progress in Brain Research*. Vol. 164. Amsterdam: Elsevier (2007). p. 323–39. doi: 10.1016/S0079-6123(07)64018-7
7. Goren CC, Sarty M, Wu PYK. Visual following and pattern discrimination of face-like stimuli by newborn infants. *Pediatrics.* (1975) 56:544–9.
8. Vuilleumier P. Facial expression and selective attention. *Curr Opin Psychiatry.* (2002) 15:291–300. doi: 10.1097/00001504-200205000-00011
9. Feldman R, Greenbaum CW, Yirmiya N. Mother–infant affect synchrony as an antecedent of the emergence of self-control. *Dev Psychol.* (1999) 35:223–31. doi: 10.1037/0012-1649.35.1.223
10. Tronick EZ. Emotions and emotional communication in infants. *Am Psychol.* (1989) 44:112–9. doi: 10.1037/0003-066X.44.2.112
11. Trevarthen C, Aitken KJ. Infant intersubjectivity: research, theory, and clinical applications. *J Child Psychol Psychiatry.* (2001) 42:3–48. doi: 10.1111/1469-7610.00701
12. Grelotti DJ, Gauthier I, Schultz RT. Social interest and the development of cortical face specialization: what autism teaches us about face processing. *Dev Psychobiol.* (2002) 40:213–25. doi: 10.1002/dev.10028
13. Johnson MH. Subcortical face processing. *Nat Rev Neurosci.* (2005) 6:766–74. doi: 10.1038/nrn1766
14. Schultz RT. Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. *Int J Dev Neurosci.* (2005) 23:125–41. doi: 10.1016/j.ijdevneu.2004.12.012
15. Chevallier C, Kohls G, Troiani V, Brodkin ES, Schultz RT. The social motivation theory of autism. *Trends Cogn Sci.* (2012) 16:231–9. doi: 10.1016/j.tics.2012.02.007
16. Dawson G, Webb SJ, McPartland J. Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. *Dev Neuropsychol.* (2005) 27:403–24. doi: 10.1207/s15326942dn2703_6
17. Pelphrey KA, Sasson NJ, Reznick JS, Paul G, Goldman BD, Piven J. Visual scanning of faces in autism. *J Autism Dev Disord.* (2002) 32:249–61. doi: 10.1023/A:1016374617369
18. Wagner JB, Hirsch SB, Vogel-Farley VK, Redcay E, Nelson CA. Eye-tracking, autonomic, and electrophysiological correlates of emotional face processing in adolescents with autism spectrum disorder. *J Autism Dev Disord.* (2013) 43:188–99. doi: 10.1007/s10803-012-1565-1
19. Bird G, Press C, Richardson DC. The role of alexithymia in reduced eye-fixation in autism spectrum conditions. *J Autism Dev Disord.* (2011) 41:1556–64. doi: 10.1007/s10803-011-1183-3
20. Chawarska K, MacAri S, Shic F. Context modulates attention to social scenes in toddlers with autism. *J Child Psychol Psychiatry Allied Discip.* (2012) 53:903–13. doi: 10.1111/j.1469-7610.2012.02538.x
21. Klin A, Jones W, Schultz R, Volkmar F, Cohen D. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Arch Gen Psychiatry.* (2002) 59:809–16. doi: 10.1001/archpsyc.59.9.809
22. Shic F, Bradshaw J, Klin A, Scassellati B, Chawarska K. Limited activity monitoring in toddlers with autism spectrum disorder. *Brain Res.* (2011) 1380:246–54. doi: 10.1016/j.brainres.2010.11.074
23. Riby DM, Hancock PJB. Do faces capture the attention of individuals with williams syndrome or autism? Evidence from tracking eye movements. *J Autism Dev Disord.* (2009) 39:421–31. doi: 10.1007/s10803-008-0641-z
24. Wilson CE, Brock J, Palermo R. Attention to social stimuli and facial identity recognition skills in autism spectrum disorder. *J Intellect Disabil Res.* (2010) 54:1104–15. doi: 10.1111/j.1365-2788.2010.01340.x
25. Pierce K, Marinero S, Hazin R, McKenna B, Barnes CC, Malige A. Eye tracking reveals abnormal visual preference for geometric images as an early biomarker of an autism spectrum disorder subtype associated with increased symptom severity. *Biol Psychiatry.* (2016) 79:657–66. doi: 10.1016/j.biopsych.2015.03.032
26. Frazier TW, Strauss M, Klingemier EW, Zetzer EE, Hardan AY, Eng C, et al. A meta-analysis of gaze differences to social and nonsocial information between individuals with and without autism. *J Am Acad Child Adolesc Psychiatry.* (2017) 56:546–55. doi: 10.1016/j.jaac.2017.05.005
27. Kemner C, van der Geest JN, Verbaten MN, van Engeland H. Effects of object complexity and type on the gaze behavior of children with pervasive developmental disorder. *Brain Cogn.* (2007) 65:107–11. doi: 10.1016/j.bandc.2006.05.006
28. Parish-Morris J, Chevallier C, Tonge N, Letzen J, Pandey J, Schultz RT. Visual attention to dynamic faces and objects is linked to face processing skills: a combined study of children with autism and controls. *Front Psychol.* (2013) 4:1–7. doi: 10.3389/fpsyg.2013.00185
29. Kuhn G, Kourkoulou A, Leekam SR. How magic changes our expectations about autism. *Psychol Sci.* (2010) 21:1487–3. doi: 10.1177/0956797610383435
30. Di Giorgio E, Frasnelli E, Rosa Salva O, Scattoni ML, Puopolo M, Tosoni D, et al. Difference in visual social predispositions between newborns at low- and high-risk for autism. *Sci Rep.* (2016) 6:26395. doi: 10.1038/srep29860
31. Elsabbagh M, Gliga T, Pickles A, Hudry K, Charman T, Johnson MH. The development of face orienting mechanisms in infants at-risk for autism. *Behav Brain Res.* (2013) 251:147–54. doi: 10.1016/j.bbr.2012.07.030
32. Macari S, Milgramm A, Reed J, Shic F, Powell KK, Macris D, et al. Context-specific dyadic attention vulnerabilities during the first year in infants later developing autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry.* (2021) 60:166–75. doi: 10.1016/j.jaac.2019.12.012
33. Falck-Ytter T, von Hofsten C. How special is social looking in ASD. In: Braddick JAO, Innocenti G editors, *Progress in Brain Research*. Elsevier B.V (2011). p. 209–222. doi: 10.1016/B978-0-444-53884-0.00026-9
34. Saitovitch A, Bargiacchi A, Chabane N, Phillipe A, Brunelle F, Boddaert N, et al. Studying gaze abnormalities in autism: which type of stimulus to use? *Open J Psychiatry.* (2013) 3:32–8. doi: 10.4236/ojpsych.2013.32A006
35. Chevallier C, Parish-Morris J, Mcvey A, Rump KM, Sasson NJ, Herrington JD, et al. Measuring social attention and motivation in autism spectrum disorder using eye-tracking: stimulus type matters. *Autism Res.* (2015) 8:620–8. doi: 10.1002/aur.1479
36. Rice K, Moriuchi JM, Jones W, Klin A. Parsing heterogeneity in autism spectrum disorders: visual scanning of dynamic social scenes in school-aged children. *J Am Acad Child Adolesc Psychiatry.* (2012) 51:238–48. doi: 10.1016/j.jaac.2011.12.017
37. Kirchner JC, Hatri A, Heekeren HR, Dziobek I. Autistic symptomatology, face processing abilities, and eye fixation patterns. *J Autism Dev Disord.* (2011) 41:158–67. doi: 10.1007/s10803-010-1032-9
38. Riby DM, Hancock PJ, Jones N, Hanley M. Spontaneous and cued gaze-following in autism and Williams syndrome. *J Neurodev Disord.* (2013) 5:13. doi: 10.1186/1866-1955-5-13
39. Shi L, Zhou Y, Ou J, Gong J, Wang S, Cui X, et al. Different visual preference patterns in response to simple and complex dynamic social stimuli in preschool-aged children with autism spectrum disorders. *PLoS ONE.* (2015) 10:e0122280. doi: 10.1371/journal.pone.0122280
40. Birmingham E, Cerf M, Adolphs R. Comparing social attention in autism and amygdala lesions: effects of stimulus and task condition. *Soc Neurosci.* (2011) 6:420–435. doi: 10.1080/17470919.2011.561547
41. Freeth M, Ropar D, Chapman P, Mitchell P. The eye gaze direction of an observed person can bias perception, memory, and attention in adolescents with and without autism spectrum disorder. *J Exp Child Psychol.* (2010) 105:20–37. doi: 10.1016/j.jecp.2009.10.001
42. Freeth M, Ropar D, Mitchell P, Chapman P, Loher S. Brief report: how adolescents with ASD process social information in complex scenes. Combining evidence from eye movements and verbal descriptions. *J Autism Dev Disord.* (2011) 41:364–71. doi: 10.1007/s10803-010-1053-4
43. Van Der Geest JN, Kemner C, Camfferman G, Verbaten MN, Van Engeland H. Looking at images with human figures: comparison between autistic and normal children. *J Autism Dev Disord.* (2002) 32:69–75. doi: 10.1023/A:1014832420206
44. Marsh LE, Pearson A, Ropar D, de Hamilton CAF. Predictive gaze during observation of irrational actions in adults with autism spectrum conditions. *J Autism Dev Disord.* (2015) 45:245–61. doi: 10.1007/s10803-014-2215-6

45. Bernardino I, Mouga S, Almeida J, van Asselen M, Oliveira G, Castelo-Branco M. A direct comparison of local-global integration in autism and other developmental disorders: implications for the central coherence hypothesis. *PLoS ONE.* (2012) 7:e39351. doi: 10.1371/journal.pone.0039351
46. Lord C, Rutter M. *Autism Diagnostic Observation Schedule-WPS (ADOS-WPS).* Los Angeles, CA: West Psychol. (1999). doi: 10.1037/t17256-000
47. Jarrold C, Brock J. To match or not to match? Methodological issues in autism-related research. *J Autism Dev Disord.* (2004) 34:81–6. doi: 10.1023/B:JADD.0000018078.82542.ab
48. Le Couteur A, Lord C, Rutter M. *The Autism Diagnostic Interview-Revised (ADI-R).* Los Angeles, CA: Western Psychological Services. (2003).
49. Risko EF, Laidlaw KEW, Freeth M, Foulsham T, Kingstone A. Social attention with real versus reel stimuli: toward an empirical approach to concerns about ecological validity. *Front Hum Neurosci.* (2012) 6:1–11. doi: 10.3389/fnhum.2012.00143
50. Kingstone A. Taking a real look at social attention. *Curr Opin Neurobiol.* (2009) 19:52–6. doi: 10.1016/j.conb.2009.05.004
51. Schauder KB, Park WJ, Tsank Y, Eckstein MP, Tadin D, Bennetto L. Initial eye gaze to faces and its functional consequence on face identification abilities in autism spectrum disorder. *J Neurodev Disord.* (2019) 11:1–20. doi: 10.1186/s11689-019-9303-z
52. Birmingham E, Bischof WF, Kingstone A. Saliency does not account for fixations to eyes within social scenes. *Vision Res.* (2009) 49:2992–3000. doi: 10.1016/j.visres.2009.09.014
53. End A, Gamer M. Preferential processing of social features and their interplay with physical saliency in complex naturalistic scenes. *Front Psychol.* (2017) 8:1–16. doi: 10.3389/fpsyg.2017.00418
54. Fletcher-Watson S, Leekam SR, Benson V, Frank MC, Findlay JM. Eye-movements reveal attention to social information in autism spectrum disorder. *Neuropsychologia.* (2009) 47:248–57. doi: 10.1016/j.neuropsychologia.2008.07.016

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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The Association Between Reading the Mind in the Eyes Test Performance and Intelligence Quotient in Children and Adolescents With Asperger Syndrome

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Background: There has been an extensive debate about a potential association between intelligence and social cognition. In this study, we aimed to assess the association between social cognition as measured with the Reading the Mind in the Eyes test (RMET) and intelligence as measured with the fourth edition of the Wechsler Intelligence Scale for Children (WISC-IV) in children and adolescents diagnosed with Asperger Syndrome (AS).

Methods: We conducted a cross-sectional study among 84 children diagnosed with AS aged 6–16 years (mean = 11.64; standard deviation = 2.75; 92.9% males). We analyzed the association between RMET performance and WISC-IV total score as well as the association between RMET performance and each of the four WISC-IV indexes (processing speed index, PSI; working memory index, WMI; perceptual reasoning index, PRI, and verbal comprehension index, VCI).

Results: We found a positive correlation between RMET performance and full-scale intelligence quotient ($r = 0.340$; $p < 0.01$), VCI ($r = 0.310$; $p < 0.01$), PRI ($r = 0.401$; $p < 0.01$), and WMI ($r = 0.292$; $p < 0.01$). In the linear regression model, age was a significant predictor of RMET score ($\beta = 0.409$; $p < 0.001$) as was PRI ($\beta = 0.309$; $p = 0.019$).

Conclusion: Our results suggest that intelligence quotient positively influences RMET performance, indicating that intelligence increases social cognition in individuals diagnosed with AS. However, weak-to-moderate size effects were found. This study contributes to understanding the mechanisms underlying the disturbance of social cognition in children and adolescents diagnosed with AS.

Keywords: RMET, intelligence, social cognition, autism spectrum disorder, reading the mind in eyes test, asperger syndrome

INTRODUCTION

The theory of mind (ToM) is defined as the capacity to understand and empathize with others. It involves correctly attributing beliefs, desires, intentions, and perspectives to others and understanding that they are different from one's own (1). ToM is crucial to understand and predict others' behaviors, facilitating successful adaptation in different environments (2). The Reading the Mind in the Eyes test (RMET) was conceived as a ToM assessment tool, and it measures an essential aspect of social cognition: the ability to recognize emotional states in others by observing their eye expressions (3, 4). The RMET has shown good test–retest reliability in different cultural settings, including the Spanish population (5–8). The majority of children diagnosed with autism spectrum disorder (ASD) have impaired development of ToM (2, 9), which translates into lower performance on the RMET (3).

Intelligence has been widely studied among individuals diagnosed with ASD. Several cognitive scales are used in autism research to separate high- and low-functioning individuals and elucidate cognitive functioning in autism (10, 11). The Wechsler scales are the most widely used for measuring the intelligence quotient (IQ) in the ASD population (12). The Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV) is one of the most commonly used intelligence tests. It comprises four intelligence indexes, which represent different cognitive skills: verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI). The WISC-IV score is expressed as the full-scale intelligence quotient (FSIQ), which combines the scores of the four WISC-IV indexes (13). The WISC-IV manual includes test scores results for special groups (14, 15) to provide information on the test's specificity and its clinical utility in the diagnostic evaluation. These special groups include individuals diagnosed with Asperger syndrome (AS), who usually obtain lower WMI and PSI scores, resulting in lower FSIQ (13, 16). On average, individuals diagnosed with AS show no significant language delay and no deficits in intelligence (13, 14). However, the difficulty in recognizing emotions is well-established in individuals with AS although it is not fully understood.

In children diagnosed with ASD, IQ may be associated with a better performance in social cognition tasks, including face-emotion recognition (17, 18). Intelligence may play a compensatory role in tasks that require emotional recognition (19). This compensatory role of intelligence could impact facial emotion recognition to a greater degree than in normal children (20).

Lately, the association between intelligence and RMET in ASD has gained some attention. In a recent meta-analysis, we explored the association between RMET performance and IQ in children diagnosed with ASD (21). We found that higher IQ was associated with higher RMET performance in controls, and in children with ASD, it had the opposite effect. However, results should be taken with caution as the meta-analysis included few studies.

In contrast, in the meta-analysis of Baker et al. (22), the authors found a positive correlation between IQ and RMET performance ($r = 0.24$) and concluded that both verbal and performance intelligence contributed equally to this association.

To our knowledge, no studies have assessed the association between different WISC-IV indexes and RMET performance in children diagnosed with AS. If certain indexes have a more significant impact than others in RMT performance, cognitive training programs could be tailored to tackle these deficits, thus improving social cognition in children diagnosed with AS. Cognitive training programs have been tested in children with ASD with good results (23) and (24). In turn, improvement in social cognition has been associated with greater functionality and quality of life (25).

We aimed to investigate whether RMET is associated with IQ as measured with the WISC-IV. We also aimed to identify which WISC-IV indexes—VCI, PRI, WMI, and PSI—were most strongly associated with RMET performance.

METHODS

This study was approved by the Regional Hospital Ethics Committee of Malaga. All procedures were conducted following the institutional research committee's ethical standards and with the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants' parents.

Sample

This is a cross-sectional study carried out among children diagnosed with AS. Participants were recruited via the Asperger Syndrome Association of Málaga (Asociación Malagueña de Síndrome de Asperger, AMSA). The AMSA is a non-governmental, free-to-join association that does not have a direct relationship with clinical facilities. This association offers memberships to any person diagnosed with AS. AMSA members are representative of community-dwelling people with AS.

Inclusion criteria were:

1. Being aged between 6 and 16 years.
2. Having a diagnosis of AS by a clinical psychologist or psychiatrist as per the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV) criteria (26) based on a clinical assessment using developmental history and a standardized scale, such as the Autism Diagnostic Interview–Revised (27) or the Autism Diagnostic Observation Schedule–Generic (28).
3. Having an IQ of 70 or higher on the WISC-IV.

There were no exclusion criteria regarding gender, ethnicity, or psychological/physical comorbidities.

Measures

All assessments were carried out by trained clinicians. We used the Spanish version of the RMET for children (4, 29). This test includes 28 pictures of eye expressions. For each picture, participants must choose one of four possible corresponding emotional states (4). The children's version of the RMET has been validated in the Spanish population (29) with mean scores in typical children of 18.51 (*SD*: 3.93). This test is particularly recommended for children aged 8–17 although it has been

employed in children as young as 6 with good results (30). In previous studies, children with high-functioning ASD scored lower than typical children (31).

We measured IQ with the Spanish version of the WISC-IV (13, 32). The WISC-IV was standardized for children aged 6–16. Norm tables were divided into 4-month age intervals. Children obtain scores that directly compare them with a representative sample of all children of the same age range (13). WISC-IV is composed of four indexes: VCI, PRI, WMI, and PSI. VCI measures verbal concept formation through the tasks similarities, vocabulary, and comprehension. PRI measures non-verbal and fluid reasoning with the tasks block design, picture concepts, and matrix reasoning subtests. WMI assesses children's working memory with the tasks digit span and letter–number sequencing. PSI measures processing speed with the tasks coding and symbol search.

Procedure

If children and adolescents, as well as their parents, showed interest in the project, they were scheduled for a baseline interview in which the details of the project were explained fully, and they were given the informed consent form. They were given enough time to read the informed consent form, and any doubts they might have were answered. After signing the informed consent form, the standardized scales were administered by trained clinicians. Each participant was assessed individually using the RMET and the WISC-IV. Sessions lasted between 90 and 120 min. Participants were allowed to take short rest breaks (10–15 min) between tasks.

Statistical Analysis

All analyses were carried out using the Statistical Package for the Social Sciences (SPSS), version 22.0. Preliminary analyses were conducted to compute descriptive statistics. The association between WISC-IV score and RMET performance was analyzed with zero-order Pearson's coefficients. Correlations between WISC-IV index scores and RMET performance were also conducted. According to Cohen (33), an absolute value of $r \leq 0.1$ means weak correlation, an absolute value of 0.1–0.3 means moderate correlation, and an absolute value of ≥ 0.5 means large correlation. To explore the unique strengths of association between RMET score and WISC-IV indexes controlling by age, we conducted a two-step hierarchical linear regression analysis. In the first step, we introduced age, and in the second step, we introduced the four WISC-IV indexes. All tests were two-tailed with statistical significance at $p < 0.05$ and 95% confidence intervals.

RESULTS

Description of the Sample

Our sample comprises 84 children diagnosed with AS with a mean age of 11.64 years (standard deviation = 2.75). The proportion of males was 92.9%. **Table 1** shows the mean scores, standard deviations, and ranges for the WISC-IV scores, including FSIQ and the four index scores (VCI, PRI, WMI, PSI) as well as RMET scores.

TABLE 1 | Demographics including age, WISC-IV index scores and FSIQ and RMET.

	Mean	SD	Range	
			Min	Max
Age (in years)	11.643	2.754	6	16
VCI	112.881	23.213	59	149
PRI	104.381	18.976	68	141
WMI	102.881	20.917	54	150
PSI	94.690	18.482	67	147
FSIQ	106.0	21.727	70	148
RMET	17.143	3.918	7	25

FSIQ, Full Scale Intelligence Quotient; Min, Minimum; Max: Maximum; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; RMET, Reading the Mind in the Eyes Test; SD, Standard Deviation; WMI, Working Memory Index.

Correlation Results Between RMET Score and IQ

We found a weak positive correlation between RMET score and FSIQ ($r = 0.215$; $p < 0.05$), PRI ($r = 0.287$; $p < 0.01$), and WMI ($r = 0.235$; $p < 0.05$). We found a weak negative correlation between age and VCI ($r = -0.221$; $p < 0.05$), PRI ($r = -0.237$; $p < 0.01$), and FSIQ ($r = -0.275$; $p < 0.05$), a moderate negative correlation between age and PSI ($r = -0.311$; $p < 0.01$), and a moderate positive correlation between age and RMET score ($r = 0.338$; $p < 0.05$). Controlling by age, there was a moderate positive correlation between RMET score and VCI ($r = 0.310$; $p < 0.01$), PRI ($r = 0.401$; $p < 0.01$), and FSIQ ($r = 0.340$; $p < 0.01$) and a significant, weak positive between RMET score and WMI ($r = 0.292$; $p < 0.01$). No significant correlation was found between RMET score and PSI ($r = 0.049$; $p > 0.10$). Full results are shown in **Table 2**.

Results of the Linear Regression Model

We carried out a linear regression model to explore the association between RMET score and WISC-IV indexes scores controlling by age. Results are shown in **Table 3.** The full model was statistically significant [$F_{(5, 78)} = 6.094$, $p < 0.001$], with a total R2 of 0.235. Age was a significant predictor of RMET score ($\beta = 0.409$, $p < 0.001$). Thus, older children showed higher RMET scores than younger children. PRI was also significantly associated with RMET score ($\beta = 0.309$, $p = 0.019$), showing that children with higher PRI scored higher on the REMT.

Figure 1 shows a scatterplot of RMET scores and unstandardized predicted values for the linear regression model (**Figure 1**).

DISCUSSION

Summary of Results

This study explored the association between RMET performance and IQ in children and adolescents with AS. After controlling by age, we found a moderate positive correlation between RMET performance and FSIQ, VCI, and PRI and a weak positive correlation between RMET and WMI. In the linear

TABLE 2 | Zero-order correlations among WISC-IV index scores and FSIQ.

	VCI	PRI	WMI	PSI	FSIQ	RMET	Age
VCI	1						
PRI	0.630**	1					
WMI	0.596**	0.516**	1				
PSI	0.358**	0.354**	0.407**	1			
FSIQ	0.870**	0.802**	0.786**	0.629**	1		
RMET	0.209	0.287**	0.235*	−0.061	0.215*	1	
RMETpc	0.310**	0.401**	0.292**	0.049	0.340**	1	
Age	−0.221*	−0.237**	−0.111	−0.311**	−0.275*	0.338*	1

RMET and age and partial correlation controlling for age between WISC-IV index and RMET.
***p < 0.01; * p <0.05.*
FSIQ, Full Scale Intelligence Quotient; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; RMET, Reading the Mind in the Eyes Test; RMETpc, Reading the Mind in the Eyes Test Partial Correlations; VCI, Verbal Comprehension Index; WMI, Working Memory Index.

TABLE 3 | Hierarchical linear regression model: associations between RMET score and WISC-IV indexes controlled by age.

Predictors	Beta	Adjusted R^2 change	*F* change	*p*
Step 1: Age	0.339	0.115	10.626	0.002
Step 2: Age + WISC-IV indexes		0.166	4.507	0.003
Age	0.409			<0.001
PRI	0.309			0.019
PSI	−0.112			0.318
VCI	0.013			0.576
WMI	0.129			0.313

PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; RMET, Reading the Mind in the Eyes Test; VCI, Verbal Comprehension Index; WMI, Working Memory Index.
Snell R^2 Total = 0.235, $F_{(5,78)} = 6.094$, $p < 0.001$.

regression analysis, we found that age and PRI were statistically significantly associated with RMET performance. Thus, perceptual components of intelligence are the areas that appear more related to social cognition. Verbal component and working memory also appear to play a role as does total IQ. However, processing speed was not associated with RMET.

We found a moderate positive correlation between age and RMET, suggesting that age might be an important factor in determining RMET performance in children and adolescents. Future research should determine whether these findings might be confirmed in other age groups as well as in longitudinal studies.

Comparison With Previous Research

The RMET mean score found in our sample (17.143, *SD*: 3.918) is slightly lower than the mean score found in the Spanish validation of the RMET, which was performed in a sample of typical children (mean score: 18.51, SD: 3.93) (29). Also, the distribution of WISC-IV index scores found in our sample was similar to that reported in the WISC-IV manual (lowest scores were WMI and PSI) (32). Some previous studies on individuals diagnosed with AS found no correlation between RMET performance and IQ (3, 4, 34, 35). In contrast, our study suggests that higher IQ attributes and higher RMET performance are associated.

Regarding visual-perceptual processing, we found that PRI is correlated with RMET performance. The PRI was, in fact, the only WISC-IV index significantly associated with RMET performance in the linear regression analysis. In contrast, some studies claim that difficulties in interpreting facial emotions are not traits of the visual-perceptual process (36, 37). However, patients diagnosed with AS frequently report abnormal sensory

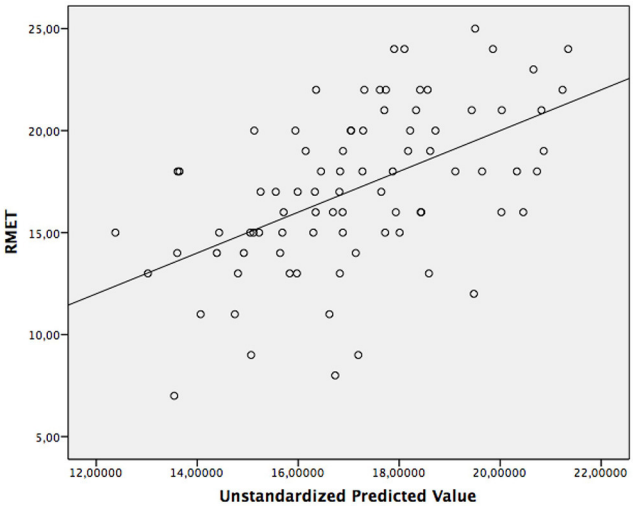

FIGURE 1 | Scatterplot of RMET and unstandardized predicted values for the final regression model with a linear fit line.

experiences (38). Also, in previous studies, individuals diagnosed with AS obtained better PRI scores than normal individuals (39, 40). As PRI refers to non-verbal intelligence, it requires accurate visual processing and then reasoning. Therefore, individuals diagnosed with AS with a better reasoning ability may perform better in RMET.

Similarly, we found a moderate positive correlation between VCI and RMET performance. Studies show that people diagnosed with ASD have pragmatic language problems (41), especially those with AS (42). This deficit may be related to weak central coherence, which is the difficulty in adjusting language to context as (43) described.

WMI was also associated with RMET performance in our study. Working memory (WM) is an essential part of executive functioning. Previous studies have found that individuals diagnosed with AS have deficits in WM after controlling for the influence of IQ (44). Finally, we found no correlation between PSI and RMET performance.

Mechanisms Underlying the Association

Different mechanisms could explain the association between intelligence and social cognition. On the one hand, social cognition and intelligence could share functional brain areas. Thus, the improvement in one area may influence the improvement in the other area and vice versa. For instance, a study showed that social cognition training increased cortical thickness in prefrontal regions (45). Conversely, cognitive training is shown to improve facial affect recognition (23).

On the other hand, higher intelligence generally increases the ability to solve problems, so individuals with AS could use their intelligence as a compensatory strategy to recognize facial expressions and other emotional indicators in the people around them. Deficits in the so-called emotional brain, which involves areas such as the amygdala, could explain the social atypicalities found in people with ASD (46). In this regard, a study used functional magnetic resonance imaging to explore which areas were activated in people with ASD and healthy controls. During an eye expression recognition task, two areas of the so-called social brain—the amygdala and the superior temporal gyrus—and the prefrontal cortex were activated in healthy controls. However, individuals with ASD did not activate their amygdala during the task, but instead relied on the activation of frontotemporal regions to perform the task (20).

Limitations

Our findings should be considered in light of some limitations. First, the cross-sectional design of our study precludes drawing conclusions about the causality of the associations found. Likewise, we cannot establish the directionality of these associations. Therefore, we should also consider the possibility that social cognition leads to better cognitive development and a higher IQ. Also, although all participants had a total IQ of 70 or above, some of them scored below 70 in some of the indexes. Finally, most of the sample was composed of males, so the conclusions derived from our study are difficult to extrapolate to the female population.

CONCLUSIONS

In conclusion, our results suggest an association between RMET performance and IQ in children diagnosed with AS. Particularly, the perceptual reasoning component was the most strongly associated with RMET. This association should be considered when evaluating RMET performance. Our results suggest that intelligence positively influences social cognition although causality cannot be established. Also, moderate size effects were found, which requires us to take these results with caution. Longitudinal research could be useful to clarify the association between social cognition and intelligence.

Among the mechanisms that could explain the association between intelligence and social cognition, the overlapping of brain areas involved in both functions and the use of intelligence as a compensatory strategy stand out. Cognitive training could be useful in improving social cognition in children and adolescents with AS. In turn, the improvement of social cognition could lead to greater functionality and quality of life in this population.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Hospital Ethics Committee of Malaga. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

IP-C designed the study, performed the data collection and scoring, and wrote the article. AS wrote the article and contributed to the final version. AP-S contributed to the search for references and contributed to the final version. F-BC-S contributed to the search for references and contributed to the final version. PF-B designed the study performed the statistical analyses and contributed to the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.642799/full#supplementary-material

REFERENCES

1. Woodruff G, Premack D, Kennel K. Conservation of liquid and solid quantity by the chimpanzee. *Science.* (1978) 202:991–4. doi: 10.1126/science.202.4371.991
2. Baron-Cohen S. *Mindblindness: An Essay on Autism and Theory of Mind*. Cambridge, MA: MIT Press/Bradford Books (1995). doi: 10.7551/mitpress/4635.001.0001
3. Baron-Cohen S, Jolliffe T, Mortimore C, Robertson M. Another advanced test of theory of mind: evidence from very high functioning adults with autism or Asperger syndrome. *J Child Psychol Psychiatr Allied Disciplines.* (1997) 38:813–22. doi: 10.1111/j.1469-7610.1997.tb01599.x
4. Baron-Cohen S, Wheelwright S, Hill J, Raste Y, Plumb I. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatr Allied Disciplines.* (2001) 42:241–51. doi: 10.1111/1469-7610.00715
5. Yildirim EA, Kaşar M, Güdük M, Ateş E, Küçükparlak I, Ozalmete EO. Investigation of the reliability of the "reading the mind in the eyes test" in a Turkish population. *Turk Psikiyatri Derg.* (2011) 22:177–86. doi: 10.5080/u6500
6. Fernández-Abascal EG, Cabello R, Fernández-Berrocal P, Baron-Cohen S. Test-retest reliability of the 'Reading the Mind in the Eyes' test: a one-year follow-up study. *Mol Autism.* (2013) 4:33. doi: 10.1186/2040-2392-4-33
7. Lee HR, Nam G, Hur JW. Development and validation of the Korean version of the reading the mind in the eyes test. *PLoS ONE.* (2020) 15:e0238309. doi: 10.1371/journal.pone.0238309
8. Megías-Robles A, Gutiérrez-Cobo MJ, Cabello R, Gómez-Leal R, Baron-Cohen S, Fernández-Berrocal P. The 'Reading the mind in the Eyes' test and emotional intelligence. *R Soc Open Sci.* (2020) 2020:7201305. doi: 10.1098/rsos.201305
9. Baron-Cohen S, Tager-Flusberg H, Cohen DJ. (editors). From attention-goal psychology to belief-desire psychology: the development of a theory of mind and its dysfunction. In: *Understanding Other Minds: Perspectives from Autism*. Oxford: Oxford University Press (1993) p. 466–80.
10. Goldstein G, Allen DN, Minshew NJ, Williams DL, Volkmar F, Klin A, et al. The structure of intelligence in children and adults with high functioning autism. *Neuropsychology.* (2008) 22:301–12. doi: 10.1037/0894-4105.22.3.301
11. Wellman HM, Cross D, Watson J. Meta-analysis of theory-of-mind development: the truth about false belief. *Child Dev.* (2001) 72:655–84. doi: 10.1111/1467-8624.00304
12. Oliveras-Rentas R, Kenworthy L, Roberson RI, Martin A, Wallace G. WISC-IV profile in high-functioning autism spectrum disorders: impaired processing speed is associated with increased autism communication symptoms and decreased adaptive communication abilities. *J Autism Dev Disord.* (2012) 42:655–64. doi: 10.1007/s10803-011-1289-7
13. Wechsler D. *Wechsler Intelligence Scale for Children, 4th Edn (WISC-IV)*. San Antonio, TX: Psychological Corporation (2003).
14. Flanagan DP, Alfonso VC, Mascolo JT, Hale JB. "The Wechsler Intelligence Scale for Children–Fourth Edition in Neuropsychological Practice," In: Davis AS, editor. *Handbook of Pediatric Neuropsychology*. New York, NY: Springer (2010). p. 397–414.
15. Hebben N. "Review of special group studies and utility of the process approach with the WISC-IV," in *Essentials of WISC-IV Assessment*, eds D. P. Flanagan and A. S.Kaufman (New York, NY: Wiley). p. 183–199.
16. Mayes SD, Calhoun SL. WISC-IV and WIAT-II profiles in children with high-functioning autism. *J Autism Dev Disord.* (2008) 38:428–39. doi: 10.1007/s10803-007-0410-4
17. Dyck MJ, Piek JP, Hay D, Smith L, Hallmayer J. Are abilities abnormally interdependent in children with autism? *J Clin Child Adolescent Psychol.* (2006) 35:20–33. doi: 10.1207/s15374424jccp3501_3
18. Wright B, Clarke N, Jordan JO, Young AW, Clarke P, Miles J, et al. Emotion recognition in faces and the use of visual context Vo in young people with high-functioning autism spectrum disorders. *Autism.* (2008) 12:607–26. doi: 10.1177/1362361308097118
19. Rutherford MD, Troje NF. IQ predicts biological motion perception in autism spectrum disorders. *J Autism Dev Disord.* (2012) 42:557–65. doi: 10.1007/s10803-011-1267-0
20. Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SC. The amygdala theory of autism. *Neurosci Biobehav Rev.* 24, 355–64. doi: 10.1016/s0149-7634(00)00011-7
21. Peñuelas-Calvo I, Sareen A, Sevilla-Llewellyn-Jones J, Fernández-Berrocal P. The "Reading the Mind in the Eyes" test in autism-spectrum disorders comparison with healthy controls: a systematic review and meta-analysis. *J Autism Dev Disord.* 49:1–14. doi: 10.1007/s10803-018-3814-4
22. Baker CA, Peterson E, Pulos S, Kirkland RA. Eyes and IQ: a meta-analysis of the relationship between intelligence and "Reading the Mind in the Eyes." *Intelligence.* (2014) 44:78–92. doi: 10.1016/j.intell.2014.03.001
23. Bölte S, Ciaramidaro A, Schlitt S, Hainz D, Kliemann D, Beyer A, et al. Training-induced plasticity of the social brain in autism spectrum disorder. *Br J Psychiatr.* (2015) 207:149–57. doi: 10.1192/bjp.bp.113.143784
24. De Vries M, Verdam MG, Prins PJ, Schmand BA, Geurts HM. Exploring possible predictors and moderators of an executive function training for children with an autism spectrum disorder. *Autism.* (2018) 22:440–9. doi: 10.1177/1362361316682622
25. Frolli A, Ricci MC, Tortorelli FA, Cavallaro A, Valenzano L, Rega A, et al. Emotional education in early onset schizophrenia and asperger's syndrome. *Behav Sci.* (2020) 10:131. doi: 10.3390/bs10090131
26. American Psychiatric Association (APA) (2000). *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision. Washington, DC: APA.
27. Lord C, Rutter M, Le Couteur A. Autism diagnostic interview–revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord.* (1994) 24:659–85. doi: 10.1007/BF02172145
28. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord.* (2000) 30:205–23. doi: 10.1023/A:1005592401947
29. Rueda P, Cabello R, Fernández-Berrocal P. Preliminary validation of Spanish "Eyes Test-Child Version." *Ansiedad y Estrés.* (2013) 19:173–84.
30. Gallant C, Lavis L, Mahy C. Developing an understanding of others' emotional states: relations among affective theory of mind and empathy measures in early childhood. *Br J Dev Psychol.* (2020) 38:151–66. doi: 10.1111/bjdp.12322
31. Vogindroukas I, Chelas EN, Petridis NE. Reading the mind in the eyes test (Children's Version): a comparison study between children with typical development, children with high-functioning autism and typically developed adults. *Folia Phoniatrica et Logopaed.* (2014) 66:18–24. doi: 10.1159/000363697
32. Wechsler D. *Manual de Aplicación y corrección del WISC-IV*. Madrid, SA: TEA Ediciones (2005).
33. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: L. Eralbuam Associates (1988).
34. Kaland N, Callesen K, Møller-Nielsen A, Mortensen EL, Smith L. Performance of children and adolescents with asperger syndrome or high-functioning autism on advanced theory of mind tasks. *J Autism Dev Disord.* (2008) 38:1112–23. doi: 10.1007/s10803-007-0496-8
35. Holt RJ, Chura LR, Lai MC, Suckling J, von dem Hagen E, Caldera J. Reading the mind in the eyes: an fMRI study of adolescents with autism and their siblings. *Psychol Med.* (2014) 44:3215–27. doi: 10.1017/S0033291714000233
36. Holdnack J, Goldstein G, Drozdick L. Social perception and WAIS-IV performance in adolescents and adults diagnosed with Asperger's syndrome and autism. *Assessment.* (2011) 18:192–200. doi: 10.1177/1073191110394771
37. Humphreys K, Minshew N, Leonard GL, Behrmann M. A fine-grained analysis of facial expression processing in high-functioning adults with autism. *Neuropsychologia.* (2007) 45:685–95. doi: 10.1016/j.neuropsychologia.2006.08.003
38. Smith RS, Sharp J. Fascination and isolation: a grounded theory exploration of unusual sensory experiences in adults with Asperger syndrome. *J Autism Dev Disord.* (2013) 43:891–910. doi: 10.1007/s10803-012-1633-6
39. Landa R, Goldberg M. Language, social, and executive functions in high functioning autism: a continuum of performance. *J Autism Dev Disord.* (2005) 35:557–73. doi: 10.1007/s10803-005-0001-1
40. Steele SD, Minshew N, Luna B, Sweeney JA. Spatial working memory deficits in Autism. *J Autism Dev Disord.* (2006) 37:605–12. doi: 10.1007/s10803-006-0202-2

41. Chahboun S, Vulchanov V, Saldaña D, Eshuis H, Vulchanova M. Can you play with fire and not hurt yourself? A comparative study in figurative language comprehension between individuals with and without autism spectrum disorder. *PLoS ONE*. (2016) 11:e0168571. doi: 10.1371/journal.pone.0168571
42. Frith U. *Autism: Explaining the Enigma*. Basil Blackwell Ltd (1989).
43. Frith U. Emanuel Miller lecture: confusions and controversies about Asperger syndrome. *J Child Psychol Psychiatr Allied Disciplines*. (2004) 45:672–86. doi: 10.1111/j.1469-7610.2004.00262.x
44. Macizo P, Soriano M, Paredes N. Phonological and visuospatial working memory in autism spectrum disorders. *J Autism Dev Disord*. (2016) 46:2956–67. doi: 10.1007/s10803-016-2835-0
45. Rosenblau G, O'Connell G, Heekeren HR, Dziobek I. Neurobiological mechanisms of social cognition treatment in high-functioning adults with autism spectrum disorder. *Psychol Med*. (2020) 50:2374–84. doi: 10.1017/S0033291719002472
46. Sato W, Uono S, Kochiyama T. Neurocognitive mechanisms underlying social atypicalities in autism: weak amygdala's emotional modulation hypothesis. *Front Psychiatr*. (2020) 11:864. doi: 10.3389/fpsyt.2020.00864

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Music Therapy for Children With Autistic Spectrum Disorder and/or Other Neurodevelopmental Disorders: A Systematic Review

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Background: Several studies have reported contradictory results regarding the benefits of music interventions in children and adolescents with neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD).

Methods: We performed a systematic review according to the PRISMA guidelines. We searched the Cochrane, PubMed and Medline databases from January 1970 to September 2020 to review all empirical findings, except case reports, measuring the effect of music therapy on youths with ASD, intellectual disability (ID), communication disorder (CD), developmental coordination disorder (DCD), specific learning disorder, and attention/deficit hyperactivity disorder (ADHD).

Results: Thirty-nine studies ($N = 1{,}774$ participants) were included in this review (ASD: $n = 22$; ID: $n = 7$; CD and dyslexia: $n = 5$; DCD: $n = 0$; ADHD: $n = 5$ studies). Two main music therapies were used: educational music therapy and improvisational music therapy. A positive effect of educational music therapy on patients with ASD was reported in most controlled studies (6/7), particularly in terms of speech production. A positive effect of improvisational music therapy was reported in most controlled studies (6/8), particularly in terms of social functioning. The subgroup of patients with both ASD and ID had a higher response rate. Data are lacking for children with other NDDs, although preliminary evidence appears encouraging for educational music therapy in children with dyslexia.

Discussion: Improvisational music therapy in children with NDDs appears relevant for individuals with both ASD and ID. More research should be encouraged to explore whether oral and written language skills may improve after educational music therapy, as preliminary data are encouraging.

Keywords: music therapy, autism spectrum disorder, intellectual disability, neurodevelopmental disorder, systematic review

INTRODUCTION

The new section of neurodevelopmental disorders (NDDs) in the DSM-5 encompasses psychiatric disorders with an onset in early childhood (1). The clinical expression of all NDDs is closely related to the child's own developmental dynamics. Several mechanisms may explain the structural abnormalities in brain structures reported in most patients with NDDs: consequences of perinatal risk factors, abnormal brain maturation, and consequences of a lack of opportunity to use functional areas. The NDD section of the DSM-5 includes autism spectrum disorder (ASD), intellectual disability (ID), attention deficit disorder with or without hyperactivity (ADHD), developmental coordination disorders (DCD), communication disorders (CD) (including language, phonological, and pragmatic social communication disorders, and stuttering) and specific learning disabilities (SLDs) (characterized by persistent difficulties in learning the fundamental academic skills of reading, writing or mathematics).

Therapeutic Interventions for ASD

ASD is characterized by two main dimensions: a deficit in communication and reciprocal social interactions and a restriction of interests with repetitive and stereotypical behaviors (1). In addition to the core symptoms of ASD, other developmental dimensions are worth investigating to document associated problems (intellectual functioning, sensory modulation impairments, language difficulties, motor skills, attentional difficulties, emotional regulation, associated medical condition (e.g., seizures), eating, and sleeping) (2). Such integrative approaches help clinicians provide tailored interventions. Three categories of therapeutic interventions for children with ASD have been distinguished:

1. Pure behavioral methods [e.g., *Applied Behavior Analysis* (ABA)] are based on a comprehensive analysis of children's behaviors to promote well-adapted behaviors based on positive reinforcement. Some behavioral methods are based on the child's preferences, such as *pivotal response training* (PRT). Some of these programs involve parents, such as the *Son Rise* program, which occurs at home (3, 4).

2. Developmental methods aim to promote the development process (e.g., *floor time* or the *Early Start Denver Model*—ESDM). In these programs, the therapist starts from the child's interests and follows their initiatives to promote communication performance using the skills of imitation and synchrony. Some of these methods include behavioral techniques, such as ESDM (5, 6).

3. Mixed methods (e.g., *Treatment and Education of Autistic and Communication Handicapped Children*—TEACCH) aim to reduce problematic behaviors in a behavioral approach while considering the child's specific developmental level. Parental guidance is an essential aspect of these programs to allow the child's emerging competences to be generalized into his natural environment (7).

These methods target the primary difficulties experienced by patients with ASD in social interaction and communication, in particular joint attention, imitation, synchrony, emotional sharing and symbolic play. The predictors of the treatment response of patients with ASD to these interventions include intensive interventions (at least 3–4 h per day), interventions provided at an early age, intervention tailored to the patient's developmental needs, interventions promoting family inclusion and spontaneous communication with peers, and interventions with repeated assessment of therapeutic goals based on the child's progress (8).

Therapeutic Interventions for Other NDDs

Children with ID require a global approach with interventions promoting cognitive skills and autonomy. Most authors recommend that a regular multidimensional evaluation of cognitive, educational, socioemotional, and adaptive skills throughout life. It usually provides a better understanding of how individuals with ID function (9). The goal regarding treatment approach is to contribute toward the planning of more appropriate strategies for learning, care, and support, leading to a better quality of life and participation in society. Specific programs are delivered according to children's developmental levels, family burdens and etiological factors (e.g., antiepileptic drug in case of seizures). Interventions provided at school or specialized institutions play a key role in enhancing pedagogic and academic achievements. Specific intervention form speech therapists, occupational therapists, reading specialists may also target a specific function (9).

For other NDDs, therapeutic approaches directly target the impaired function: speech therapists for children with communication disorders, reading specialists for children with written language difficulties, and occupational therapists for children with motor disorders. Children with ADHD may benefit from attention remediation and cognitive therapy. ADHD is also the only NDD for which effective medications are available (e.g., methylphenidate).

Music Therapy

From the biblical scene of David playing harp to the *Gnaoua* ritual in Maghreb, anecdotal testimonies of the healing effect of music are reported in all cultures. In the history of psychiatry, music was a component of the moral treatment advocated by Pinel in the eighteenth century. Since music remains one aspect of the milieu and occupational therapy of patients receiving ambulatory care for chronic mental health conditions. It is after the Second World War that music therapy became a structured psychotherapy in North America to treat veteran (10). Nordoff and Robbins (11) created a structured method known as "creative musical therapy" based on the principle of a relational component of music.

Among music therapies, a traditional distinction exists between receptive music therapy techniques (based on listening) and active music therapy techniques (based on sound production by voice, body percussion, or use of instruments). This distinction has been questioned because listening may also involve an active component. Current research usually distinguishes three techniques: music listening, interactive music therapy and improvisational music therapy (12). Interactive music therapy is essentially a structured method including techniques for educational purposes or musical games. For

clarity, in this article, the term educational music therapy will be used for this category. Improvisational music therapy uses children's music production to promote spontaneous non-verbal communication. As the distinction between these categories is somewhat arbitrary, a mixed method category also exists.

Music Therapy for Patients With ASD and/or Other NDDs

The particular interest in music of patients with autism was already noted in the historical description by Kanner (13). He observed that some non-verbal patients are able to sing or hum. Some other patients are able to recognize complex melodies. Several reasons for the hypothesis that music therapy represents a useful adjunct treatment in youths with autism have been documented. Music therapy is regarded as a way of promoting preverbal communication through the improvement of joint attention, motor imitation, and ultimately synchronous rhythm (14). Music therapy has also been used to enhance some cognitive functions, such as attention or memory (15). As impairments in social interactions are also often reported at some point in youths with other NDDs, the effects of music therapy are worth investigating in patients with these other conditions. In this review, we aimed to review the evidence examining the use of music therapy in youths with ASD and/or other NDDs.

METHODS

Design

The systematic review was conducted according to the recommendations outlined in the PRISMA guidelines (16). Titles and abstracts were scanned for relevance. Full texts were ordered in cases of uncertainty. Reference lists of retrieved systematic reviews were checked. All full texts were assessed for eligibility. Any original study was eligible for inclusion in this review. Abstracts, editorials, and case series with only one evaluation were excluded. Systematic reviews and meta-analyses were examined for references but not included.

We included studies that measured the effect of music therapy intervention (music listening, interactive or educational music therapy, improvisational music therapy, or mixed method), in children or adolescents (participants aged up to 18 years), diagnosed with ASD and/or another NDD. Other NDD were ADHD, ID, DCD, CD, and SLD. Exclusion criteria were: (1) study without outcomes derived from a distinct subgroup of subjects with ASD and/or other NDD; (2) study reporting pooled results without distinction between adults and youths; (3) study that did not provide new empirical data or without objective assessment of clinical outcome; (4) study reporting the effect of music therapy in neurological/neurodevelopmental disorder different from the list mentioned above (e.g., epilepsy).

Search Method Used to Identify Studies

Relevant articles were obtained by searching the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and Medline databases. Each database was searched from January 1970 to September 2020. In addition, we hand searched reference lists of identified articles and pertinent reviews for additional studies. Only studies in English, French or German were included. References from the reviewed articles were also screened to find more articles of interest. We used the following search terms: ("*music*" OR "*music therapy*") AND ("*autism*" OR "*pervasive developmental disorder*" OR "*intellectual disability*" OR "*dyslexia*" *OR "written language disorder*" OR "*attention deficit disorder*" OR "*hyperkinetic disorder*" OR "*communication disorder*" OR "*oral language disorder*" OR "*specific learning disorder*" OR *"social relationship"* OR *"social skills"* OR *"social responsive behaviours"* OR *"social motivation"* OR *"communication"* OR *"nonverbal"* OR *"joint attention"*). The systematic review yielded 2,778 hits, and 2,725 hits were excluded based on the information in the title or abstract. The full texts of the remaining 54 hits were critically reviewed, leading to the exclusion of another 15 articles because they were only reviews or comments and no new original data were included; alternatively, the research did not present objective outcomes or did not present music therapy intervention or child or adolescent population. One full-text was not found (17). Thirty-nine studies were included: 22 studies of children with ASD, 7 studies of children with ID, 5 studies of children with ADHD, and 5 studies of children with CD and SLD (dyslexia). No study was found for children with DCD, but one ASD study evaluates motor impairment associated with ASD (18). **Figure 1** summarizes the PRISMA flowchart of the study.

Data Analysis

Data and information were independently extracted from each study by the first two authors. In cases of disagreement, a consensus approach was adopted that included the third author. For each study under review, the year of publication and references were extracted. In each report, we collected the following information: (i) description of the sociodemographic and clinical characteristics of the participants (age, gender, and method of diagnosis), (ii) description of the interventions (method of music therapy, duration, frequency, and setting), and (iii) clinical outcomes (effect of the intervention and possible side effects). Considering the disparity in music therapy methods used for children with ASD, the results were presented according to the category of music therapy, i.e., educational music therapy or improvisational music therapy. Only one study included in our review offered a music listening technique, but results were not presented in tables due to severe methodological problems (19). The diverse statistical methods and measurement practices used across studies did not allow for the calculation of pooled effect sizes, such as those used in meta-analyses.

An evaluation of the different risk of bias was performed by the first author according to the Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) tool (20) and the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (21). Results are presented in **Supplementary Table 1**.

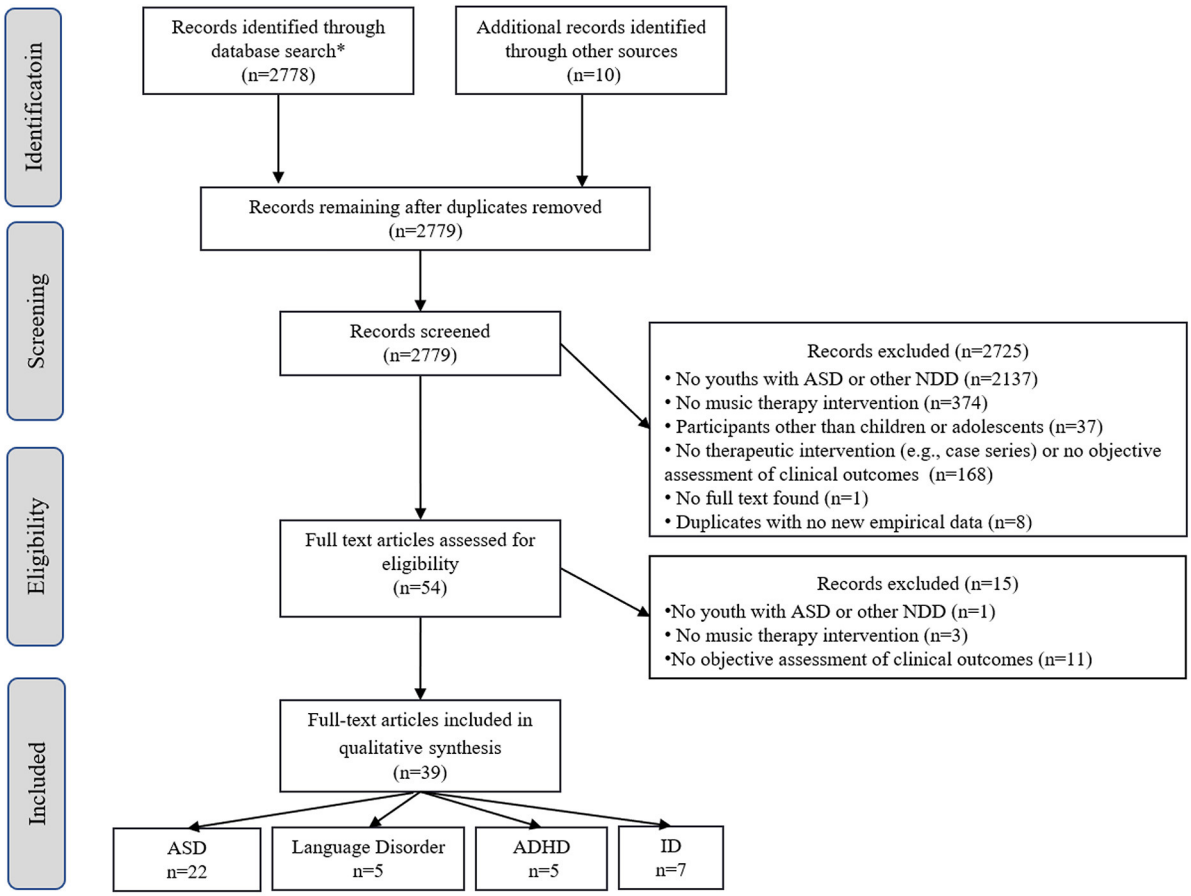

FIGURE 1 | Flowchart of the study.

RESULTS

Music Therapy for Children With ASD

Educational Music Therapy ($n = 272$)

Ten studies evaluated the effects of educational music therapy in youths with ASD: five uncontrolled studies (22–26) and seven controlled studies (18, 27–32). They are all summarized in **Table 1**.

Only one study examined the effect of an educational music therapy intervention on the severity of autistic symptoms (32). The authors observed a small effect of the intervention on the Social Responsiveness Scale (SRS) score (partial $\eta^2 = 0.29$) within the 4 days following the last session. Other studies assessed the effect of educational music therapy on other developmental dimensions. Four studies evaluated the benefit of educational music therapy on joint attention (23, 25, 26, 32). Joint attention was assessed with videos of adult-child interactions by collecting data on pointing behaviors (23, 32), direction of gaze toward an object/person (26, 32), and spontaneous reactions or in response to adults' behaviors (25, 26). None of these studies reported a statistically significant effect of these interventions on the joint attention of children with ASD (23, 25, 26, 32). Paul et al. (26) suggests a positive effect of sung directives during different activities compared to spoken directives on graphic analyzes. Pasiali et al. (24) assessed the effect of music therapy on different components of attention using TEA-Ch (Test of Everyday Attention for Children) in youths with ASD. The authors reported that youths with ASD who received music therapy achieved higher performance in selective and divided attention than at baseline; however, no change in sustained attention was observed before and after the intervention. Another study evaluated the effect of musical therapy on the recognition of emotions in youths with ASD. Katagiri (29) examined whether a piano melody congruent with the emotional valence of a facial expression presented with a picture or a drawing influenced the performance on an emotional recognition task. The authors did not obtain any significant results.

Cibrian et al. (18) evaluated two different music therapy interventions in the motor impairments of young patients with ASD. The reported outcome suggests a positive effect of music therapy on coordination and timing synchronization.

TABLE 1 | Studies assessing educational musicotherapy in patients with autism spectrum disorder (ASD).

Author Year	Study design	Population	Diagnostic	Interventions	Assessment	Main findings	Limitations/Comments
NON-CONTROLLED STUDIES							
Lim and Draper (22)	Pre/post evaluation	*N* = 22 Age = 3–5 y.o. Gender: 17 boys Recruitment: na	ASD Dg tool: na ID: na Severity: children were verbal or preverbal with immediate echolalia	**Three different conditions:** Music training: "music incorporated ABA Verbal Behavior"; sung instructions, songs with target words shown on pictures and target phrases with echoic training (A) Speech training: ABA method with the same instructions without singing (B) No specific intervention (C) The order of the three conditions was randomly assigned Settings: individual sessions three times a week for 2 weeks. Duration of each session: na	**Clinical symptom:** no **Interaction:** Observations of behavior in videotaped posttest sessions: Verbal production evaluation scale including semantics, phonology, prosody, and pragmatics **Other assessment:** no	Positive effect on speech production: Verbal production SMD = 9.227 (p = 0.000) for MT vs. no training	However, no significant difference in verbal production was observed between music training and speech training The participants scored much higher on echolalia production than in response to questions
Kalas (23)	Pre/post evaluation	*N* = 30 Age = 4–7 y.o. Gender: 28 boys Recruitment: community outpatient activity	ASD Dg tool: na ID: na Severity: CARS: 15 with severe ASD, 15 with mild/moderate ASD	**Two experimental groups:** With simple music condition: simple melody and accompaniment on keyboard With complex music condition: complex melody and complex accompaniment on keyboard (with syncopation or dotted rhythms) Settings: individual 10 min sessions twice a week for 3 weeks	**Clinical symptoms:** no **Interaction:** Behaviors observed in videotaped sessions: ESCS: Joint attention measured by the number of times the child responded to a bid for joint attention by following a pointing gesture toward the object or instrument of interest. RJA score ICC = 0.86 **Other assessment:** no	Statistically significant interaction between the music modality and level of functioning. $F_{(1)}$ = 20.089, p = 0.001	The effect of simple vs. complex music depended on the level of functioning. Specifically, the simple music condition was more effective at eliciting RJA in children diagnosed with severe ASD, whereas the complex music condition was more effective at eliciting RJA in children diagnosed with mild/moderate ASD
Pasiali et al. (24)	Pre/post evaluation	*N* = 9 Age = 13–20 y.o. Gender: 4 boys Recruitment: special education facilities	ASD Dg tool: na ID: yes Severity: CARS: 3 with severe ASD, 4 with mild/moderate ASD	**Intervention:** Interactive music therapy: "musical attention control training" Settings: 45 min sessions once to twice a week for 6 weeks	**Clinical symptoms:** no **Interaction:** no **Other assessment:** TEA-Ch	Positive changes in scores on tests related to selective attention and attentional control/switching, but no difference in sustained attention	
Paul et al. (26)	Pre/post evaluation	*N* = 3 Age = 3–4 y.o. Gender: 3 boys Recruitment: na	ASD Dg tool: na ID: na Severity: CARS: 1 child with mild to moderate autism, 2 with severe autism	**Interventions** During activities (block matching, picture matching, clay play) (A) Spoken oral instructions (B) Sung oral instructions Settings: individual 15 min sessions once or twice a week, during 3 months. 9 sessions with each condition	**Clinical symptom:** no **Interaction:** Behavior observation of videotaped sessions: performance, frequency of social gesture and eye contact (ICC value correct-to-excellent) **Other assessment:** no	Visual graphic analyze: all participants scored higher in the sung condition compared to spoken condition for all measures	Small sample size No control group

(Continued)

TABLE 1 | Continued

Author Year	Study design	Population	Diagnostic	Interventions	Assessment	Main findings	Limitations/Comments
Davis (25)	Pre/post evaluation	*N* = 4 Age = 6–7 y.o. Gender: 4 boys Recruitment: special education facilities	ASD Dg tool: na ID: na Severity: 2 patients (50%) are verbal	**Experimental group:** Interactive music therapy Three different conditions: cooperative music therapy (A), cooperative play (B) and independent play (C) Settings: individual 20 min sessions once or twice a week for 5 weeks	**Clinical symptoms:** no **Interaction:** Behaviors observed in videotaped sessions: joint attention behaviors: interaction (responding to joint attention) and requesting (initiation) behaviors **Other assessment:** no	Interaction: mean difference in scores for MT/independent play = 71 Requesting: mean difference in scores MT/independent play: negative value = −16.875	Increase in interaction behaviors for all subjects during cooperative play and MT compared with independent play, but discordant results for requesting behavior
CONTROLLED STUDIES							
Buday (27)	Crossover	*N* = 10 Age = 4–9 y.o. Gender: 8 boys Recruitment: public school	ASD Dg tool: na ID: 70% Severity: CARS: 5 with severe ASD, 5 with mild/moderate ASD	**Two conditions:** (A) Interactive music therapy: songs used to teach signs and speech (B) Rhythmic speech used to teach signs and speech Settings: individual 3 min sessions four times a week for 2 weeks (4 sessions in the first week with one condition and 4 sessions in the second week with the other condition)	**Clinical symptoms:** no **Interaction:** Behaviors observed in videotaped sessions: sign and speech imitating behaviors. ICC 98% **Other assessment:** no	For sign imitation: MT group: M = 5.1 Control group: M = 4.0 $\Omega^2 = 0.35$/estimated $d = 0.39$ $p < 0.05$ For speech imitation: MT group: M = 4.2 Control group: M = 3.2 $\Omega^2 = 0.42$/estimated $d = 0.30$ $p < 0.02$	Large effect of music vs. rhythm form on both sign and word learning Limitations: small sample size and only children who have shown an interest in music (obvious attention or enjoyment) were included. Crossover
Farmer (28)	RCT	*N* = 10 Age = 2–5 y.o. Gender: 9 boys Recruitment: na	ASD Dg tool: na ID: na Severity: na	**Experimental group:** Interactive music therapy sessions: guitar playing, songs, games, name and point at body parts, imitation of animals **Control group:** Sessions without music Settings: individual daily 20 min sessions for 5 days	**Clinical symptoms:** no **Interaction:** Behaviors observed in videotaped sessions: Frequency of appropriate verbal and gestural responses **Other assessment:** no	Graphical analysis: Positive effect on verbal responses and gestural responses	Sessions in different conditions (home, school, etc.)
Katagiri (29)	Controlled study	*N* = 12 Age = 9–15 y.o. Gender: na Recruitment: community outpatient activity	ASD Dg tool: na ID: na Severity: na	**Two experimental groups** with background music: prerecorded piano improvisations structured to reference four basic emotions with singing songs: music with lyrics **Active control group**: Verbal instructions Settings: individual 30 min sessions twice a week for 4 weeks **No-intervention control group:** no specific intervention	**Clinical symptoms:** no **Interaction:** no **Other assessment:** Behavioral task: explicit emotional labeling based on facial expression (photographs or schematic drawing) after a learning period	$F = 2.09$, df = 3, $p = 0.13$ Secondary exploratory analysis: Analysis of covariance using pretest scores as a covariate reveals that the background music condition may be the most effective $F = 8.28$ df = 3, $p = 0.01$	None of the four conditions was significantly more effective than the others in improving participants' understanding of the four emotions

(Continued)

TABLE 1 | Continued

Author Year	Study design	Population	Diagnostic	Interventions	Assessment	Main findings	Limitations/Comments
Lim (30)	RCT	*N* = 50 Age = 3–5 y.o. Gender: na Recruitment: community outpatient activity	ASD Dg tool: na ID: na Severity: CARS or ADI-R: 25 with moderate/severe ASD, 25 with mild ASD	**Experimental group:** Music training: "Developmental Speech and Language Training through Music"; videotaped songs with target words shown on pictures (PECS) **Active control group**: Speech training: videotaped spoken stories with target words Settings: individual 10 min sessions twice a day for 3 days **No-intervention control group:** no specific intervention	**Clinical symptoms:** no **Interaction:** Behaviors observed in videotaped posttest sessions: Frequency of appropriate verbal responses **Other assessment:** no	Positive effect on speech production: Verbal production ($p < 0.001$) $d = 1.275$ for the MT group vs. no training group	However, no significant difference was observed between the MT group and the speech training group
Sandiford et al. (31)	RCT	*N* = 12 Age = 5–7 y.o. Gender: 11 boys Recruitment: local advertisement	ASD Dg tool: ADOS ID: na Severity: Only children with limited or no functional verbal communication were included	**Experimental group:** Melodic Based Communication Therapy (MBCT): in addition to the traditional word elicitation approach, a combination of listening, hand clapping, singing of the word by the therapist and the child Settings: individual 45 min weekly sessions for 5 weeks **Control group:** Traditional language therapy	**Clinical symptoms:** no **Interaction:** Behaviors observed in videotaped sessions (first and last sessions): number of imitative attempts ICC 96% **Other assessments:** Vocabulary testing based on the International Phonetic Alphabet (assessor is blinded to the intervention): number of verbal attempts and number of correct words Parent survey: number of words reported by the parent	Increase in the number of verbal attempts from weeks 1 through 4 and number of correct words after weeks 1 and 3 in experimental group, while the control group progressed significantly after weeks 4 and 5 No significant differences in the number of verbal attempts ($z = -1.4$, $p = 0.08$) or number of correct words ($z = -0.2$; $p = 0.05$) were observed between the experimental and control groups A significant number of new words were heard in the home environment for the experimental group ($z = -2.0$, $p = 0.04$), but no significant difference was observed between the two groups ($z = -0.75$; $p = 0.45$) Participants in the experimental group had more imitative attempts ($z = -2.2$; $p = 0.03$)	Small sample size Lack of follow-up: missing data for parent survey

(Continued)

TABLE 1 | Continued

Author Year	Study design	Population	Diagnostic	Interventions	Assessment	Main findings	Limitations/Comments
LaGasse (32)	RCT	*N* = 17 Age = 6–9 y.o. Gender: 13 boys Recruitment: local advertisement	ASD Dg tool: na ID: na Severity: CARS2 (values na)	**Experimental group:** Music therapy group: Transformational Design Model, music experiences to facilitate the participants' desired social skills, music-making Settings: 50 min group (3–4 children) sessions, twice a week for 5 weeks **Control group:** Social skills group: cooperative play, including board games and word games. Group interaction included a ball game	**Clinical symptoms:** Parent-rated assessments: SRS (primary outcomes pretest: first group session, posttest: within 4 days of the last group session), ATEC **Interaction: Behaviors observed in videotaped posttest sessions:** eye gaze (ICC 0.934), joint attention (ICC 0.841), initiation of communication (ICC 0.935), response to communication (ICC 0.858), withdrawal behaviors (ICC 0.941) communication (initiation, response and withdrawal) in the first and last sessions **Other assessment:** no	SRS: Significantly greater improvement in the experimental group compared to control group ($p = 0.032$, partial $\eta^2 = 0.287$) ATEC: Nonsignificant difference between the two groups ($p = 0.0549$) Significant between-group differences in eye gaze toward persons ($p = 0.022$, partial $\eta 2 = 0.323$) and joint attention with peers ($p = 0.031$ partial $\eta 2 = 0.291$). No significant between-group differences in joint attention with adults, initiation of communication with another child, initiation of communication with an adult, response to communication, or social withdrawal behaviors	Joint attention increased with peers and decreased with adults. Promotion of peer-to-peer interaction Limitations: ATEC may be an inappropriate tool for measuring changes in social skills. Bias due to parental rating Small sample size Higher attrition in the control group. Missing data due to a lack of follow-up
Cibrian et al. (18)	RCT	*N* = 22 Age = 4–8 y.o. Gender: na Recruitment: special education facilities	ASD Dg tool: na ID: developmental age Mean = 5.72, SD = 1.2 Severity: na	**Two experimental groups:** Sound production based on child motor activities (touching, tapping or pinching a spandex fabric with animated background) and different motor exercises using tambourines Settings: individual sessions once a week during 8 weeks, duration of each session na	**Clinical symptom:** Developmental coordination disorder questionnaire **Interaction:** no **Other assessment:** Engagement in music survey: playing in touch questionnaire (clinician-rated) Timing synchronization	Improvements in motor coordination for 27% of participants, and in timing synchronization for all participants	DCD questionnaire may be inappropriate

y.o., years old; Dg, diagnostic; na, not available; ID, intellectual disability; ICC, Internal Consistency Coefficient; ABA, Applied Behavior Analysis; MT, music therapy; CARS, Children Autism Rating Scale; ESCS, Early Social Communication Scales; RJA, responses to joint attention; TEA-Ch, Test of Everyday Attention for Children; ADI-R, Autism Diagnostic Interview- Revised; PECS, Picture Exchange Communication System; ADOS, Autism Diagnostic Observation Schedule; SRS, Social Responsiveness Scale, completed by guardians; ATEC, Autism Treatment Evaluation Checklist, which was designed to evaluate new treatments through questions on speech and language skills, social skills, physical well-being, and sensory/cognition. The checklist has four areas: speech and communication (14 items), sociability (20 items), sensory/cognitive awareness (18 items), and health/physical behavior (25 items). A lower score indicates higher functioning. The scale was completed by guardians.

TABLE 2 | Studies assessing improvisational music therapy in patients with autism spectrum disorder (ASD).

Authors	Methods	Population	Dg	Interventions	Assessment	Findings	Limitations/Comments
NON-CONTROLLED STUDIES							
Yoo and Kim (33)	Pre/post evaluation	*N* = 9 Age = Mean 10.8 y.o. Gender: 8 boys Recruitment: community outpatient activity, special education facilities	ASD Dg tool: na ID: na Severity: CARS: mild to moderate autism Mean = 28.1, SD = 5.7	**Intervention:** Improvisational music therapy, simple rhythmic patterns using dyadic drum playing Settings: 8 individual 30 min sessions. Duration and frequency na	**Clinical symptom:** Parent-rated or teacher-rated assessments: K-SSRS (subscales: cooperation, assertion, and self-control) **Interaction:** Behavior observation of videotaped sessions: occurrence of target behaviors (eye gaze, engagement in joint action, synchronous movements) ICC excellent **Other assessment:** Imitation tasks, asynchrony measures during drum tapping tasks	SSIS: Significant increase in cooperation ($z = -1.992$; $p = 0.046$), self-control ($z = -2.201$; $p = 0.028$) and total score ($z = -2.201$; $p = 0.028$) between pre and posttest No significant improvement in imitation tasks performance, in asynchrony measures Increase in all target behaviors between the first and the last session	No control group Small sample size
CONTROLLED STUDIES							
Kim et al. (34)	Crossover	*N* = 10 Age = 3–5 y.o. Gender: 10 boys Recruitment: Child and adolescent psychiatry department in the hospital	ASD Dg tools: DSM-IV TR and ADOS ID: Developmental quotient (PEP) mean 70; range 60–89; SD = 9.97 Severity: 5 children (50%) were non-verbal mean CARS mean = 36.1, range 32–42, SD = 3.41	**Two conditions:** (A) Improvisational music therapy (B) Play sessions with toys Settings: Individual 30 min sessions weekly for 8 months (12 sessions under each condition)	**Clinical symptoms:** no **Interaction:** Behaviors observed in videotaped sessions (mothers and clinicians): - PDDBI rated by mothers and clinicians The ICC between mothers and clinicians was very low (19% pretreatment, 51% between treatments, and 67% posttreatment) The ICC between clinicians ranged from good to excellent - ESCS rated by two independent clinicians: initiation of joint attention (low level: eye contact, high level: pointing) and responding to joint attention bids (number of times the child follows the tester's pointing gesture) The ICC ranged from good to excellent - target behaviors: eye contact duration and turn-taking duration **Other assessment:** no	PDDBI: ANOVA revealed a significant interaction between time and group ($p = 0.0001$) For clinicians' ratings, change during MT vs. change during play: $d = 0.79$ [−014;1.71] ESCS: ANOVA revealed a significant interaction between time and group ($p = 0.01$) Medium effect size in the comparison of scores after MT with scores after play (ignoring sequences): $d = 0.63$ [0.31; 0.95], recalculated based on the change score between data points: $d = 0.97$ [0.21; 1.74]. For the subscales, changes were observed in low initiation of joint attention and responses, but no changes in high level initiation (pointing) Significant effects were observed for eye contact duration ($p < 0.0001$) and turn taking duration ($p < 0.0001$) in the music therapy condition compared with play condition	Overall results generally favored music therapy over the play condition in improving joint attention behaviors Differences in mothers' ratings compared to clinicians': mothers found improvements in both conditions (music and play therapy), whereas clinicians suggested greater improvements after music therapy Marked improvement in joint visual attention skills (eye contact, alternating eye contact with the adult and the object) during and after music therapy compared to play therapy Limitations: small sample size, crossover design, attrition bias

(Continued)

TABLE 2 | Continued

Authors	Methods	Population	Dg	Interventions	Assessment	Findings	Limitations/Comments
Gattino et al. (35)	RCT	*N* = 24 Age = 7–12 y.o. Gender: 24 boys Recruitment: daily ambulatory care	ASD Dg tools: DSM-IV-TR (autistic disorder, PDD or Asperger syndrome) and ADI-R ID: 30% Severity: CARS-BR mean score = 35.8, range 27–44, SD = 4.4	**Experimental group:** Improvisational music therapy Settings: individual 30 min weekly sessions for 20 weeks **Control group:** no specific intervention	**Clinical symptoms:** CARS-BR: verbal communication, nonverbal communication and social communication **Interaction**: no **Other assessment**: no	Verbal: $p = 0.50$ SMD 0.28, 95% CI [−0.01; 0.57] Nonverbal: $p = 0.35$ SMD 0.39, 95% CI [−0.21; 0.57] Social: $p = 0.34$ SMD 0.39, 95% CI [−0.08; 0.86]	Subgroup analysis: difference across diagnoses (non-verbal communication improved in ASD group but not in PDD or Asperger groups) ($p = 0.008$) Limitations: small sample size, the use of CARS as an assessment may be inappropriate
Thompson et al. (36)	RCT	*N* = 23 Age = 3–6 y.o. Gender: 19 boys Recruitment: community outpatient activity	ASD Dg tool: DSM-IV-TR ID: na Severity: only children with limited or no functional verbal communication were included	**Experimental group:** Songs, improvisation, structured music interactions, in addition to usual care Settings: individual home-based 30 min weekly sessions for 16 weeks including the family **Control group:** Usual care (family-centered early childhood intervention program)	**Clinical symptoms:** Parent-rated assessments: VSEEC (primary outcome), SRS-PS, and MBCDI-W&G **Interactions:** Behaviors observed in videotaped sessions (first and penultimate sessions): MTDA (child engagement in the music therapy sessions) ICC 60% **Other assessments:** PCRI Qualitative data: semi-structured interview of parents	Decrease in the VSEEC score ($p < 0.001$) $d = 1.96$ 95% CI [0.92; 3.00] SRS-PS: NS: $p = 0.341$, $d = 0.42$ MBCDI: NS: $p = 0.553$, $d = 0.26$: improvement in both groups, but no significant treatment effect PCRI: NS effect of treatment $p = 0.099$, but $d = 0.80$ MTDA: $p = 0.001$	Significant effect on social engagement (VSEEC and MTDA) Limitations: small sample size Use of parent-reported assessment when parents are not blinded to the intervention
Ghasemtabar et al. (37)	Pre/post evaluation	*N* = 27 Age = 7–12 y.o. Gender: 14 boys Recruitment: community outpatient activity	ASD Dg tool: na ID: na Severity: CARS: mild to moderate Mean = 33.0, SD = 1.9	**Experimental group:** Improvisational music therapy: music hearing, singing songs, hand clapping, dancing, free and creative playing of instruments Settings: group 1 h sessions, twice a week during 6 weeks **Control group:** Usual care	**Clinical symptom:** Parent-rated assessments: SSRS (sub-scales of cooperation, assertions, self-control and responsibility) **Interaction:** no **Other assessment**: no	Significant higher improvement in SSRS score in posttest in the experimental group compared to controls, however no significant difference was observed at follow-up (2 months after the last session)	Small sample size Use of parent-reported assessment whereas parents are not blind to the intervention Non-cooperative children were excluded, attrition bias
Porter et al. (47)	Subgroup analysis of RCT	*N* = 34 Age = 8–16 y.o. Gender: na Recruitment: community outpatient activity	ASD-NS Dg tool: na ID: na Severity: na	**Experimental group:** Improvisational music therapy: Voice, movement and instrument playing Settings: individual 30 min weekly sessions during 12 weeks **Control group:** Usual care	**Clinical symptom:** Parent-rated assessments: SSIS (primary outcome) Social functioning subscale of the CBCL, CES-D **Interaction:** no **Other assessment:** Rosenberg self-esteem scale Family functioning scale	Non-significant difference between experimental and control groups with regards to SSIS total score at week 13 (mean difference 3.6 [95%: −4.6;12.0], $p = 0.37$)	Subgroup analysis

(Continued)

TABLE 2 | Continued

Authors	Methods	Population	Dg	Interventions	Assessment	Findings	Limitations/Comments
Bieleninik et al. (38)	RCT	*N* = 364 Age = 4–6 y.o. Gender: 308 boys Recruitment: community outpatient activity	ASD Dg tools: CIM10, ADOS, and ADI-R ID: 46% Severity: ADOS (mean value at baseline = 17.7)	**Experimental groups:** Improvisational musicotherapy Settings: individual 30 min sessions, possibly joined by family members for 5 months, with two different frequencies: High intensity MT: 3 times a week Low intensity MT: once a week **Control group:** Usual care Follow up: 1 y	**Clinical symptoms:** ADOS SRS (parent-rated) **Interaction:** no **Other assessment**: no	Primary outcome: ADOS (5 M) MD 0.06 [95%: −0.70;0.81] $p = 0.88$ Significant results obtained for several secondary outcomes: Greater improvement in SRS-social awareness for the low-intensity MT group compared with the control group at 2 months ($p = 0.004$) Greater improvement in SRS-social motivation scores for the MT (low+high intensity) than in the control group at 12 months ($p = 0.007$) Greater improvement in SRS-autistic mannerisms scores for the high intensity MT group compared with the control group at 5 months ($p = 0.009$)	Large RCT and encouraging secondary analysis (see discussion) Limitations: Observed differences in scores on social responsiveness subscales may be artifacts attributable to multiplicity and lack of blinding
Sharda et al. (39)	RCT	*N* = 51 Age = 6–12 y.o. Gender: 33 boys Recruitment: community outpatient activity	ASD Dg tool: DSM IV-TR, ADOS, ADI-R or CARS ID: no (WASI-II full-scale scores M 100, SD 15) Severity: ADOS (mean ∼15)	**Experimental group:** Improvisational music therapy approaches: musical instruments, songs and rhythmic cues while targeting communication, turn-taking, sensorimotor integration, social appropriateness and musical interaction Settings: individual 45 min sessions weekly for 8 to 12 weeks **Control group:** Play-based intervention	**Clinical symptoms:** Parent-rated assessments: CCC-2, SRS-II, PPVT-4, FQoL and the maladaptive behaviors subdomain of the VABS (VABS-MB) Language ability assessments: CELF-4 and PPVT-4 **Interaction: no** **Other assessment:** Functional neuroimaging: resting-state connectivity of frontotemporal brain networks	Primary outcomes: "social communication battery": CCC-2, SRS-II and PPVT-4: Increase in the communication score of the CCC-2 in the experimental group after the intervention compared to the control group ($p = 0.01$) $d = 0.34$ Improvements were specific to pragmatics, reduction of inappropriate initiations and better social relations and interests. No significant results were obtained for SRS-II or PPVT-4 Secondary outcomes: FQol and VABS-MB Significant effect of music therapy on FQoL ($p = 0.01$, $d = 0.57$) compared to the control group. Both groups showed a reduction in the VABS-MB score (post-intervention $p = 0.01$) Post-intervention resting-state brain functional connectivity was i) greater between auditory and subcortical regions and auditory and fronto-motor regions and ii) lower between auditory and visual regions in the music compared to the non-music groups	Improvement only in the CCC-2 score, which measures pragmatic communication. MT may have exerted a limited effect on the ASD symptom severity or on improving receptive vocabulary Music employs a structured approach similar to social communication, which may otherwise be hindered by sensory and social difficulties Changes in brain connectivity were related to improvements in children's communication skills after MT. Music might play a modulatory role in reducing the overconnectivity between sensory cortices, subsequently improving communication processes Limitations: small sample size

(Continued)

TABLE 2 | Continued

Authors	Methods	Population	Dg	Interventions	Assessment	Findings	Limitations/Comments
Rabeyron et al. (14)	RCT	$N = 36$ Age = 4–7 y.o. Gender: 31 boys Recruitment: na	ASD Dg tool: na ID: na Severity: CARS, ABC	**Two experimental groups:** Improvisational music therapy Music listening Settings: group (3–5 children) 30 min sessions, weekly for 8 months	**Clinical symptoms:** CGI, CARS, and ABC **Interaction:** no **Other assessment:** Qualitative patient-centered analysis	Primary outcome: CGI: d (estimated) = 0.75; $p = 0.028$ Secondary outcomes: CARS, ABC: no effect	Blind assessment of the primary outcome Limitations: small sample size

y.o., years old; dg, diagnostic; na, not available; ADOS, Autism Diagnostic Observation Schedule; ID, intellectual disability; SSIS, Social Skills Improvement System rating scale; CBCL, Child Behaviour checklist; CES-D, Center for Epidemiological studies depression; PEP, Psycho-Educational Profile; CARS, Childhood Autism Rating Scale; PDDBI, Pervasive Developmental Disorder Behavior Inventory; ESCS, Early Social Communication Scale; MT, music therapy; PDD, pervasive developmental disorder; ADI-R, Autism Diagnostic Interview-Revised; CARS-BR, Childhood Autism Rating Scale adapted for Brazil: 3 measured outcomes: verbal communication, non-verbal communication and social communication; CARS2, Childhood Autism Rating Scale- second edition; ATEC, Autism Treatment Evaluation Checklist, which was designed to evaluate new treatments through questions on speech and language skills, social skills, physical well-being, and sensory/cognition. The checklist has four areas: speech and communication (14 items), sociability (20 items), sensory/cognitive awareness (18 items), and health/physical behavior (25 items). A lower score indicates higher functioning. The scale was completed by guardians. SRS, Social Responsiveness Scale: completed by guardians; SRS-PS, Social Responsiveness Scale, preschool version for 3 y.o. It assesses impairments independent of the child's IQ in repetitive behaviors, interpersonal behavior and communication. VSEEC, Vineland Social Emotional Early Childhood scale. The parent assessed the quality of the child's interactions in the home and community according to how well the child gives attention, enters into intentional social interactions, and understands and expresses emotion. Only two of the three subscales were used in the study by Thompson et al. (36): interpersonal relationship and play/leisure time. MBCDI-W&G, MacArthur-Bates Communicative Development Inventories, Words & Gestures: assessment of early language skills in the areas of vocabulary comprehension and production, and use of communicative gestures; PCRI, The Parent–Child Relationship Inventory: assesses parent attitude toward parenting and their child; MTDA, Music Therapy Diagnostic Assessment: child engagement in the music therapy sessions; ABC, Aberrant Behavior Checklist; CCC-2, Children's Communication Checklist; VABS-MB, maladaptive behavior subscale of the Vineland Adaptive Behavior Scales; SRS-II, Social Responsiveness Scale; FQoL, Beach family Quality of Life scale; WASI-II, Wechsler's Abbreviated Intelligence Scale; CELF-4, Clinical Evaluation of Language Fundamentals; PPVT-4, Peabody Picture Vocabulary Test; CGI, Clinical Global Impression, K-SSRS, Korean-Social Skills Rating System.

Finally, five studies evaluated the benefits of educational music therapy on language and communication skills (22, 27, 28, 30, 31). In these studies, language was assessed using different methods: list of new words learned (27, 28, 30, 31), spontaneous verbal production (22), and number of words reported by parents (31). Four of five studies showed statistically significant results (22, 27, 28, 30). According to Buday (27), youths with ASD who learned a word list with rhythmic music achieved better results than youths who participated in sessions using the rhythm alone ($d = 0.30$). Farmer (28) observed a tendency in children with ASD who received an intervention with structured musical games to express more appropriate verbal responses than children who received an intervention with non-musical games. Lim (30) showed that the use of music videos facilitated the learning of target words ($d = 1.28$) in children with autism compared to those in a control group that did not receive the intervention. This difference, however, was not statistically significant compared to the group receiving a language intervention based on non-music videos ($d = 1.14$). The same team showed that singing instructions inspired by the ABA method exerted a positive effect on learning target words compared to a control group that did not receive any intervention. This difference was again not statistically significant compared to the group receiving the language intervention (22). Sandiford, Mainess (31) did not report any significant difference in the rate of new words learned between the group of children with ASD who received an intervention using mixed music therapy methods (singing, listening to music and rhythmic hand clapping) compared to children who underwent classical speech therapy sessions. However, an analysis of learning trajectories showed faster progress in the group with music therapy.

Improvisational Music Therapy ($n = 578$)

One uncontrolled study (33) and eight controlled studies (14, 34–39, 47) evaluated the effect of improvisational music therapy on youths with ASD (**Table 2**). Thompson, McFerran (36) measured the effects of home-based improvisational music therapy sessions including family members on the severity of clinical symptoms and the overall level of functioning of youths with ASD. The authors noted that the youths who participated in music therapy sessions had a lower score on the Vineland scale ($d = 1.96$) than the control group who received the current standard of care. No difference was observed in scores on the SRS scale (secondary outcome) between the two groups. Sharda et al. (39) described positive effects of improvisational music therapy sessions compared to games sessions on the level of pragmatic of language (Children's Communication Checklist-2, CCC-2 score) and the quality of life, but no effect on the other main primary outcomes (SRS score and score on the Peabody vocabulary test). Rabeyron et al. (14) documented a higher clinical improvement in the primary outcome (change in Clinical Global Impression, CGI, score, $d = 0.75$) of youths who participated in improvisational music therapy sessions than youths who received an intervention with listening music therapy sessions. The changes observed in the secondary outcomes (i.e., Childhood Autism Rating Scale, CARS, and Autism Behavior Checklist, ABC, scores) were not significantly different between

TABLE 3 | Studies assessing musicotherapy in youths with intellectual disability (ID).

Authors	Methods	Population	Dg	Intervention	Assessments	Findings	Limitations/Comments
NON-CONTROLLED STUDIES							
Rainey Perry (40)	Qualitative case study	*N* = 10 Age = 5–12 y.o. Gender: 8 boys Recruitment: na	ID Severe and multiple disabilities; mostly sensory impairment and neurological disorders	**Intervention:** improvisational music therapy Settings: 5 individual sessions. Duration of each session and frequency: na	Analysis of videotaped sessions: rating of a "communication profile." Describe turn taking, type of improvisation and interactions (musical and non-musical)	Descriptions of interactions in one chosen videotaped session for each child	This study suggests that children may need the possibility of responding to an interaction at their level, and may benefit from being encouraged in their engagement in communication: singing or playing together and not only taking turns, similar to early preverbal communication
Williams et al. (41)	Pre/post evaluation	*N* = 201 Age = 3–60 months Gender: na Recruitment: community outpatient activity	Global developmental delay (32%), ASD (15%), speech and language impairments (18%)	**Intervention:** singing songs with movements, playing instruments, quiet music to encourage parent-child bonding Settings: group (8–10 parent-child pairs) 60 min sessions once a week for 10 weeks	Parent-reported assessments: Parental mental health symptoms (Kessler K6, auto questionnaire) Parenting self-efficacy Parent-child interactions: parental responsiveness/warmth (child rearing questionnaire), irritable parenting (parental perceptions and behaviors scale), parental engagement in home learning activities with their child Child behaviors (mood and behavior subscale of the NEILS scales of developmental competency) Social play skills, receptive communication skills (subscale of the NEILS scales of developmental competency) Social support, satisfaction and perceived benefits Clinician assessments: 6-item observational checklist for the first two and last two sessions evaluating quality of parental behavior toward the child and child behavior toward the parent and others. A second observer independently coded behavior. The ICC was excellent	Symptoms Improvement in parents' mental health, child's communication, and child's social play No change in child's behavior problems, activities with child, parenting irritability, self-efficacy and warmth Behaviors Improvements in all measures (parent sensitivity, parent engagement, parent acceptance, child responsiveness, child interest, child social engagement)	
Mendelson et al. (42)	Pre/post evaluation	*N* = 33 Age = na, 2nd graders Gender: na Recruitment: special education facilities	ID 5 children with ASD, 32 without ASD Severity: na	**Intervention**: VOICSS method (vocal interactive communication and social strategies): interactive music therapy using songs with a high expectation of a reciprocal response, turn taking Settings: group, classroom-based 45 min sessions once a week during 7 weeks (short-term music therapy) or 15 weeks (long term music therapy)	Teachers' ratings: Social Skills Improvement System-Rating Scale (SSIS-RS) Behavioral observations: child's verbal and social responses coded on a Likert scale by two raters during live observations in the classroom. The ICC was fair to excellent	SSIS-RS: no significant difference During the therapy sessions, levels of social and communicative responses showed significant differences in the long-term program, but not in the short-term program	Probable dose-effect

(Continued)

TABLE 3 | Continued

Authors	Methods	Population	Dg	Intervention	Assessments	Findings	Limitations/Comments
Yang (43)	Pre/post evaluation	*N* = 26 (parent-child pairs) Age = 1–3 y.o. Gender: 20 boys Recruitment: community outpatient activity	ASD (46%) ID (23%) Language delay (19%) Severity: na	**Intervention:** interactive music therapy (singing songs together, musical games) with the child and his parent Settings: individual home-based 40 min sessions once a week for 6 weeks	Analysis of videotaped sessions: - parent-child interaction (children initiations and parents' response during free-play sessions) coded by two independent raters. The ICC was excellent - parent-child synchrony (same focus of attention, matched affect and reciprocal and responsive exchanges): Likert scale. The ICC was excellent	Significant improvements between pre and posttest scores for parents' physical and verbal responses, for children's verbal initiation and for parent-child synchrony No significant difference in children's physical initiation	
Zyga et al. (44)	Pre/post evaluation	*N* = 47 Age = na, 1st grade to 12th grade Gender: na Recruitment: special education facilities	ID ASD, attention disorder, specific learning disorder Severity: na	**Intervention:** Kids Love Music program: learning the story, choreography and songs from The Wizard of Oz Settings: in-school 30–45 min group sessions (5–12 children) twice a week for 4 weeks	Analysis of videotaped sessions (first and last sessions): socioemotional skill scale: eye contact, turn taking, engagement, social awareness, symbolic flexibility, and emotional understanding	Significant changes in all domains	Missing data on population Not controlled results
CONTROLLED STUDIES							
Aldridge et al. (45)	Crossover	*N* = 12 Age = 4–6.5 y.o. Gender: 3 boys Recruitment: community outpatient activity	ID Severity: na	**Two conditions:** (A) Improvisational music therapy Settings: individual 30 min sessions once a week for 2 weeks. (B) Waiting list	Griffiths tests (locomotor developmental, personal-social hearing and speech, hand-eye coordination, performance, and practical reasoning)	Significant change during the first study period; when the Waiting List Group was treated and then tested at Test 2, the newly treated children started to catch up in their development	The activity of listening in a structured musical improvisational context without the lexical demands of language is a platform for improving communication Hand-eye coordination, which depends on a wider body awareness, appears to be a vital component of developmental changes
Duffy and Fuller (46)	Case control study	*N* = 32 Age = 5–10 y.o. Gender: na Recruitment: special education facilities	ID Severity: moderate	**Experimental group:** group music therapy social skills program using prerecorded music **Control group**: non-music group Settings: 30 min group sessions twice a week for 8 weeks	Likert scale evaluating social skills, based on the analysis of the first and the last videotaped sessions - social skill measure specifically developed for the study including turn-taking, imitation, vocalization, initiation and eye contact - researcher and independent observer	Significant increase in all dimensions, but no difference between the two groups. The music therapy appeared to show a tendency toward being more effective only one skill area (i.e., imitation)	

y.o., years old; dg, diagnostic; na, not available; ASD, autism spectrum disorder.

the two groups after the music therapy sessions. Kim et al. (34) observed a positive effect of music therapy sessions on joint attention and prosocial behaviors. Impact of improvisational music therapy on social skills were contradictory: two studies (33, 37) showed an improvement of the Social Skills Improvements System Rating Scale after music therapy sessions, while no significant differences were found in another study (47). Gattino et al. (35) did not find any statistically significant difference in the CARS score between the group receiving music therapy and the group receiving the usual treatment.

The study by Bieleninik et al. (38) deserves more attention, as the study included 364 young patients with ASD in 9 different country sites. They did not observe a significant difference in the Autism Diagnostic Observation Schedule (ADOS) or SRS score (primary outcomes) at 2, 5, and 12 months between the three arms: treatment as usual, non-intensive music therapy, and intensive music therapy. However, they identified some differences in scores for SRS subscales, with a greater improvement in the score for the social motivation subscale of the music therapy group at 12 months and in the score for the autistic mannerisms subscale at 5 months. In addition, the authors presented at a congress unpublished data stressing that the subgroups of subjects with both ASD and ID had a higher response rate for the primary outcome ADOS (risk ratio = 1.43 [95% CI: 1–2.05], $p = 0.049$).

Music Therapy for Children With Other NDDs

Intellectual Disability ($n = 361$)

Five non-controlled studies (40–44) and two controlled studies (45, 46) evaluated the effect of music therapy on youths with ID (**Table 3**). Two studies showed a positive effect of music therapy sessions on parent-child interactions, with increased spontaneous demands by the child and adapted parental responses (41, 43), more synchronous behaviors between parents and children (43), and an improvement in parents' mental health (41). Zyga et al. (44) also reported an improvement in the socioemotional abilities of children who participated in mixed music therapy sessions, including singing, dancing and theater. Mendelson et al. (42) documented a positive effect of educational music therapy sessions delivered in the classroom on peer interactions during the sessions. However, this effect was observed only in subjects who participated in a 15 week program and not in participants who received a shorter 7 week intervention.

Regarding controlled studies, Aldridge et al. (45) showed a non-significant trend for a positive effect of improvisational music therapy sessions on a global measure of the developmental level in children with ID. Specifically, the authors stressed the importance of the improvement in hand-eye coordination. Duffy and Fuller (46) did not detect a significant difference in the rate of progress in terms of imitation, vocalization, initiation of interaction, eye contact and turn-taking between children who received music therapy and those who did not.

Attention Deficit Hyperactivity Disorder ($n = 443$)

Three non-controlled studies (48–50) and two controlled study (51, 52) evaluated the effect of music therapy on youths with ADHD (**Table 4**). These studies presented significant methodological biases. The largest study ($n = 268$) was based on a questionnaire administered to music therapists (34). Rothmann et al. (52) showed significant improvements in attentional performance tests and in quality of life after music therapy among children with suspected ADHD compared to those who received usual care. Montello and Coons (48) suggested that school-based educational music therapy sessions using rhythms are associated with increased attention and motivation and decreased hostility in children with behavioral problems based on teacher reports.

Communication Disorders and Specific Learning Disabilities (Dyslexia) ($n = 120$)

Four studies were conducted in youths with dyslexia, and one study was conducted in youths with language delay (**Table 5**). Two non-controlled studies examined the effect of educational music therapy on children with dyslexia (53, 54). Overy (53) reported a positive effect of school-based music therapy sessions on reading competence in nine children with dyslexia. Habib et al. (54) documented an improvement in several domains of written language competence in 12 children with dyslexia after music therapy sessions, such as phonological perception, pseudoword repetition, word reading, and auditory attention.

Two randomized controlled studies were conducted to document the effect of educational music therapy on children with dyslexia. Register et al. (55) observed an improvement in vocabulary and reading comprehension test scores in children with written language difficulties who participated in school-based music therapy sessions compared to children who participated in a traditional program for learning difficulties. Flaugnacco et al. (56) found that children with dyslexia who participated in school-based music therapy group sessions presented increased phonological awareness and reading skills (for accuracy but not speed) compared to children who had participated painting sessions during the same time. The authors noted that rhythm perception during the sessions was a predictor of a positive treatment response.

Finally, one non-controlled study (57) evaluated the effect of improvisational music therapy on 18 children with language delay. The authors observed a significant increase in developmental age (in particular phonological memory and sentence understanding) after a 6 week individual improvisational music therapy program.

DISCUSSION

Main Findings

Considering the diversity of music therapy approaches, improvisational and educational music therapy programs provided to youths with ASD and other NDDs were distinguished. Regarding educational music therapy, our findings support a positive but small effect of educational music therapy on children with NDDs, particularly patients with ASD and/or ID. Two major limitations in the results obtained for

TABLE 4 | Studies assessing musicotherapy in youths with attention deficit hyperactivity disorder (ADHD).

Authors	Methods	Population	Dg	Interventions	Assessments	Findings	Limitations/Comments
NON-CONTROLLED STUDIES							
Montello and Coons (48)	Pre/post evaluation	*N* = 16 Age = 11–14 y.o. Gender: 14 boys Recruitment: special education facilities	"emotional disturbance," learning disabilities and/or attention deficit disorder Dg tool: na ID: na Severity: na	**Two interventions:** "Active group": rhythm-based intervention "Passive group": listening-based intervention **Three groups:** A: active and passive B: passive and passive C: passive and active Settings: group 45 min sessions once a week for 12 weeks	Teacher's interview (Achenbach) evaluating attention, motivation and hostility	Improvements were observed in the groups using the rhythm-based intervention	
Jackson (49)	Review of clinical practice	268 questionnaires completed by music therapists	ADHD Dg tool: na ID: na Severity: na	Several music therapy interventions	Perceived effectiveness of musicotherapy on ADHD	Most of the therapists describe music therapy as effective in children with ADHD	
Gooding (50)	Pre/post evaluation	*N* = 45 Age = 6–17 y.o. Gender: na Recruitment: public school	ADHD, dyslexia, specific learning disabilities and/or Asperger, PTSD, anxiety disorder Dg tool: na ID: no Severity: na	Music therapy-based social skills intervention program at school, home and after school care settings 50 min weekly group sessions for 5 weeks	Likert-type ratings of participants by teachers, researchers and the participants themselves evaluating social functioning after the first and fifth sessions. Appropriate communication behaviors during the observation period	Non-significant results	Substantial heterogeneity in participants and intervention settings Not randomized
CONTROLLED STUDIES							
Rickson (51)	Case control study	*N* = 13 Age = 11–16 Gender: 13 boys Recruitment: special education facilities	ADHD Dg tool: DSM-IV ID: most have mild ID Severity: treated with stimulants	**Two experimental groups:** - Instructional intervention: structured rhythmic exercises, positive reinforcement - Improvisational intervention **Control group:** waiting list	Conner's rating scale for parents and teachers Synchronized tapping tasks	No significant results	Not randomized
Rothmann et al. (52)	Case control study	*N* = 101 Age = 5–10 y.o. Gender: 75 boys Recruitment: community outpatient activity	ADHD or suspicion of attention difficulties Dg tool: na ID: na Severity: naïve of medication	**Experimental group:** Educational music therapy program involving rhythm exercises with percussion instruments and musical games Settings: Group (4–6 children) 1 h session once a week during 18 weeks **Control group:** Usual care	Test of attentional performance for children Quality of life ratings Symptom checklist for ADHD Symptom checklist for conduct disorder	Significant improvement in attention performance ($p < 0.0001$) and in quality of life ($p < 0.0001$) in the experimental group compared to control group	No formal diagnostic of ADHD No active control group

y.o., years old; dg, diagnostic; na, not available.

TABLE 5 | Studies assessing musicotherapy in children with communication/oral and written language disorder.

Authors	Methods	Population	Dg	Interventions	Assessments	Findings	Limitations/Comments
NON-CONTROLLED STUDIES							
Overy (53)	Pre/post evaluation	*N* = 9 Age = mean 8,8 y.o. Gender: 9 boys Recruitment: public school	Dyslexia Dg tool: dyslexia screening test ID: na Severity: na	**Intervention**: instructional program with singing songs Settings: school-based 20 min group lessons three times a week for 15 weeks	Language and literacy tests	Significant positive effect of the music program on rhythm copying, rapid auditory processing, phonological ability, and spelling ability	
Groβ (57)	Pre/post evaluation	*N* = 18 Age = 3.5–6 y.o. Gender :12 boys Recruitment: public school	Delayed speech (excluding ASD and/or muteness or speech developmental disorder) Dg tool: na ID: na	**Intervention:** improvisational music therapy (Nordoff and Robbin's method): singing songs, percussion instruments and piano playing Settings: individual 25 min sessions. Frequency and number of sessions: not available	- Standardized speech development test: understanding of sentences, speech production, and memory of speech - Nonverbal developmental test - Analysis of videotaped sessions: child-therapist relationship in musical activity and "musical communicative activity." ICC: 82%	Positive trends for phonological memory and understanding of sentences Better relationship between child and therapist over time Significant decrease in the difference between developmental and chronological ages	
Habib et al. (54)	Pre/post evaluation	*N* = 12 Age = 7–12 y.o. Gender: 8 boys Recruitment : special education facilities	Dyslexia Dg tool: na ID: na Severity: severe dyslexia, mean difference between chronological age and reading age at 36 months	**Intervention:** "Cognitive-Musical Training": transmodal intervention, use of rhythm with body parts and piano keyboard. Structured intervention Settings: Two 30 min group sessions (group of 4 children with the same level) and 2 1 h group sessions all 12 children per week for 6 weeks	Several tasks selected from the NEPSY II battery, which evaluate categorical perception of syllables, attentional processing and phonological, reading tasks, visual and writing tasks	After the intervention, improved categorical perception of syllables, auditory attention, pseudowords repetition, reading words, phonological awareness and comparison of letter strings	Methodology tested on a pilot study including 12 subjects receiving 3 days of musical training
CONTROLLED STUDIES							
Register et al. (55)	RCT	*N* = 33 (8 students with specific disability in reading) Age = na, 2nd graders Gender: na Recruitment: public school	Dyslexia Dg tool: na ID: na Severity : na	**Experimental group:** instructional program with singing songs **Control group:** traditional program Settings: group school-based sessions three times a week for 4 weeks. Duration of each session: na	Vocabulary and reading comprehension tests	For students with a specific disability in reading, the musical program may effectively improve reading comprehension	

(Continued)

TABLE 5 | Continued

Authors	Methods	Population	Dg	Interventions	Assessments	Findings	Limitations/Comments
Flaugnacco et al. (56)	RCT	*N* = 48 Age = 8–11 y.o. Gender: 34 boys Recruitment : community outpatient activity	Dyslexia Dg tools: anamnestic interview and neuropsychological assessment ID : no Severity: na	**Experimental group**: music training: use rhythm (percussive instruments and rhythmic body movement) and sensorimotor synchronization games **Control group:** painting training Settings: 1 h group sessions (5–6 children) twice a week for 30 weeks (excluding holidays)	**Symptoms:** - phonological awareness (pseudoword repetition test of the Promea Battery): phonemic blending and phonemic segmentation - reading abilities: reading a text aloud (MT reading test), DDE-2: reading single words and pseudowords (primary outcome) aloud **Other assessments:** Working memory (WISC III) and self-esteem (multidimensional test of self-esteem-TMA)	Improvements in several reading tasks in both groups (no difference in reading speed between two groups), better improvement in the experimental group compared to control group in: - text reading: 50% fewer poor performers in the experimental group compared to the control group after the intervention - accuracy in reading pseudowords - phonological abilities - working memory - auditory attention The outcome in the rhythm production task is a predictor of phonological awareness (phonemic blending and phonemic segmentation). A greater improvement in rhythmic abilities indicates a greater improvement in phonological awareness (bending task) ($p = 0.002$)	Supports the hypothesis of a causal role for rhythm-based processing in language acquisition and phonological development Recommends an interest in the use of music as a complementary tool in reeducation

y.o., years old; dg, diagnostic; ID, intellectual disability; NEPSY, a developmental NEuroPSYchological Assessment; DDE-2, Assessment Battery for Developmental Dyslexia and Dysorthography, second version; MT, music therapy; WISC III, Wechsler's Intelligence Scale for Children, third edition; TMA, multidimensional self-esteem test: the Italian version of the Multidimensional Self-Concept Scale.

children with ASD are noted. First, only one study used core ASD symptoms as a primary outcome (32), leading to difficulties in generalizing the results. Second, the results for improving joint attention are mixed. The determination of whether educational music therapy interventions are ineffective or whether these effects are difficult to demonstrate is challenging. Indeed, joint attention measures are rarely standardized, questioning their validity.

Studies evaluating the effect of educational music therapy on language and communication skills in children with ASD reported three main results. First, a significant effect on learning target words based on imitation skills was observed. Second, a study showed that educational music therapy sessions were associated with improvements in several components of oral language (phonology, semantics, prosody, and pragmatics) (30). Third, a positive effect was observed for the music therapy group compared to the group without treatment, but not for the active control group using non-musical techniques.

Regarding improvisational music therapy, we found few empirical findings supporting a positive effect of improvisational music therapy sessions on youths with NDD, but some findings appear interesting for children with ASD and/or ID. The most methodologically robust study conducted by Bieleninik, Geretsegger (38) did not report a significant improvement in the primary outcome (ADOS) and a positive effect of music therapy sessions only on a few secondary outcomes. However, they observed a significant effect on the subgroup of participants with ASD and ID. In a secondary analysis based on what aspects of improvisational music therapy predicted an improvement, the authors performed a microanalysis of the video therapy sessions and showed that a high level of relational adjustment between the child and the therapist was a strong predictor of positive outcomes (58). These authors concluded that the intervention is more effective when the therapist adopts a relational pattern similar to the child's pattern. A similar hypothesis was formulated by Rainey Perry (40) based on their work with children with severe and multiple disabilities. The therapist uses a relational mode that fits the child's "communication profile" to provide the child opportunities to respond to interactions.

The choice of the primary outcomes in the reviewed studies should be discussed. In the study conducted by Bieleninik, Geretsegger (38), the primary outcome was the social affect score of the ADOS at 5 months (i.e., encompassing problematic reciprocal social interactions and communication). However, the ADOS is a diagnostic tool that was not specifically designed to assess variations in clinical severity over time. However, the studies that used clinical scales such as the SRS or the CARS to track changes in the severity of autistic symptoms did not present significant findings. However, several reviewed studies showed a positive effect of improvisational music therapy sessions on children with ASD or/and ID using measures of subjective clinical improvement (e.g., CGI) and the level of global functioning or quality of life (14, 36, 39). Finally, music interventions including family members exerted a stronger effect than other types of interventions for youths with ID (36). This finding is a possible argument supporting the inclusion of family in improvisational music intervention sessions in youths with ID. However, so far, no direct comparison between therapy sessions including family members or not has been conducted to test this hypothesis.

Regarding children with NDDs other than ASD and/or ID, two observations can be made from the preliminary data on the effect of musicotherapy. First, a positive trend for music therapy sessions using rhythm on the written language of children with dyslexia was reported. However, the number of studies and the total number of children included ($n = 120$) remain limited. Second, the quality of evidence supporting a positive effect of music therapy on children with ADHD remains poor.

Limitations

Currently, many limitations exist regarding the studies included in the current review. The main limitation of this review is related to the methodological quality of the studies analyzed, with small sample sizes and wide age ranges (**Supplementary Table 1**). Most studies had a non-controlled design, and when a control group existed the allocation of the treatment was not necessarily randomized (e.g., case-control study) questioning the impact of possible confounding biases. Second, music therapy interventions are extremely heterogeneous, particularly in the context of educational music therapy, making cross-study comparisons difficult and meta-analysis calculations invalid. Third, the primary outcomes used varied widely between studies. A lack of information about the measures of interaction, if any, contributes to the heterogeneity of the studies. Associated evaluations of clinical dimensions have rarely been performed. In particular, no study included a standardized assessment of anxiety symptoms, while previous reports show a benefit of music therapy sessions in patients with these symptoms (59). Finally, the conclusion of this review may be influenced by the process of study selection and the limitations inherent to the search strategy (e.g., lacking of keywords, studies in other language, publication bias).

Implications

How useful is the addition of music therapy sessions to the traditional care of children with NDDs? A number of methodological biases prevents us from generating any firm conclusions based on the studies reviewed. Among the different combinations of music therapy sessions and clinical characteristics of the patients tested, a stronger effect was observed for the use of improvisational music therapy in children with both ASD and ID (22, 24, 31). While these interventions failed to significantly reduce the level of autistic symptoms in most published studies, several authors reported a positive effect on other clinical dimensions (22), on the overall level of functioning (e.g., CGI) (24), and on quality of life (39, 41). Notably, the effect was enhanced when family members were included in sessions (36, 41, 43).

Further studies would be particularly inspired to document the potential mediators of the therapeutic effects (e.g., age of the participants; cognitive characteristics), in addition to the measurements of clinical symptoms and level of functioning (58). Among other hypotheses, music therapy sessions might exert a

positive effect by increasing the quantity and quality of adult-child interactions. The child-therapist relation might be regarded as an "experimental" relation for children, where he/she learns to attune his/her behaviors to adult behaviors. Another promising finding that deserves attention is the positive effect of educational music therapy on children with dyslexia, but more research is needed to conclude any definitive positive effect. For children with other NDDs, more substantial studies are needed before a conclusion can be made on the value of their use.

AUTHOR CONTRIBUTIONS

DC and HM-B designed the study and wrote the first draft of the manuscript. HM-B, XB, and FV performed the study search. HM-B and XB extracted the data from the studies. FV checked the data for consensus agreement. All authors contributed to the final version of the manuscript.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition. Arlington, VA: American Psychiatric Association (2013).
2. Xavier J, Bursztejn C, Stiskin M, Canitano R, Cohen D. Autism spectrum disorders: an historical synthesis and a multidimensional assessment toward a tailored therapeutic program. *Res Autism Spect Disord.* (2015) 18:21–33. doi: 10.1016/j.rasd.2015.06.011
3. Reichow B, Hume K, Barton EE, Boyd BA. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). *Cochrane Database Syst Rev.* (2018) 5:Cd009260. doi: 10.1002/14651858.CD009260.pub3
4. Virués-Ortega J. Applied behavior analytic intervention for autism in early childhood: meta-analysis, meta-regression and dose-response meta-analysis of multiple outcomes. *Clin Psychol Rev.* (2010) 30:387–99. doi: 10.1016/j.cpr.2010.01.008
5. Rogers SJ, Dawson G. Early start denver model for young children with autism: promoting language, learning and engagement. *J Autism Dev Disord.* (2011) 41:978–80. doi: 10.1007/s10803-010-1041-8
6. Ospina MB, Krebs Seida J, Clark B, Karkhaneh M, Hartling L, Tjosvold L, et al. Behavioural and developmental interventions for autism spectrum disorder: a clinical systematic review. *PLoS ONE.* (2008) 3:e3755. doi: 10.1371/journal.pone.0003755
7. Virues-Ortega J, Julio FM, Pastor-Barriuso R. The TEACCH program for children and adults with autism: a meta-analysis of intervention studies. *Clin Psychol Rev.* (2013) 33:940–53. doi: 10.1016/j.cpr.2013.07.005
8. Narzisi A, Costanza C, Umberto B, Muratori F. Non-pharmacological treatments in autism spectrum disorders: an overview on early interventions for pre-schoolers. *Curr Clin Pharmacol.* (2014) 9:17–26. doi: 10.2174/15748847113086660071
9. Szymanski L, King BH. Practice parameters for the assessment and treatment of children, adolescents, and adults with mental retardation and comorbid mental disorders. American Academy of Child and Adolescent Psychiatry Working Group on Quality Issues. *J Am Acad Child Adolesc Psychiatry.* (1999) 38(Suppl. 12):5–31s. doi: 10.1016/S0890-8567(99)80002-1
10. Gaston ET. *Music in Therapy*. New York, NY: Sixth Book of Proceedings of the National Association for Music Therapy (1968).
11. Nordoff P, Robbins C. *Creative Music Therapy: Individualized Treatment for the Handicapped Child*. New York, NY (1977).
12. Lecourt É. *Chapitre 3. La Musicothérapie. Les Art-Thérapies*. Paris: Armand Colin (2017). p. 75–119.
13. Kanner L. Autistic disturbances of affective contact. *Nervous Child.* (1943) 2:217–50.
14. Rabeyron T, Saumon O, Dozsa N, Carasco E, Bonnot O. De la Médiation musicotherapique dans la prise en charge des troubles du spectre autistique chez l'enfant : evaluation, processus et modelisation. *La Psychiatr l'enfant.* (2019) 62:147–71. doi: 10.3917/psye.621.0147
15. Ho YC, Cheung MC, Chan AS. Music training improves verbal but not visual memory: cross-sectional and longitudinal explorations in children. *Neuropsychology.* (2003) 17:439–50. doi: 10.1037/0894-4105.17.3.439
16. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* (2009) 339:b2535. doi: 10.1136/bmj.b2535
17. Thomas E, Egnal NS, van Eeden F, Bond A. The effects of music therapy on a group of institutionalised mentally retarded boys. *S Afr Med J.* (1974) 48:1723–8.
18. Cibrian FL, Madrigal M, Avelais M, Tentori M. Supporting coordination of children with ASD using neurological music therapy: a pilot randomized control trial comparing an elastic touch-display with tambourines. *Res Dev Disabil.* (2020) 106:103741. doi: 10.1016/j.ridd.2020.103741
19. Lanovaz MJ, Sladeczek IE, Rapp JT. Effects of music on vocal stereotypy in children with autism. *J Appl Behav Anal.* (2011) 44:647–51. doi: 10.1901/jaba.2011.44-647
20. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* (2016) 355:i4919. doi: 10.1136/bmj.i4919
21. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* (2011) 343:d5928. doi: 10.1136/bmj.d5928
22. Lim AH, Draper E. The effects of music therapy incorporated with applied behavior analysis verbal behavior approach for children with autism spectrum disorders. *J Music Ther.* (2011) 48:532–50. doi: 10.1093/jmt/48.4.532
23. Kalas A. Joint attention responses of children with autism spectrum disorder to simple versus complex music. *J Music Ther.* (2012) 49:430–52. doi: 10.1093/jmt/49.4.430
24. Pasiali V, LaGasse AB, Penn SL. The effect of musical attention control training (MACT) on attention skills of adolescents with neurodevelopmental delays: a pilot study. *J Music Ther.* (2014) 51:333–54. doi: 10.1093/jmt/thu030
25. Davis M. *The Effect of Music Therapy on Joint Attention Skills in Children with Autism Spectrum Disorder*. University of Kansas (2016).
26. Paul A, Sharda M, Menon S, Arora I, Kansal N, Arora K, et al. The effect of sung speech on socio-communicative responsiveness in children with autism spectrum disorders. *Front Hum Neurosci.* (2015) 9:555. doi: 10.3389/fnhum.2015.00555
27. Buday EM. The Effects of Signed and Spoken Words Taught with Music on Sign and Speech Imitation by Children with Autism. *J Music Ther.* (1995) 32:189–202. doi: 10.1093/jmt/32.3.189
28. Farmer KJ. *The Effect of Music vs. Nonmusic Paired With Gestures on Spontaneous Verbal and Nonverbal Communication Skills of Children With Autism Between the Ages 1-5*. Florida State University (2003).

29. Katagiri J. The effects of background music and song texts ont he emotional understanding of children with autism. *J Music Ther.* (2009) 46:15–31. doi: 10.1093/jmt/46.1.15
30. Lim AH. Effect of "Developmental speech and language training through music" on speech production in children with autism spectrum disorders. *J Music Ther.* (2010) 47:2–26. doi: 10.1093/jmt/47.1.2
31. Sandiford GA, Mainess KJ, Daher NS. A pilot study on the efficacy of melodic based communication therapy for eliciting speech in nonverbal children with autism. *J Autism Dev Disord.* (2013) 43:1298–307. doi: 10.1007/s10803-012-1672-z
32. LaGasse AB. Effects of a music therapy group intervention on enhancing social skills in children with autism. *J Music Ther.* (2014) 51:250–75. doi: 10.1093/jmt/thu012
33. Yoo GE, Kim SJ. Dyadic drum playing and social skills: implications for rhythm-mediated intervention for children with autism spectrum disorder. *J Music Ther.* (2018) 55:340–75. doi: 10.1093/jmt/thy013
34. Kim J, Wigram T, Gold C. The effects of improvisational music therapy on joint attention behaviors in autistic children: a randomized controlled study. *J Autism Dev Disord.* (2008) 38:1758–66. doi: 10.1007/s10803-008-0566-6
35. Gattino GS, Riesgo RdS, Longo D, Leite JCL, Faccini LS. Effects of relational music therapy on communication of children with autism: a randomized controlled study. *Nordic J Music Ther.* (2011) 20:142–54. doi: 10.1080/08098131.2011.566933
36. Thompson GA, McFerran KS, Gold C. Family-centred music therapy to promote social engagement in young children with severe autism spectrum disorder: a randomized controlled study. *Child Care Health Dev.* (2014) 40:840–52. doi: 10.1111/cch.12121
37. Ghasemtabar SN, Hosseini M, Fayyaz I, Arab S, Naghashian H, Poudineh Z. Music therapy: an effective approach in improving social skills of children with autism. *Adv Biomed Res.* (2015) 4:157. doi: 10.4103/2277-9175.161584
38. Bieleninik L, Geretsegger M, Mossler K, Assmus J, Thompson G, Gattino G, et al. Effects of improvisational music therapy vs. enhanced standard care on symptom severity among children with autism spectrum disorder: the time-a randomized clinical trial. *JAMA.* (2017) 318:525–35. doi: 10.1001/jama.2017.9478
39. Sharda M, Tuerk C, Chowdhury R, Jamey K, Foster N, Custo-Blanch M, et al. Music improves social communication and auditory-motor connectivity in children with autism. *Transl Psychiatry.* (2018) 8:231. doi: 10.1038/s41398-018-0287-3
40. Rainey Perry MM. Relating improvisational music therapy with severely and multiply disabled children to communication development. *J Music Ther.* (2003) 40:227–46. doi: 10.1093/jmt/40.3.227
41. Williams KE, Berthelsen D, Nicholson JM, Walker S, Abad V. The effectiveness of a short-term group music therapy intervention for parents who have a child with a disability. *J Music Ther.* (2012) 49:23–44. doi: 10.1093/jmt/49.1.23
42. Mendelson J, White Y, Hans L, Adebari R, Schmid L, Riggsbee J, et al. A preliminary investigation of a specialized music therapy model for children with disabilities delivered in a classroom setting. *Autism Res Treat.* (2016) 2016:1–8. doi: 10.1155/2016/1284790
43. Yang YH. Parents and young children with disabilities: the effects of a home-based music therapy program on parent-child interactions. *J Music Ther.* (2016) 53:27–54. doi: 10.1093/jmt/thv018
44. Zyga O, Russ SW, Meeker H, Kirk J. A preliminary investigation of a school-based musical theater intervention program for children with intellectual disabilities. *J Intellect Disabil.* (2018) 22:262–78. doi: 10.1177/1744629517699334
45. Aldridge D, Gustroff D, Neugebauer L. A pilot study of music therapy in the treatment of children with developmental delay. *Comple. Ther. Med.* (1995) 3:197–205. doi: 10.1016/S0965-2299(95)80072-7
46. Duffy B, Fuller R. Role of music therapy in social skills development in children with moderate intellectual disability. *J Appl Res Intellect Disabil.* (2001) 13:77–89. doi: 10.1046/j.1468-3148.2000.00011.x
47. Porter S, McConnell T, McLaughlin K, Lynn F, Cardwell C, Braiden H-J, et al. Music therapy for children and adolescents with behavioural and emotional problems: a randomised controlled trial. *J Child Psychol Psychiatr.* (2017) 58:586–94. doi: 10.1111/jcpp.12656
48. Montello L, Coons EE. Effects of active versus passive group music therapy on preadolescents with emotional, learning, and behavioral disorders. *J Music Ther.* (1998) 35:49–67. doi: 10.1093/jmt/35.1.49
49. Jackson NA. A survey of music therapy methods and their role in the treatment of early elementary school children with ADHD. *J Music Ther.* (2003) 40:302–23. doi: 10.1093/jmt/40.4.302
50. Gooding LF. The effect of a music therapy social skills training program on improving social competence in children and adolescents with social skills deficits. *J Music Ther.* (2011) 48:440–62. doi: 10.1093/jmt/48.4.440
51. Rickson D. Instructional and improvisational models of music therapy with adolescents who have attention deficit hyperactivity disorder (ADHD): a comparison of the effects on motor impulsivity. *J Music Ther.* (2006) 43:39–62. doi: 10.1093/jmt/43.1.39
52. Rothmann K, Hillmer JM, Hosser D. [Evaluation of the Musical Concentration Training with Pepe (MusiKo mit Pepe) for children with attention deficits]. *Z Kinder Jugendpsychiatr Psychother.* (2014) 42:325–35. doi: 10.1024/1422-4917/a000308
53. Overy K. Dyslexia and music. From timing deficits to musical intervention. *Ann N Y Acad Sci.* (2003) 999:497–505. doi: 10.1196/annals.1284.060
54. Habib M, Lardy C, Desiles T, Commeiras C, Chobert J, Besson M. Music and dyslexia: a new musical training method to improve reading and related disorders. *Front Psychol.* (2016) 7:26. doi: 10.3389/fpsyg.2016.00026
55. Register D, Darrow AA, Standley J, Swedberg O. The use of music to enhance reading skills of second grade students and students with reading disabilities. *J Music Ther.* (2007) 44:23–37. doi: 10.1093/jmt/44.1.23
56. Flaugnacco E, Lopez L, Terribili C, Montico M, Zoia S, Schon D. Music training increases phonological awareness and reading skills in developmental dyslexia: a randomized control trial. *PLoS ONE.* (2015) 10:e0138715. doi: 10.1371/journal.pone.0138715
57. Groß W, Linden U, Ostermann, T. Effects of music therapy in the treatment of children with delayed speech development - results of a pilot study. *BMC Complement Altern Med.* (2010) 10:39. doi: 10.1186/1472-6882-10-39
58. Mossler K, Schmid W, Assmus J, Fusar-Poli L, Gold C. Attunement in music therapy for young children with autism: revisiting qualities of relationship as mechanisms of change. *J Autism Dev Disord.* (2020) 50:3921–34. doi: 10.1007/s10803-020-04448-w
59. Yinger OS, Gooding L. Music therapy and music medicine for children and adolescents. *Child Adolesc Psychiatr Clin N Am.* (2014) 23:535–53. doi: 10.1016/j.chc.2013.03.003

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Use of a Sensing Device to Visualizes Group Participation in Social Skills Learning Groups

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Children with autism spectrum disorders (ASD) have difficulties in developing stable peer relationships. Interventions for learning social skills (SS) for such children are often conducted in a group. Behavioral imaging and social imaging, which have been called for in recent years, are methods for visualizing children's behaviors and interpersonal relationships. To examine the usefulness of visualizing face-to-face interaction with others in the social skills learning scene of children with ASD, we use a business microscope that can qualify and visualize face-to-face interactions automatically. We highlight two boys' face-to-face interaction changes in the same SS learning group of five children. The device's use may provide a more objective measurement that complements the observer's subjective evaluation in case of the intervention's validation. It is expected that information on face-to-face interactions will be used to determine the SS learning process in the future.

Keywords: autism spectrum disorder, social skills intervention, group participation, visualizing behaviors, social network

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INTRODUCTION

Autism spectrum disorders (ASD) are characterized by difficulty in communicating and interacting in social settings and limited and repetitive behaviors, interests, and activities (1). Children with ASD may face challenges in group interactions (e.g., while they spend time with others from the same age group) at school. Regarding the peer relationships of children with ASD, it has been observed that such children are often involved only at the periphery and not at the center of a class, they tend to be a part of a relatively small group, and they lack reciprocity (2).

It has been established that one of the factors influencing the formation of peer relationships is the development of social skills (SS); however, children with ASD have difficulty learning such skills (3). Interventions for learning SS, such as SS training for school-aged children with ASD, have thus been implemented (4). Specifically, interventions for SS learning, based on cognitive behavioral therapy and social learning theory (5), often consist of structured classes related to specific skills, modeling skills, role-playing and rehearsing skills, and offering feedback on children's role-play/performance (6). In addition to effects such as improved social competence (6) and increased prosocial behavior [(7), etc.], psychological effects, such as improvements in (or development of) actual friendships (6), decreased depression and anxiety (8), and improved mental health

(9), have been observed. Therefore, SS learning programs in groups (i.e., Group Social Skills Intervention; GSSI) are often implemented (10).

In addition to practicing skills with multiple partners and groups, which is effective in SS teaching (11), the importance of relationships and connections within groups in group-based SS learning has been highlighted (12). For this reason, some GSSI group studies have attempted to identify changes in the approaches of children with ASD toward other children through behavioral observation methods. However, this approach is not practical since these behavioral observations are rarely conducted in a blind manner (7).

BEHAVIORAL IMAGING AND SOCIAL IMAGING

In recent years, attempts have been made to visualize children's behavior with ASD using various technologies. Behavioral imaging comprises computational sensing and modeling technology, used to measure, analyze, and understand human behavior, and provides a quantitative understanding of human behavior and development. Imaging technologies to monitor these behaviors and social interactions are diverse and include video, audio, and sensing technologies such as body sensors and location-based systems (13). Such technologies have been used to diagnose and assess ASD and help with the intervention (13). Furthermore, Suzuki (14), focusing on interpersonal interactions specifically, proposed social imaging as a method for visualizing interactions between several people. They created a device that measures and enhances interpersonal interactions by wearing a headband that glows when face-to-face interactions occur. (15). In GSSI, these technologies can also be applied to quantify and visualize the relationship between children with ASD and the group(s), using the obtained knowledge to provide intervention in learning situations.

Business microscopes (herein, BMS, (16)) are sensing devices that can quantify communication with others. This device can be worn on the body naturally like the nametag. The main components of the sensor include infrared transmission/reception systems and built-in 3D activity trackers. The infrared sensor detects face-to-face events at a distance of 2–3 m and within a 120-degree ° angle, either right or left. The person facing the device was recorded. It should be noted that the device used has a built-in tri-axis accelerometer that records the wearer's physical activity in Hz. The infrared sensor data and physical activity data were sent to the Human Big Data Cloud Service and analyzed. The analyzed data can be downloaded from the server by specifying the time and format (e.g., the time series CSV data about face-to-face partner and physical activity, the value calculated by the time series CSV data, and the network diagram). The type of communication can be estimated by physical movements (any physical movement with 2.0 Hz or more was defined as an active state, while any movement measuring <2.0 Hz was defined as a non-active state) and face-to-face interactions automatically.

When there was face-to-face interaction where the participant was active and the other party was non-active, the participant was defined as the "pitcher" of the communication (e.g., talking). Conversely, if the participant was non-active, but the other party was active, the participant was described as the "catcher" of the communication. If both parties were active, the communication was defined as "two-way." If both parties were non-active, they were deemed "face-to-face." Additionally, a network diagram can be drawn from the measured data automatically based on the face-to-face time between participants. In this diagram, the edge connecting the nodes (i.e., each person) appears thicker as the face-to-face time increases.

Although such diagrams were initially developed to visualize communication and improve productivity in business [e.g., performance in call centers (17)], in recent years, research regarding the visualization of communication has been conducted concerning pedagogy and developmental psychology (18). Efforts have also been made to use these diagrams to better understand changes associated with development in groups (18) and improve classes for teachers in physical education (19). It has been suggested that the real-time visualization of communication can provide an objective view for childcare workers and teachers. However, few to no studies have been conducted on children with ASD who have difficulty with social interaction. Therefore, it is necessary to examine the adaptation of children with ASD within a group of peers.

THE PILOT STUDY ABOUT MEASURING CHILDREN'S BEHAVIOR CHANGE BY BMS

In order to examine the effectiveness of visualizing face-to-face interaction in SS learning groups, the data of face-to-face interaction during free playtime in the SS learning group were collected by BMS. Five children with ASD, ranging from third to fourth-grade elementary students, participated in this study's SS learning program. Children had been under medical examination as part of their developmental disorder outpatient treatment. According to the Diagnostic and Statistical Manual of Mental Disorders, all participants were diagnosed (1). Given our study's preliminary stage, we will highlight two boys, Boy A (fourth grade) and Boy B (third grade) (**Figure 1**).

The STSSE (20) was modified to create a program that taught verbal communication skills (e.g., listen, explain, converse, and negotiate) to participants for a total of 10 sessions. Each session lasted about an hour and a half and included teaching, modeling, role-playing, rehearsing, feedback, and homework related to the target skills. Aside from the five children who took part in the program, a trainer and sub-trainer responsible for teaching the program and three clinical psychology students participated in this study as staff members. On the same day as the children's respective sessions, their caregivers participated in a program to encourage their children to extend the SS they had learned during each session to their home and school environments. This program was created by modifying the STSSE. The parents' sessions comprised group discussion, role-play, watching a

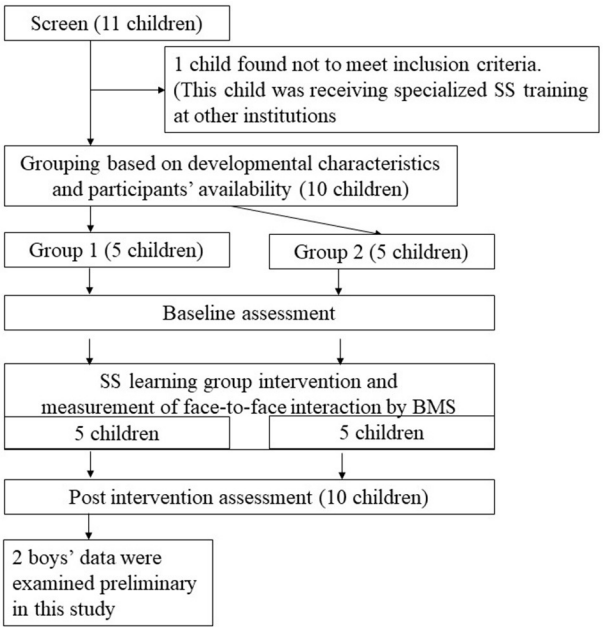


FIGURE 1 | Flow diagram showing enrollment and study design.

videotaped recording of their children's sessions, and weekly homework assignments.

In this study, a mat was laid at the back of the room during the allocated free playtime. Further, toys for playing games with rules, toys for playing with imagination, construction toys, toys with a cause and effect, and cushions were placed on the mat. After arriving at the room, the participants and trainers began each session by hanging their BMS devices around their necks. Children were explained BMS device as the nametag and hanged it through the GSSI sessions. Each device was customized with participants/trainers' names. None of the participants had a problem related to wearing the BMS devices.

Changes in the type of face-to-face communication were measured every 2.5 s to capture the changes in the face-to-face behavior (i.e., face-to-face interaction partner). This was performed in both the first and ninth sessions (in the first session, a free play activity time was held for the first time, and in the ninth session, a free play activity time was held for the last time) between the participants and the person they were facing. A face-to-face network diagram was also drawn. A network diagram was drawn using the free play activity scene's behavior to measure this behavior in a natural setting, in which the staff provided the least prompts. In this study, Cytoscape 3.8.0 was used for visual clarity. The edge connecting the nodes (i.e., each person) has a thickness of five levels—the longer the face-to-face time, the thicker and darker the color appears in this diagram. The network diagrams of the first and ninth network sessions were then compared. The first free-play activity scene was 16 min long, and the ninth free-play activity scene was 15 min long.

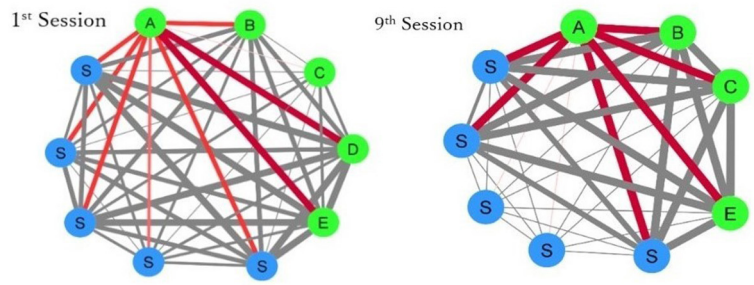
Supplementary, the child's classroom teacher completed the Social Skills Scale (herein, "SS scale"; (21)) at two-time points to understand the acquisition of SS before and after the intervention. The SS Scale is an itemized questionnaire rated by those who can directly observe children's behavior in a group setting. This scale comprises four areas: group behavior skills, communication skills, self-control skills, and peer relationship skills. The mean of the standard scores was 10 (1–15).

Boy A: Boy A, 9 years 9 months old, is in the fourth grade of elementary school. He has a full-scale IQ (FSIQ) of 80, with a comprehensive verbal index of 72, perceptual reasoning index of 95, working memory index of 82, processing speed index of 86. Boy A fulfilled the criteria for ASD and ADHD. He scored 63 on the Social Responses scale (Awareness 52, Cognition 68, Communication 55, Motivation 70, and Mannerism 63). As a toddler, he had difficulties communicating (e.g., language delay, immediate echolalia), little interest in other children, obsession, and restricted interest in one character. Although he was not administrated Autism Diagnosis Observation Scale (ADOS), his severity of autism was estimated as mild based on his symptoms and developmental history. When starting GSSI sessions, his obsession had decreased, but difficulties of asking for help and challenges of group participation had persisted. The parents reported about his friendship, "It is unclear to me as to whether or not he interacts with others." He participated in nine of ten GSSI sessions. He demonstrated a change in the percentage of time when he was not facing anyone through GSSI sessions (8.1% in the first session and 0% in the ninth session). Conversely, the time he spent with other children increased from 9.9% in the first session to 35.8% in the ninth session (**Figure 2A**). Concerning the type of communication, Boy A, regardless of the face-to-face interaction partner, remained less likely to engage in a voluntary approach (i.e., being the pitcher in the communication). However, there was an increase in his two-way communication with other children (1st 1.56% → 9th 12.22%) and in cases where other children approached him (Catcher 1st 8.33% → 9th 23.61%). As seen in the network diagram, D and E's network was strong in the first session. There was little interaction with B and C. Furthermore, his network with the staff members, who mainly participated in the free play activities, was narrow. In the ninth session, Boy A's network among other children was strong, and his interaction with the three staff members, who were mainly involved in the free play activities, was also strong. However, Boy A did not show more interaction with specific children (**Figure 2A**). On the SS-scale, the skills that changed by more than 1 standard deviation were: group behavior (7 points → 13 points) and peer relationships (7 points → 14 points)

Boy B: Boy B, 8 years 4 months old, is in the third grade of elementary school. He has a full-scale IQ (FSIQ) of 105, with a comprehensive verbal index of 123, perceptual reasoning index of 106, working memory index of 100, processing speed index of 78. He scored 83 on the Social Responses scale (Awareness 49, Cognition 76, Communication 79, Motivation 75, and Mannerism 103). Boy B fulfilled the criteria for ASD and ADHD. As a toddler, he lacked interest in others and obsessed with orders, restricted interest in the train, and sensory sensibility. At the time of starting GSSI sessions, he had little interest in others, difficulties in conversation, restricted interest. He was administrated ADOS at 7 years, his severity of autism

A

Face-to-face interaction partner	1st Session (%)	9th Session (%)	Communication pattern	1st Session (%)	9th Session (%)
Trainer and child(ren)	78.65	59.72	Two-way	28.13	25.56
			Pitcher	0.26	0.28
			Catcher	49.48	33.33
			Only face-to-face	0.78	0.56
Child(ren)	9.90	35.83	Two-way	1.56	12.22
			Pitcher	0	0
			Catcher	8.33	23.61
			Only face-to-face	0	0
Trainer	3.39	4.44	Two-way	1.04	1.39
			Pitcher	0	0
			Catcher	2.08	3.06
			Only face-to-face	0.26	0
No face-to-face	8.07	0			



B

Face-to-face interaction partner	1st Session (%)	9th Session (%)	Communication pattern	1st Session (%)	9th Session (%)
Trainer and child(ren)	61.46	77.78	Two-way	41.15	55.00
			Pitcher	0	0.83
			Catcher	19.79	21.39
			Only face-to-face	0.52	0.56
Child(ren)	4.95	10.28	Two-way	3.13	6.39
			Pitcher	0	0
			Catcher	1.82	3.89
			Only face-to-face	0	0
Trainer	4.17	11.94	Two-way	2.34	8.89
			Pitcher	0	0
			Catcher	1.82	3.06
			Only face-to-face	0	0
No face-to-face	29.43	0			

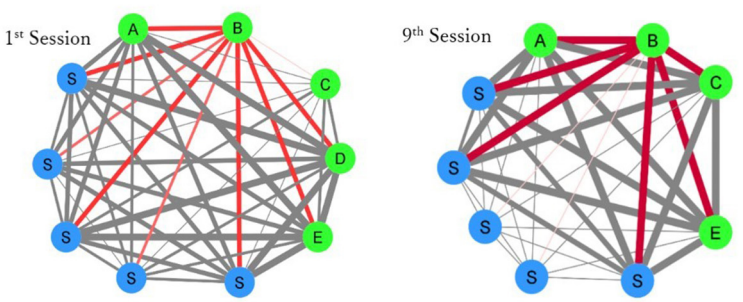


FIGURE 2 | Boy **(A)** changed of percentages that participants faced people and percentage of their communication pattern (above) and the network diagrams (below). Boy **(B)** changed of percentages that participants faced people and percentage of their communication pattern (above) and the network diagrams (below). The thinnest line in the network diagram indicates face-to-face interaction was the least, while the thickest line indicates that face-to-face interaction was the most.

was mild. The parents stated, "He looks like he has no interest in other children." He participated in seven of ten GSSI sessions. He demonstrated a change in the percentage of time when he was not facing anyone (1st 29.4% →9th 0%). The time he spent with other children increased from 5.0% in the first session to 10.3% in the ninth session. Furthermore, his two-way communication increased regardless of the face-to-face interaction partner (1st 46.61% → 9th 70.28%). There is evidence that he had little to no interaction with the staff and other children in the first session in the network diagram but started showing a network line with maximum thickness in the ninth session (**Figure 2B**). He only showed changes in peer relationships (8 points → 12 points) at the SS-scale.

DISCUSSION

This study attempted to visualize and quantify communication in a group of SS learning programs using a business microscope.

In terms of face-to-face interaction partners, in the free play activity scene, the time that the participants did not spend with anyone decreased, and the time they spent with other children increased. Concerning the type of communication, although there was no significant change in Boy A's voluntary approach (i.e., toward becoming a communication pitcher), he experienced increased occurrences of being approached by other children. Furthermore, Boy B showed an increase in his two-way communication, regardless of whom he was communicating with. In the video footage of their behavior, both Boy A and Boy B were seen taking part in a face-to-face play with staff members in the first session, engaging in cooperative play, and social play with simple rules with other children in the eighth session. Changes in face-to-face interaction partners and their communication types are believed to reflect their behavioral differences. It has been noted that children's appropriate social approaches within groups increase when they are provided with opportunities to learn SS (7, 22). The current study further supports this previous finding.

Further, the encouragement of participating staff to interact with other children helped them gain necessary social skills. There was also an increase in the participants' peer relationship skills at school. As observed in the BMS, it is presumed that such improvements would also be observed in their school settings.

The observer's issue knowing that intervention occurs during behavioral observations in SS groups for children with ASD has already been highlighted (23). To address this issue, in this study, although behavior observation was performed using a business microscope, the observation would be useful in the sense that the viewpoint of the observer was not included since the use of a sensor device allowed for an objective evaluation. The use of the device is potentially being a more objective measurement which complements the subjective evaluation.

Moreover, the utilization of a sensor device that visualizes interpersonal information in GSSI allows for the easy identification of detailed information such as interactions with multiple people. Thus, immediate feedback of intervention results may facilitate intervention policy modification (13). Nakajima et al. (24) conducted an initiative that involved middle school teachers who conducted physical education classes.

The authors showed them a network diagram, gave feedback on verbal communication, and improved their physical education classes. Similarly, network diagrams for the training of trainers/caregivers of autistic children may lead to appropriate interventions for children with ASD who tend to have difficulty in dealing with people.

However, BMS cannot be used immediately in clinical situations. Although BMS data can be used to evaluate quantifiable changes, such as the amount of body movement or a person with whom one comes into face-to-face contact, it is challenging to evaluate the noted behavior's social suitability. In the future, it will be necessary to enable the objective evaluation of the content of approaches by combining the BMS with other devices that allow for the analysis of the content of the communication. Furthermore, for evidence-based evaluation, it is essential to examine the relationship between face-to-face communication and children's skills enhancement. However, only two cases were considered, and statistical analysis was absent in this study. Therefore, larger sample sizes and data from different types of children with ASD should be considered.

Furthermore, although many SST trainers may feel that the relationship between children in the group improves growth, it has not been examined quantitatively. In the future, quantifying face-to-face interaction by BMS enables us to determine how interactions with others affect social skills learning.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Osaka University Clinical Research Review Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TY: study design, data collection, data analysis, and writing manuscript. HO: data collection and writing manuscript. AT: study design and data collection. IM: data collection and writing manuscript. MT: writing manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* 5th ed. Arlington, VA: American Psychiatric Association (2013).
2. Kasari C, Locke J, Gulsrud A, Rotheram-Fuller E. Social networks and friendships at school: comparing children with and without ASD. *J Autism Dev Disord*. (2011) 41:533–44. doi: 10.1007/s10803-010-1076-x
3. Orsmond GI, Krauss MW, Seltzer MM. Peer Relationships and Social and Recreational Activities Among Adolescents and Adults with Autism. *J Autism Dev Disord*. (2004) 34:245–56. doi: 10.1023/B:JADD.0000029547.96610.df
4. White SW, Keonig K, Scahill L. Social Skills Development in children with autism spectrum disorders: a review of the intervention research. *J Autism Dev Disord*. (2007) 37:1858–68. doi: 10.1007/s10803-006-0320-x
5. Dupper DR, Krishef CH. School-based social-cognitive skills training for middle school students with school behavior problems. *Child Youth Serv Rev*. (1993) 15:131–42. doi: 10.1016/0190-7409(93)90040-G
6. Reichow B, Steiner AM, Volkmar F. Social skills groups for people aged 6 to 21 with autism spectrum disorder(ASD). *Campbell System Rev*. (2013) 8:1–76. doi: 10.4073/csr.2012.16
7. Kylliäinen A, Häkkinen S, Eränen S, Rantanen K, Ebeling H, Bölte S, et al. Social competence group intervention(SOCO) for children with autism spectrum disorders:a pilot study. *Scand J Psychol*. (2020) 61:835–45. doi: 10.1111/sjop.12675
8. Rumney HL, MacMahon K. Do social skills interventions positively influence mood in children and young people with autism? A systematic review. *Mental Health Prev*. (2017) 5:12–20. doi: 10.1016/j.mhp.2016.12.001
9. Hotton M, Coles S. The effectiveness of social skills training groups for individuals with autism spectrum disorder. *J Autism Dev Disord*. (2016) 3:68–81. doi: 10.1007/s40489-015-0066-5
10. Wolstencroft J, Robinson L, Srinivasan R, Kerry E, Mandy W, Skuse DA. Systematic review of group social skills interventions, and meta-analysis of outcomes, for children with high functioning ASD. *J Autism Dev Disord*. (2018) 48:2293–2307. doi: 10.1007/s10803-018-3485-1
11. Krasny L, Williams BJ, Provencal S, Ozonoff SJ. Social skills interventions for the autism spectrum: essential ingredients and a model curriculum. *Child Adolesc Psychiatr Clin N Am*. (2003) 12:107–22. doi: 10.1016/S1056-4993(02)00051-2
12. Cotugno AJ. *Group Interventions for Children With Autism Spectrum* Disorders: *A Focus on Social Competency and Social Skills*. London; Philadelphia, PA: Jessica Kingsley Publishers (2009).
13. Rehg JM, Rozga A, Abowd GD, Goodwin MS. Behavioral imaging and autism. *IEEE Pervasive Computing*. (2014) 13:84–7. doi: 10.1109/MPRV.2014.23
14. Suzuki K. Social Imaging Technology to Identify and Represent Social Behaviors. UbiComp/ISWC'15 Adjunct: Adjunct Proceedings of the 2015 ACM International Joint Conference on Pervasive and Ubiquitous Computing and Proceedings of the 2015 ACM International Symposium on Wearable Computers. (2015). 907–908 doi: 10.1145/2800835.2815379
15. Hachisu T, Pan Y, Matsuda S, Bourreau B, Suzuki K. FaceLooks: a smart headband fir sugnaling face-to-face behavior. *Sensor*. (2018) 18:2066–86. doi: 10.3390/s18072066
16. Gouda N. Business microscope that enable to implement Human BigData in society. *Manufact Technol*. (2015) 67:46–52.
17. Moriwaki N, Watanabe J, Yano K. Measuring communication in Business. *J Institute Electronics Inform Commun Engineers*. (2013) 96:621–5.
18. Yamamoto S, Hanai T. Attempt of visualization of infant relationship with Business Microscope -The case of 5-year-old kindergarten class-. *Japanese J Sports Health Sci*. (2015) 38:25–34.
19. Nakajima T, Ito T, Kawata M. Phases of communication in physical education classes. *J Phys Exercise Sports Sci*. (2018) 23:125–32.
20. Okuno H, Yamamoto T, Tatsumi A, Mohri I, Taniike M. Simultaneous training for children with autism spectrum disorder and their parents with a focus on social skills enhancement. *Int J Environ Res Public Health*. (2016) 13:590–604. doi: 10.3390/ijerph13060590
21. Ueno K, Okada S. *Social Skill Manual*. Tokyo: Meijitosho Shuppan Corporation (2006).
22. Bauminger N. The facilitation of social-emotional understanding and social interaction in high-functioning children with autism: intervention outcomes. *J Autism Dev Disord*. (2002) 32:283–98. doi: 10.1023/A:1016378718278
23. Rao PA, Beidel DC, Murray MJ. Social skills interventions for children with asperger's syndrome or high-functioning autism: a review and recommendations. *J Autism Dev Disord*. (2008) 38:353–61. doi: 10.1007/s10803-007-0402-4
24. Nakajima T, Kawamoto T, Takahashi M. Experiment of class improvement by feedback of verbal communication data to teacher in junior high school physical education –Focusing on students' interactive learning activities in dance classes–. *Hokkaido J Phys Educ Health Sport Sci*. (2019) 54:125–32.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Toward a Gender-Sensitive Approach of Psychiatric Rehabilitation in Autism Spectrum Disorder (ASD): A Systematic Review of Women Needs in the Domains of Romantic Relationships and Reproductive Health

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Later age of diagnosis, better expressive behaviors, increased use of camouflage strategies but also increased psychiatric symptoms, more unmet needs, and a general lower quality of life are characteristics often associated with female gender in autism spectrum disorder (ASD). Psychiatric rehabilitation has shown small to moderate effectiveness in improving patients' outcomes in ASD. Few gender differences have been found in the response to psychiatric rehabilitation. This might be related to the predominance of males in research samples, but also to the lack of programs directly addressing women's unmet needs. The objectives of the present paper were: (i) to review the needs for care of autistic women in romantic relationships and reproductive health; (ii) to review the existing psychosocial treatments in these domains; and (iii) to evaluate the strengths and limitations of the current body of evidence to guide future research. A systematic electronic database search (PubMed and PsycINFO), following PRISMA guidelines, was conducted on autistic women's needs for care relating to psychiatric rehabilitation in romantic relationships and reproductive health. Out of 27 articles, 22 reported on romantic relationships and 16 used a quantitative design. Most studies were cross-sectional ($n = 21$) and conducted in North America or Europe. Eight studies reported on interventions addressing romantic relationships; no published study reported on interventions on reproductive health or parenting. Most interventions did not include gender-sensitive content (i.e., gender variance and gender-related social norms, roles, and expectations). Autistic women and autistic gender-diverse individuals may face unique challenges in the domains of romantic relationships and reproductive health (high levels of stigma, high risk of sexual abuse, increased psychiatric symptoms, and more

unmet needs). We discussed the potential implications for improving women's access to psychiatric and psychosocial treatment, for designing gender-sensitive recovery-oriented interventions, and for future research.

Keywords: autism spectrum disorder, women, gender-diverse, unmet needs, psychiatric rehabilitation

INTRODUCTION

Increasing research interest on potential sex/gender differences in autism spectrum disorder (ASD) has led to the description of a "female phenotype" of ASD characterized by similarities in core ASD symptoms (i.e., lifelong social impairment, communication deficits, and repetitive behavior), better expressive behaviors (e.g., sharing interests or more vivid gestures), increased use of camouflage strategies, later age of diagnosis, but also higher increased depression and anxiety, and a general lower quality of life (1). In the present study, we used the term *sex* to refer to biological characteristics and the term *gender* to refer to sociocultural norms, roles, expressions, and expectations (2). Given the high frequency of gender variance (i.e., gender identity or gender expression that does not conform to masculine or feminine gender norms) (3) in ASD, we used self-reported gender identity (i.e., cisgender women, but also transgender or non-binary women) to define female gender in this study (4).

Psychiatric rehabilitation is a person-centered approach that aims to help people with serious mental illness (SMI) or ASD to "be successful and satisfied in the living, working, learning, and social environments of their choice" (5). Therapeutic tools are selected based on people's strengths, weaknesses, needs for care, and personal life goals as part of a customized recovery-oriented action plan (6, 7). The action plan can include strength-based case management, improvements in physical and mental health, peer support interventions, joint crisis plans, cognitive remediation (CR), cognitive behavior therapy (CBT), social skills training (SST), self-stigma reduction, family support, and supported housing and supported employment (SE) (6, 7). Psychiatric rehabilitation interventions have shown small to moderate effectiveness in improving patients'outcomes in adults with ASD (8–11).

Although no gender differences were found in social participation and the employment rates, women were less likely than men to have long-standing friendships and to maintain post-secondary/employment over time (12–14). To date, three studies have looked for potential gender differences in the response to psychosocial treatment in adults with ASD (15, 16). McVey et al. (15) and Visser et al. (17) found no gender differences in treatment outcomes for SST, whereas Sung et al. (16) reported that men benefited more from vocational rehabilitation.

The predominance of males in research samples may induce gender-related biases affecting the development of psychosocial interventions (18). Two recent systematic reviews have reported a large predominance of males in studies on cognitive remediation or social skills training [up to 100% in some studies (8, 19)]. Similar proportions have been reported in studies targeting social skills in dating contexts (20, 21). Autistic women report more unmet needs with respect to their mental health concerns and vocational services (21, 22) and report a higher risk of sexual abuse (×2.2) (23, 24). Gender variance has been associated with higher depression and reduced well-being in autistic women (25). It could be associated with the higher risk of sexual abuse (25). Reproductive and parenting issues, which may be more salient in women with ASD than in men, remain underinvestigated (26, 27).

The objectives of the present paper were: (i) to review the needs for care of autistic women in romantic relationships and reproductive health; (ii) to review the existing psychosocial treatments in these domains; and (iii) to evaluate the strengths and limitations of the current body of evidence to guide future research.

MATERIALS AND METHODS

A stepwise systematic literature review (PRISMA guidelines) (28) was conducted by searching PubMed, MEDLINE, and PsycINFO for published peer-reviewed papers using the following keywords: "sexu*" OR "romantic relationship" OR "intimate relationship" OR "parent*" OR "reproductive health" OR "mother*" OR "pregn*" AND "women" OR "gender diverse" OR "transgender" OR "non-binary" AND "autism" NOT "valproate" NOT "22q11." No time restriction was set. Only published papers in English or French were included in the review. The reference list of seven literature reviews on sexuality and autism were screened for additional relevant articles. To be included in this review, the articles had to meet all of the following criteria: (a) have a main focus on women's outcomes; (b) concern a diagnosis of autism spectrum disorder; (c) report on romantic relationships or parenting; and (d) use a quantitative, qualitative, or mixed-methods design. The first author applied the eligibility criteria and screened the records to select the included studies. The last author reviewed each decision. Disputed items were solved through discussion and by reading the paper in detail to reach a final decision. For each study, we extracted the following information: general information (author, year of publication, country, design, population considered, setting, total number of participants, and mean age or age range), outcome measure (scale), the main findings, and the variables relating to quality assessment. Quality assessment was performed using the Mixed Methods Appraisal Tool (MMAT) (29). This tool comprises five sets of criteria for: (a) qualitative, (b) randomized controlled trials, (c) non-randomized trials, (d) descriptive studies, and (e) mixed-methods studies. For the mixed-methods studies, raters assess the qualitative set, the quantitative set, and the mixed-methods set. An overall quality score (low, moderate, high, or very high)

was determined based on adequacy in the corresponding set of criteria.

RESULTS

Our search on January 13, 2021 found 672 articles on PubMed and 187 on PsycINFO. After manually removing all duplicates, there were 450 remaining references. Based on their titles and abstracts, 404 papers were excluded for lack of relevance. Most of these articles focused on other populations (e.g., parents of children or adolescents with autism, healthcare professionals, other neurodevelopmental conditions, and autistic traits in the general public) or other topics (e.g., biological sex differences, physical health, and vocational function). Our search strategy yielded 46 full-text articles. After conducting a full-text analysis of all these papers and excluding those that did not meet the inclusion criteria, we ended up with 27 relevant papers (**Figure 1**).

The 27 papers included were characterized by the heterogeneity of their samples, methods, and reported outcomes. Most papers reported on romantic relationships ($n = 22$, 81.4%) and used a quantitative design ($n = 16$, 59.3%). Ten studies were qualitative and one was mixed methods. Most studies used cross-sectional designs ($n = 21$, 77.8%). Six studies reported on interventions (22.2%). Two studies were a randomized controlled trials (RCTs) and four studies used quasi-experimental or non-controlled designs. Eleven studies were conducted in North America (40.8%), nine in Europe (33.3%), and seven in Australia (25.9%). Most studies included adult participants ($n = 22$, 81.5%). One study included only adolescents (3.7%) and two studies had mixed samples (7.4%). Three studies (11.1%) included both parents and ASD participants. Of the studies using a quantitative or a mixed-methods design, most reported on sexuality-related outcomes (e.g., sexual desire, sexual awareness, sexual well-being, and sexual assertiveness; $n = 10$, 62.5%). One study reported on social skills in the context of dating (21) and one on general social skills (30). Two quantitative studies used self-reported assessments for parenting-related outcomes (27, 31). The quality ratings of the included studies obtained using MMAT ranged from low to moderate. The results are shown in **Table 1**.

Romantic/Intimate Relationships

Loneliness, negative self-perceptions, self-stigma, sensory sensitivity, and impaired social communication related to dating situations have been identified as barriers to romantic relationships in ASD (33). Women with ASD may face unique challenges in their adolescence and during the transition to adulthood, such as decrypting dating situations (e.g., judging subtle social cues in dating situations such as flirting, aggression, or coercion) and adopting assertive behaviors in intimate relationships (34). Compared with non-autistic women, autistic women have less sexual interest, but had more experiences and received more unwanted sexual advances (24, 35, 36). They report lower sexual well-being and have an increased risk of sexual abuse (24, 34, 37). Engagement in sexual behaviors to reduce social exclusion and alcohol use to reduce social anxiety could increase the risk of victimization in women with ASD (24, 32, 34).

This risk might be higher for non-binary or transgender autistic women who may also face unique challenges in romantic relationships (e.g., relating to the intersection of ASD and the gender identity stigma) (25, 33, 38). Bargiela et al. (34) and Kanfiszer et al. (32) reported that, after being diagnosed with ASD, autistic women needed to reframe past negative experiences and to discuss gender-related social roles and expectations. Compared with typically developing women and autistic men, autistic women expressed less desire to live with a partner (32, 39, 40). Those living with a typically developing partner reported social and communications challenges, but also to have resources to deal with them (41). Marital satisfaction was higher for autistic women living with an autistic partner (40). Support from healthcare and social professionals was often described as inadequate (41). **Table 2** presents the characteristics of the included studies on romantic relationships.

Four interventions addressed romantic relationships in women with ASD. One was a general SST program including social skills in dating (Program for the Education and Enrichment of Relationship Skills, PEERS) (15) and the other a social skills in dating program (Ready for Love) (21). Two programs were psychosexual trainings for autistic adolescents [socio-sexual training (43) and Tackling Teenage (17)]. Participants in these interventions were mostly male (>75%) (15, 17, 21). McVey et al. (15) and Visser et al. (17) reported no gender differences in treatment effects for PEERS and Tackling Teenage. One SST intervention was designed for autistic female adolescents (the Girls Night Out model) (30), but did not address dating or romantic relationships. Two qualitative studies assessed stakeholders' needs to design new interventions (38, 44). Common factors to these interventions were the emphasis put on: (i) group-based interventions to receive support from other participants; (ii) peer support; (iii) discussions about gender variance and gender-related social roles and expectations; iv) improving social cognition and social skills; and v) interventions supporting the relatives (38, 43, 44). Descriptions of the interventions are shown on **Table 3**.

Reproductive Health/Parenting

To date, a few qualitative studies and two quantitative studies have investigated the experiences of motherhood in ASD. Kanfiszer et al. (32) reported that some autistic women identified motherhood as a potential trigger of stress more than a rewarding experience and reported to have "no maternal instinct." In a sample comparing the experiences of 355 mothers with ASD with those of 132 non-autistic mothers, Pohl et al. (27) have found that autistic mothers had an increased frequency of perinatal depression. Although most autistic mothers described parenting as a rewarding experience, they were more prone than non-autistic mothers to find it also challenging and isolating (27). Autistic mothers were more likely to report parenting difficulties (e.g., with household responsibilities or with the multitasking demands of parenting) and to be dissatisfied with service provision during perinatal care (e.g., feeling judged in their parenting

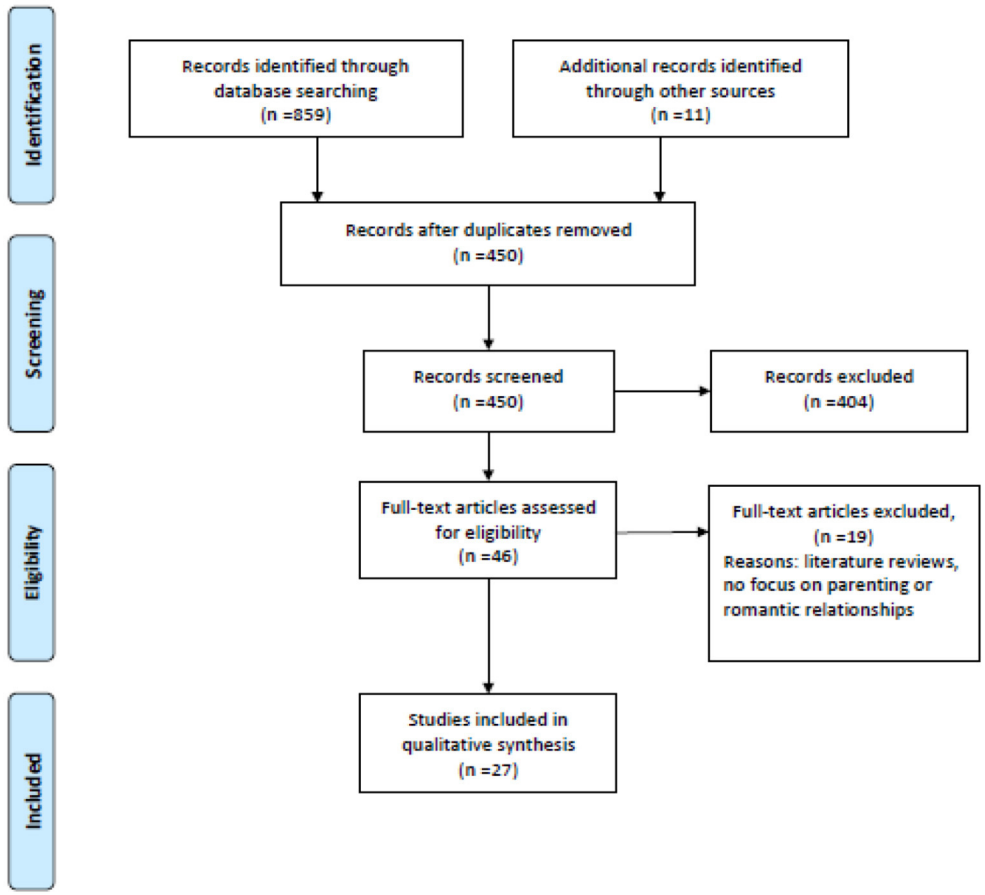

FIGURE 1 | Review process (PRISMA flow diagram).

abilities) (27, 46, 47). They described stressful and negative experiences in communicating with healthcare professionals and social workers about their child (27, 46, 47). Some women reported to have concealed their diagnosis to providers to avoid stigmatizing behaviors and child protective services implications (46, 47). Other factors associated with negative experiences in perinatal care included uncertain and stressful environment and sensory sensitivity (46–48). Sundelin et al. (31) have reported that, compared to children of non-autistic mothers, those of autistic mothers had poorer obstetrical and neonatal outcomes (e.g., pre-term birth, preeclampsia, and cesarean delivery). **Table 4** shows the characteristics of the included studies on parenting.

According to Pohl et al. (27), autistic mothers were dissatisfied of the support they received during perinatal care and felt that they should be offered extra support because of their autism. Gardner et al. (46), Rogers et al. (47), and Pohl et al. (27) reported a need for clear and accurate information about normal pregnancy, potential complications, delivery, and post-partum care. To our knowledge, no published studies described interventions to improve reproductive health outcomes and to support parenting in autistic mothers. In the FondaMental Advanced Center of Expertise for ASD (FACE-ASD) of Grenoble, consultation with a trained midwife has been added to the diagnosis and functional assessment. The objectives were: (i) to assess the desire to become a parent; (ii) to answer questions relating to ASD, pregnancy, and perinatal health outcomes (e.g., concerns about passing on ASD to their child, information about the stay in the maternity ward, cesarean section, circadian rhythms, and lactation); (iii) to propose strengths-based case management and a shared recovery-oriented action plan to improve well-being and pregnancy-related outcomes; (iv) to provide individual and/or family psychoeducation; and (v) to improve the communication with perinatal health professionals and social workers. Actions addressing mothers and their partners' needs or aiming to improve knowledge of perinatal health professionals about ASD and to reduce ASD-related stigma could be provided during the perinatal period (i.e., from preconception to 1 year after childbirth). A group-based program on reproductive health and parenting issues for women with ASD and their partners was also developed. It includes three 2-h sessions during which participants and facilitators discuss issues related to reproductive health and parenting (e.g., concerns about heredity or communication with healthcare professionals). A detailed description of these actions is presented in **Table 5**.

TABLE 1 | Research characteristics of the 27 studies included in the review.

	Studies about reproductive health/parenting (*N* = 6)	Studies about romantic relationships and sexuality (*N* = 22)	Total (*N* = 27[a])
Type of study			
Quantitative study	2 (33.3%)	14 (63.6%)	16 (59.3%)
Qualitative study/case study	4 (66.7%)	7 (31.8%)	10 (37.0%)
Mixed method	0 (0%)	1 (4.6%)	1 (3.7%)
Design			
Cross-sectional	6 (100%)	16 (72.7%)	21 (77.8%)
Longitudinal	0 (0%)	6 (27.3%)	6 (22.2%)
Interventions	0 (0%)	6 (27.3%)	6 (22.2%)
RCT	0 (0%)	2 (9.0%)	2 (7.4%)
Quasi-experimental	0 (0%)	1 (4.6%)	1 (3.7%)
Uncontrolled	0 (0%)	3 (13.6%)	3 (11.1%)
Geographical area			
North America	2 (33.3%)	9 (40.9%)	11 (40.8%)
Europa	3 (50%)	7 (31.8%)	9 (33.3%)
Australia	1 (16.7%)	6 (27.3%)	7 (25.9%)
Proportion of women			
100%	6 (100%)	6 (27.3%)	11 (40.8%)
>50%	0 (0%)	6 (27.3%)	6 (22.2%)
<50%	0 (0%)	7 (31.8%)	7 (25.9%)
NR	0 (0%)	3 (13.6%)	3 (11.1%)
Age of participants			
<18	0 (0%)	1 (4.6%)	1 (3.7%)
>18	5 (83.3%)	18 (81.8%)	22 (81.5%)
Studies included people less 18	0 (0%)	2 (9.0%)	2 (7.4%)
NR	1 (16.7%)	1 (4.6%)	2 (7.4%)
Quality of the studies			
*	3 (50%)	3 (13.6%)	6 (22.2%)
**	2 (33.3%)	11 (50%)	12 (44.5%)
***	1 (16.7%)	8 (36.4%)	9 (33.3%)
****	0 (0%)	0 (0%)	0 (0%)

[a] *The total is not equal to the sum of the numbers in each category because one article (32) was included in both categories (romantic relationships/reproductive health). *means low quality, **means moderate quality, ***means high quality, ****means very high quality.*

DISCUSSION

Main Findings

Altogether, the results of this systematic review may be summarized as follows: (i) women report several unmet needs in the domains of romantic relationships and reproductive health; (ii) psychosocial treatment addressing skills related to romantic relationships remains underdeveloped and is often inadequate to women's needs for care; (iii) research on reproductive health and parenting in autistic mothers is almost inexistent, and there is a lack of interventions supporting future mothers or mothers with ASD; and (iv) stigma reduction could improve women's outcomes in romantic relationships and reproductive health.

Interpretation of the Results

Access to Adequate Healthcare

While there are few gender differences in the pattern of service utilization, women report more unmet needs and more negative experiences with healthcare providers and social workers (22, 27). Compared with autistic men and typically developing women, women with ASD report more often comorbid physical health conditions (e.g., polycystic ovary syndrome, 7.8 *vs.* 3.5% in the general population) (49) and less utilization of women's health services (OR = 0.59, 95% CI = 0.48–0.72) (50). The barriers to accessing adequate healthcare include providers' lack of knowledge and dedicated training regarding autistic women' needs for care and the lack of specific services for adults with ASD (22, 49, 50). Although it has been proposed that autistic women's lower access to women's health services could be explained by less frequent sexual experiences (50), several studies have reported the opposite (23, 24, 34). A higher motivation to engage in social relationships, a higher desire to fit in social contexts and to meet gender-related social expectations, preference for opposite-sex friendships, and increased use of camouflage strategies are characteristics often associated with female gender (32, 34, 51, 52).

TABLE 2 | Included studies reporting on romantic relationships/sexuality in autistic women.

References	Country	Design	Intervention	Sample participant details Sample size description Diagnostic criteria	Scale	Outcomes/findings	Quality
Quantitative studies							
Bejerot and Eriksson (35)	Sweden	Cross-sectional	No	ASD group: 50 adults with intelligence within the normal range (26 males and 24 females) Control group: 53 typically developing controls (28 males and 25 females) Age: 20–47	- Swedish modification of the Bem Sex Role Inventory - Questions on sexuality and gender designed for the purpose of the study	- Higher gender variance and proportion of people reporting to have no experience of romantic relationships in the ASD group - Lower libido in the ASD group	**
Busch (36)	USA	Cross-sectional	No	*N* = 248 women with ASD (professional diagnosis or self-identified) *N* = 179 women without ASD Mean age: ASD group: 23.2 (18–30) Control group: 21.8 (18–30)	- Sexual History Questionnaire (SHQ) - Sexual Desire Inventory (SDI) - Sexual Experience Questionnaire (SEQ) (adapted 19-item version) - Sexual Satisfaction Scale for Women (SSSW) - Sexual Awareness Questionnaire (SAQ)	- Participants with ASD reported less sexual desire, fewer sexual behaviors, and less sexual awareness than those without ASD - Comparable sexual satisfaction in the ASD and control group	***
Byers et al. (37)	Canada and USA	Cross-sectional	No	*N* = 141 (56 men and 85 women) with HFA/AS (professional diagnosis) 60% in romantic relationship Mean age 39.6 (21–73)	- Global Measure of Sexual Satisfaction (GMSEX) - Self-Esteem Subscale of the Sexuality Scale - Hurlbert Index of Sexual Assertiveness - Sexual Arousability and Sexual Anxiety Inventory - Sexual Desire Inventory - Sexual Activity Questionnaire - Sexual Functioning Questionnaire - Sexual Knowledge Questionnaire. - Sexual Cognitions Checklist (SCC)	Less ASD symptoms are associated with greater sexual well-being for autistic men	**
Corona et al. (42)	USA	Uncontrolled	Yes. Six-2h sessions over the course of 3 months.	*N* = 8 adolescent with ASD (2 females and 6 males) +one parent for each adolescent (six mothers, two fathers) Mean age of adolescents: 13.4 (12–16)	- Sexual Behavior Scale (SBS) - Adolescent Knowledge Questionnaire - Parent Questionnaire - Parent Satisfaction Questionnaire	- Higher number of sexuality-related topics discussed between parents and adolescents at post-treatment - No difference in the comfort felt when discussing these topics at post-treatment	*
Cunningham et al. (21)	USA	Quasi-experimental	Relationship Enhancement (RE) "Ready for Love"	RE-ASD group *N* = 19 (16 males and 3 females) RE group *N* = 19 (14 males and 5 females) Age>18 (76.3% between 18 and 29)	- Dating and Assertion Questionnaire (DAQ) - EQ - SRS	- Improved parent-report social responsiveness in both groups - No significant difference in treatment effectiveness between the two groups	**

(Continued)

TABLE 2 | Continued

References	Country	Design	Intervention	Sample participant details Sample size description Diagnostic criteria	Scale	Outcomes/findings	Quality
Georges and Stokes (25)	Australia	Cross-sectional		ASD group: *N* = 309 (219 females and 90 males) Control group: *N* = 261 (158 females and 103 males) Mean age ASD group: 31.01 Control group: 30.20	- Sell Scale of Sexual Orientation - Gender - Identity/ Gender - Dysphoria - Questionnaire for Adolescents and Adults (GIDYQ-AA) - Depression, Anxiety, and Stress Scale-21 (DASS-21) - Personal Well-being Index scale	- Higher psychiatric comorbidities and reduced well-being in autistic individuals compared to typically developing controls - Higher psychiatric comorbidities and reduced well-being in gender variant autistic individuals compared to other autistic participants	***
Hénault (43)	Canada	Uncontrolled	Psychosexual program	NR	- Australian Scale for Asperger's Syndrome - Aberrant Behavior Checkist - Friendship Skills Observation Checklist - Inventaire du fonctionnement sexuel de Derogatis	Improvement in skills related to friendships and intimacy	*
Jamison et Schuttler (30)	USA	Uncontrolled	The Girls Night Out Model	*N* = 33 adolescents females (28 with ASD, 2 with learning disability, 3 with learning disability and significant social impairment) *N* = 22 parents Mean age: 15.97 (14–19)	- Social Skill Improvement System (SSIS) - Self Perception Profile for Adolescents (SPPA) - Youth Quality of Life-Research Version (YQoL-R) - satisfaction data from parents, participants, and peers.	- Improvements in self-reported social competence, self-reported internalizing symptoms and quality of life - No significant improvements following intervention on the parent-report social competence scale	**
McVey (15)	USA	Randomized controlled trial	PEERS (sixteen 1.5h-session)	*N* = 177 HFA (27 females and 150 males) Experimental group: *N* = 88 Control group: *N* = 89 Age > 18	- SRS parent - SSIS-RS (variant of SSRS) - Empathy quotient - LSAS (social anxiety) - TYASSK: social knowledge - SELSA loneliness scale	No gender differences in treatment effectiveness	***
Pecora et al. (24)	Australia	Cross-sectional	No	ASD group: *N* = 231 (135 females and 96 males) (self-reported formal diagnosis of HFA or AS) Control group: *N* = 227 (161 females and 66 males) Mean age: ASD group: 25.13 Control group: 22.16	Sexual Behavior Scale: Version 3 (SBS-III)	- Less sexual interest but more sexual experiences in autistic women compared to non-autistic women - More autistic women reported engaging in sexual behaviors that were later regretted, unwanted, or receiving unwanted sexual advances	***
Pecora et al. (45)	Australia	Cross-sectional	No	ASD group: *N* = 134 autistic females Control group: *N* = 161 females Mean age: ASD group: 26.2 (18–56) Control group: 22.0 (18–48)	Sexual Behavior Scale-III (SBS-III)	- Higher gender variance and non-heterosexual orientation in autistic women - More negative sexual experiences in autistic homosexual women compared to heterosexual autistic women - More unwanted sexual experiences in autistic homosexual women compared to non-autistic women	***

(Continued)

TABLE 2 | Continued

References	Country	Design	Intervention	Sample participant details Sample size description Diagnostic criteria	Scale	Outcomes/findings	Quality
Strunz et al. (40)	Germany	Cross-sectional	No	*N* = 229 high-functioning adults with ASD (professional diagnosis) (137 females and 92 males) Three groups: Currently in relationship, History of relationship Never been in relationship Mean age: 34.9 (18, 20–41, 43, 46–62)	- Need for Social Support subscale of the Berlin Social Support Scales - Personal Distress subscale of the Interpersonal Reactivity Index (IRI) - Dyadic Adjustment Scale (DAS) - Original questionnaire items that assessed the desire for romantic relationships and the reasons for not being in a romantic relationship	- 73% indicated romantic relationship experience and only 7% had no desire to be in a romantic relationship. - Higher marital satisfaction in people whose partner was also on the ASD spectrum - Reasons for being single: tiredness (65%), fear of not meeting the partner's expectations (61%) and not knowing how to meet someone (57%)	**
Turner et al. (63)	Germany	Cross-sectional	No	ASD group: *N* = 96 (40 females and 56 males) (professional diagnosis) Control group: *N* = 96 (39 females and 57 males) Mean age: ASD group: 39.2 Control group: 37.9	- International Index of Erectile Function (IIEF) - Female Sexual Function Index (FSFI) - Sexual Inhibition/Sexual Excitation Scales-Short Form (SIS/SES-SF)	- Higher sexual dysfunctions and reduced libido and less sexual satisfaction in autistic women compared to non-autistic women - No difference in sexual satisfaction between autistic men and autistic women	***
Visser et al. (17)	Netherlands	Longitudinal randomized controlled trial	Yes (Tackling Teenage psychosexual training program) 18 weekly individual sessions	Intervention group: *N* = 95 (73 males and 25 females) Waiting-list control condition: *N* = 94 (79 males and 15 females) Full IQ ≥ 85 Mean age: Intervention group: 14.4 (12.1–18.8) Control condition: 14.5 (12.0–18.5)	- Sex Problems scale of the Child Behavior Checklist (CBCL) - Self-report and a parent-reported scale measuring specific ASD-related inappropriate sexual behavior	- Improvements in psychosexual knowledge at post-treatment - Higher treatment effects for younger adolescents - No gender differences in treatment effectiveness	***
Qualitative studies							
Bargiela et al. (34)	UK	Qualitative	No	*N* = 14 women with ASD (formal diagnosis) IQ>70 Age: 26.7 (22–30)	NA	- Four main themes including "passive to assertive" et "forging an identity as a woman with ASD" - High incidence of sexual abuse (9 of 14 participants) - Difficulties to "read" other people's intentions, and struggle to understand if a man was just being friendly or was sexually attracted to them. - Experiences of peer rejection resulted in higher desire for social acceptance and thus increased risk of sexual abuse - Some reported not having known that they could say "no" when they had wanted to refuse sex or other people's advances. Others reported that they had not known how to say "no" or how to leave a situation until it was too late	

(Continued)

TABLE 2 | Continued

References	Country	Design	Intervention	Sample participant details Sample size description Diagnostic criteria	Scale	Outcomes/findings	Quality
						- Women do not readily identify to gender-related stereotypes and report a sense of loss of identity when trying to meet gender-related social expectations	**
Barnett et al. (64)	USA	Qualitative	No	*N* = 24 adults with ASD (13 with a feminine identity, 6 with a masculine identity and 5 gender queer or androgynous) (self-identifies as ASD) Mean age: 37 (18–61)	/	- High frequency of gender variance and non-heterosexual orientation - Concerns: courtship difficulties, sensory sensitivity, difficulties in understanding non-verbal communication, difficulties in showing romantic interest, inappropriate sex education experiences - Strategies: using sensory barriers; planning when and how to have sex; negotiating alternatives to sexual scripts predicated on non-disabled experience; and practicing explicit and intentional communication.	*
Dubreucq et al. (44)	France	Qualitative	Yes	*N* = 7 women with ASD (professional diagnosis) Mean age: 37.7 (25–52)	/	- Autistic women reported not to readily identify with gendered social norms, roles and expectations - Autistic women reported the need to forge an integrated identity as women with ASD - Challenges in romantic relationships/sexuality: fear to attract unwanted sexual attention (e.g., sending involuntarily non-verbal cues of seduction during social interactions); decoding dating contexts in general and when personally involved; knowing what is acceptable or not in romantic relationships; learning how to cope with dating situations/unwanted sexual attention; prevention of sexual abuse	**
Kanfiszer et al. (32)	UK	Multi-stage narrative analysis	No	*N* = 7 women with ASD (professional diagnosis) Age: 20–59	/	- Autistic women do not readily identify to gender-related social norms, roles and expectations - High frequency of sexual abuse (difficulty to know how to say no to an unwanted relation)	**

(Continued)

TABLE 2 | Continued

References	Country	Design	Intervention	Sample participant details Sample size description Diagnostic criteria	Scale	Outcomes/findings	Quality
Sala et al. (33)	Australia	Qualitative	No	ASD group: *N* = 31 (14 females, 10 males and 7 "non-binary") Control group: *N* = 26 (20 females, 5 males and 1 "non-binary") Mean age: ASD group: 32.29 (19–54) Control group: 33.1 (20–57)	/	- Most of the enablers/barriers of intimacy were common to both groups - ASD-specific barriers included anticipated stigma, self-stigma, uncertainty about relationships and communication.	***
Smith et al. (41)	Australia	Qualitative	No	*N* = 13 persons in neurodiverse relationship Age: 25–>65	/	- Challenges in neurodiverse relationships: communication, difficulties in reading and interpreting emotions - Facilitators: strengths-based roles of each partner; care and support for each other - Inadequacy of the existing counseling service provision	**
Strang et al. (38)	USA	Qualitative	Yes	Autistic/neurodiverse gender-diverse (A/ND-GD) youth with gender dysphoria and ASD or social communication disorder (*N* = 31) Mean age: 15.92 (12–19) Parents of A/ND-GD youth (30 mothers and 16 fathers) (N = 46)	/	- Priorities for adolescents: importance of connecting with other gender diverse youth; experiencing a range of gender-diverse role models to make gender exploration and/or gender affirmation more concrete - Priority for parents: the need for ASD- related supports for their children (e.g., social skills training) as well as provision of an ASD-friendly environment that fosters exploration of a range of gender expressions/options.	***
Mixed method							
Baldwin and Costley (39)	Australia	Cross-sectional Mixed-methods	No	*N* = 282 (82 females and 200 males) with HFA (Professional diagnosis) IQ>70 Mean age: Women group: 32.7 (18–64) Men group: 33.2 (18–70)	- 28 items divided across six main sections, namely, (1) health and well-being, (2) education, (3) employment, (4) social and community activities, (5) support needs and (6) future aspirations.	- 56% of those not already in a relationship included "dating and relationships" as one of the areas in which they would like more support. - 19% of these people listed marriage or a relationship as one of their top three hopes and aspirations for the future. - Females were significantly less likely (19%) than males (40%) to list marriage or a romantic relationship as one of their top three hopes and aspirations for the future	**

*AS, Asperger syndrome; ASD, autism syndrome disorder; HFA, high-functioning autism; IQ, intellectual quotient; NA, not applicable; NR, not reported. *means low quality, **means moderate quality, ***means high quality, ****means very high quality.*

TABLE 3 | Interventions targeting romantic relationships/sexuality.

Name of the intervention	Type of intervention	Public	Topics	Main results
PEERS® for Young Adults (Program for the Education and Enrichment of Relational Skill) (15)	16 –session Group-based Social Skills Training	Adults with ASD (>18 years old)	1. Trading Information and Starting Conversations 2. Trading Information and Maintaining Conversations 3. Finding a Source of Friends 4. Electronic Communication 5. Appropriate Use of Humor 6. Entering Group Conversations 7. Exiting Conversations 8. Get-Togethers 9. Dating Etiquette I: Letting Someone Know You Like Them 10. Dating Etiquette II: Asking Someone on a Date 11. Dating Etiquette III: Going on Dates 12. Dating Etiquette IV: Dating Do's and Don't 13. Handling Disagreements 14. Handling Direct Bullying 15. Handling Indirect Bullying 16. Moving Forward and Graduation	No gender differences in treatment effectiveness
"Ready for Love" (Relationship Enhancement/RE-ASD) (21)	Eight 2-h weekly group sessions Dating social skills program	Adults with ASD (>18 years old)	How to flirt, assessing if someone likes you, and asking someone out on a date	- Improved parent-report social responsiveness in both groups - No significant difference in treatment effectiveness between the two groups
Girls Night Out Model (30)	12–16 2-h weekly group SST sessions	Adolescents females with ASD and peers without ASD	- No session on dating social skills - Content related to social interaction, self-care skills, self-determination and leisure activities	Improvements in self-reported social competence, self-reported internalizing symptoms and quality of life No significant improvements following intervention on the parent-report social competence scale
Tackling Teenage psychosexual training program (17)	18 weekly individual sessions Psychosexual trainings for autistic adolescents	Adolescents with ASD and their parents	Discussing puberty, appearances, first impressions, physical and emotional developments in adolescence, friendships, falling in love and dating, sexuality and sex (e.g., sexual orientation, masturbation, and intercourse), pregnancy, setting and respecting boundaries and safe internet use	Improvements in psychosexual knowledge at post-treatment Higher treatment effects for younger adolescents No gender differences in treatment effectiveness
Asperger's syndrome and sexuality (43)	12 weekly group-sessions Psychosexual trainings for autistic adolescents	Adolescents or adults with high-functioning autism	Love and friendship Sexual intercourse and other behaviors Emotions Sexual diseases and prevention Sexual orientation Alcohol, drugs and sexuality Sexual abuse and inappropriate behaviors Theory of mind, communication and intimacy	Improvement in skills related to friendships and intimacy
Program about sexuality and relationships (42)	Six 2-h weekly group sessions	Adolescents with ASD and their parents	Discussing puberty, intimacy, hygiene, relationships, dating, sexuality and sex (e.g., sexual orientation, masturbation, and intercourse), preventing abuse	Higher number of sexuality-related topics discussed between parents and adolescents at post-treatment No difference in the comfort felt when discussing these topics at post-treatment
Strang et al. (38)	Qualitative study assessing parent and adolescents' needs to design new interventions	Gender diverse autistic adolescents	Need for group-based sessions: - How to deal with issues specific to gender diverse adolescents - Support gender expression/style - Provide gender-diverse role models and gender exploration opportunities - Provide opportunities for group members to chat during the group - Improve executive function and social skills - Learn how to notice and avoid risky situations Need for group-based sessions for relatives too	/

(Continued)

TABLE 3 | Continued

Name of the intervention	Type of intervention	Public	Topics	Main results
Dubreucq et al. (44)	Qualitative study assessing autistic women' needs to design new interventions Eight 2-h weekly group sessions	Adults women with ASD	Need to discuss gender-related social norms, roles, expectations and pressures Need to discuss gender variance and to forge an integrated identity as a woman with ASD Need to learn about: non-verbal cues of seduction/disinterest, how to avoid unwanted attention, decoding dating contexts and reading the other's intentions, what is acceptable or not in a relationship; taking stock on one's strengths and limitations; how to deal with dating contexts; how to deal with unwanted attention/risky situations	/

Camouflaging, Stigma, and Personal Identity: Implications for Psychiatric Rehabilitation

Qualitative research reported that women found social relationships challenging and felt exhaustion or identity loss feelings when using camouflage strategies (32, 34, 51). Camouflaging refers to the use of conscious or unconscious strategies to minimize or mask autistic characteristics during a social interaction (1). Reasons for camouflaging include the desire to fit in a non-autistic world, anticipated stigma, concerns about the impression made when not camouflaging, and self-stigma (53). Cooper et al. (3) have reported that autistic women identified less with their gender group and had lower in-group value (i.e., one's perception of his own group) compared to autistic men and typically developing women. Hull et al. (1) have found an increased use of camouflage strategies in non-binary autistic individuals and women compared to autistic men. The negative effects of camouflaging strategies on psychiatric symptoms (i.e., higher psychological distress, anxiety, and depression) (53) might be more pronounced in this population (1).

SST is a group-based intervention that encompasses a set of behavioral strategies for teaching new skills based on social learning theory (54). Compensation strategies refer to the use of alternative cognitive routes to compensate for ASD-related social-cognitive difficulties (e.g., impairments in theory of mind) (55). They have been associated with higher verbal abilities, preserved executive function, and improved social skills, but also poorer mental health (56, 57). Although it has been proposed that compensation could be an adaptive coping strategy contributing to SST effectiveness on social skills, it may partially overlap with camouflaging (1, 56). SST could increase the use of camouflage strategies and indirectly contribute to increased psychological distress and suicidal ideation (1, 4, 58). To our knowledge, existing SST interventions do not address the distinction between compensation and camouflaging and their respective consequences on treatment outcomes and mental health. Future programs should address this distinction to improve compensation while reducing camouflaging (56, 57). SST also carries the risk of reinforcing common gender stereotypes about how a person should act in a given sociocultural context (4, 59). The inclusion of gender-sensitive content (e.g., discussing gender variance and gender-related social roles, norms, and expectations) in SST programs could prevent the internalization of gender social norms and improve treatment effectiveness in autistic women and gender-diverse individuals (4, 38).

Camouflaging has been related to secrecy coping and could be used to avoid the stigma of being labeled with ASD (60). Experienced stigma, anticipated stigma, and self-stigma were identified as barriers to intimacy in ASD (33). This concurs with findings in serious mental illness where self-stigma has been associated with reduced capacity for intimacy and more negative parenting experiences (61). Self-stigma has been found to affect one in five people with ASD (7, 62). It has been associated with poorer recovery-related outcomes (i.e., reduced self-esteem and well-being and higher depression and suicide risk) (7). Gender-diverse autistic individuals are confronted with multiple sources of stigma (e.g., intersection of ASD and gender identity stigma) and may be at particular risk of self-stigma (33). Future research should further investigate perceived stigma, experienced stigma, anticipated stigma, and self-stigma in gender-diverse autistic individuals. Self-stigma reduction [e.g., narrative enhancement and cognitive therapy (65) or peer-delivered interventions (61)] might improve the clinical and functional outcomes in autistic women, although this remains to be investigated. A longitudinal examination is needed to investigate the potential relationships between camouflage strategies, stigma-related issues, capacity for intimacy, and parenting experiences.

Cage and Troxell-Whitman (53) have found that autistic women were more likely than men to endorse "conventional reasons" for camouflaging (e.g., fitting in university or work contexts). Nagib and Wilton (66) have reported that gender-related assumptions about stereotypical jobs to which they should aspire limited autistic women in their vocational insertions. This might contribute to the lower satisfaction and benefits from vocational support services in autistic women compared with men (16, 22). Future research should investigate whether the integration of gender-sensitive content (i.e., taking into account gender variance and discussing gender-related sociocultural norms, roles, and expectations) in psychiatric rehabilitation (e.g., in cognitive behavior therapy) and vocational support services improves treatment outcomes or not.

TABLE 4 | Included studies reporting on reproductive health/parenting in women with autism.

Quantitative studies

References	Country	Design	Intervention	Samples	Scale	Outcomes/findings	Quality
Pohl et al. (27)	UK	Cross-sectional	No	ASD group: *N* = 355 autistic mothers (professional diagnosis and self-identified as autistic) Control group: *N* = 132 non-autistic mothers	/	Compared to non-autistic mothers, autistic mothers reported: higher frequency of perinatal depression, higher parenting difficulties (e.g., multi-tasking or household responsibilities), more stressful interactions with professionals, more feelings of being misunderstood by professionals, more worries about others judging their parenting and less support in parenting. Motherhood was described more frequently as an isolating experience and less often as a rewarding experience	**
				Mean age: ASD group: 42.7 Control group: 44.6		Most of autistic mothers reported however mothering as a rewarding experience	
Sundelin et al. (31)	Sweden	Nationwide population-based cohort study	No	ASD group: *N* = 2,198 births to 1,382 women with autism Control group: *N* = 877,742 births to 503,846 women never diagnosed with autism		Women with autism were at increased risk of preterm birth. Maternal autism was also associated with an increased risk of elective cesarean delivery and preeclampsia	***
Donovan (48)	USA	Qualitative	No	*N* = 24 women with ASD Age: NR	/	Three main themes: Having Difficulty Communicating, Feeling Stressed in an Uncertain Environment, and Being an Autistic Mother Challenges: difficulty to communicate with professionals, feelings of being misunderstood (e.g., pain when facial expression was not in adequacy with their internal feelings), fear of child protective services involvement; need for more time before answering and for explicit communication	*
Gardner et al. (46)	USA	Qualitative	No	*N* = 8 women with ASD Mean age: 39 (27–52)	/	Four major themes: Processing Sensations, Needing to Have Control, Walking in the Dark, and Motherhood on My Own Terms - Pre-natal needs: taking into account sensory sensitivity; need for direct answers and clear information - Delivery: sensory sensitivity and need for having control on the situation - Post-natal period: feelings of being judged in their parenting by professionals	*
Kanfiszer et al. (32)	UK	Qualitative	No	*N* = 7 women with ASD (professional diagnosis) Age: 20–59	/	Motherhood perceived as a "daunting" and stressful experience; diagnosis helpful in reframing past experiences for those who chose not to have children; the "daunting" nature of motherhood is a barrier to start a family.	**
Rogers et al. (47)	Australia	Case study	No	*N* = 1 woman with ASD (professional diagnosis) Age: 26 years-old	/	Difficulties to communicate with professionals Sensory sensitivity Feeling of being judged in mothering ability	*

**means low quality, **means moderate quality, ***means high quality, ****means very high quality.*

Reproductive Health and Psychiatric Rehabilitation

Compared to non-autistic mothers, autistic mothers had higher risks of perinatal depression and poorer obstetrical and neonatal outcomes (27, 31). Clinical implications from qualitative research included a need for clear and accurate information (e.g., about normal pregnancy, potential complications, delivery, and post-partum care), for stigma reduction (e.g., reducing the feeling of being judged by perinatal health providers), and for improved self-agency and empowerment (27, 46, 47). Awareness actions toward women's health professionals could improve their understanding of autistic women's needs (e.g., heightened sensory processing and medical examinations) and reduce the stigma associated with autism (27, 46, 47). Strategic disclosure programs result in people making empowered decisions about whether to disclose their diagnosis or not (67). A strengths-based case management by a trained midwife, shared decision-making, and shared action plans during the perinatal period (i.e., from preconception to 1 year after childbirth) could improve self-agency, empowerment, and maternal and children's outcomes (68–70). Future studies should investigate

TABLE 5 | Example of interventions to support autistic women in reproductive health (FondaMental Advanced Center of Expertise for ASD (FACE-ASD) center of Grenoble).

	Individual interventions	Group-based interventions
Interventions toward women with ASD	**Assessment by a trained midwife** - Physical health - Reproductive health history and needs for care - History of childhood/domestic abuse - Conception of gender social norms, roles, expectations and pressures (e.g., gender variance, desire to become mother or not, centrality of mothering…) - Fears about becoming mother (e.g., fears about pregnancy, delivery or post-partum care, being an autistic mother, communication with healthcare and childcare professionals, etc…) **Strengths-based case-management from preconception to post-partum care by a trained midwife** - Assess strengths/Building on strengths - Answer to questions relating to ASD, pregnancy and perinatal health outcomes (e.g., concerns about passing on ASD to their child, information about the stay in the maternity ward, cesarean section, circadian rhythms and lactation, fear of being judged by others on mothering, prevention of perinatal depression) - Shared strengths-based action plan to improve well-being and pregnancy-related outcomes - Making empowered decisions about whether to disclose or not the diagnosis of ASD - Working on how to communicate with perinatal health professionals and social workers - Coping with stigma - Getting support	**Four-session group-based psychoeducation:** - Factors influencing decision-making about becoming mother or not - ASD and perinatal outcomes - Getting support - Making empowered decisions about disclosure
Interventions toward perinatal professionals	- Facilitate the communication between the mother and perinatal health professionals - Provide support to help professionals to meet ASD-related needs for care - Reducing stigma - Prevent unnecessary child protective services involvement	- Awareness and training actions: ASD and perinatal outcomes, screening of perinatal depression, ASD-related needs for care in the maternity ward (e.g., reducing sensory sensitivity issues and improving communication with autistic mothers), stigma-related issues, ASD and parenting

the potential effectiveness of these interventions in ASD. In other conditions such as serious mental illness, mothers report concerns about passing on their condition to their children (71). This might also be the case for autistic mothers, although this should be further investigated. Psychoeducation and family psychoeducation (e.g., ASD and pregnancy-related outcomes, heredity, risk factors for perinatal depression and how to deal with them, early detection, and intervention of ASD in children) provided during the perinatal period could prevent perinatal depression and improve maternal and children's outcomes.

Psychiatric rehabilitation interventions on reproductive health should also discuss the centrality of motherhood for autistic women (or, in contrast, their self-reported "absence of maternal instinct") (32) and its impact on a person's sense of personal identity.

Gender Differences in Treatment Effectiveness: Implications for Designing Interventions

Among the psychosocial interventions addressing romantic relationships or reproductive health in autistic people, no gender differences were reported on treatment outcomes after SST or psychosexual training (15, 17). Although it has been proposed that autistic women and men had similar needs for care and could benefit from the same interventions (15), autistic women may face unique challenges when subjective aspects (e.g., impact of gender-related social norms, roles, and expectations on a person's sense of identity) (32, 34) and specific domains (e.g., romantic relationships and reproductive health) (24, 26, 27, 34, 45) are considered.

While recent epidemiological studies have found lower male-to-female ratios than previously reported (18), the predominance of males in research samples could have affected both the

development and the evaluation of psychosocial treatments (18, 19). It can be hypothesized that men, presumed to have poorer social function, are all referred to psychosocial treatment, whereas only the women with severe social communication impairments are referred (19). Another hypothesis could be that existing interventions (mostly developed in male samples) do not meet the unique needs for care of women and gender-diverse individuals (e.g., discussing gender variance and gender-related social norms, roles, and expectations, prevention of sexual abuse, and reproductive health) (4, 26, 44). The development of strengths-based, gender-sensitive (i.e., taking into account gender variance, autistic people's lived experience, and women's needs for care) interventions addressing romantic relationships and reproductive health is needed (4, 13).

LIMITATIONS

There are some limitations to this review due to the heterogeneity in samples, in the methods, scales, interventions, and the reported outcomes. Few studies reported longitudinal outcomes, and only a small number of psychosocial treatments addressed romantic relationships or reproductive health from the perspective of autistic women or autistic gender-diverse individuals. The low–moderate quality of the included studies is also a limitation. This review excluded studies where women's outcomes in specific domains (i.e., romantic relationships and reproductive health) were not the main focus, which means that some needs for care in other domains (e.g., vocational function or leisure activities) might have been overlooked. However, by focusing on these domains using a broad definition of female gender (i.e., cisgender and gender-diverse individuals), this review provides a more accurate understanding of this population's needs for care relating to psychosocial treatments. The underreporting of negative or non-significant results due to publication bias from this review might have limited the accuracy of the synthesis.

In short, gender may influence a person's needs for care and treatment outcomes in autistic people, but this remains underinvestigated. Psychosocial treatments addressing romantic relationships or reproductive health remain underdeveloped and are often inadequate for women's and gender-diverse individuals' needs for care. High-quality research taking into account the perspectives and lived experiences of autistic women and gender-diverse individuals relating to their needs for care in romantic relationships and reproductive health is needed to guide the development of new interventions. Adopting a woman's health lens during the care of autistic women (e.g., with an evaluation and interventions by a trained midwife or by integrating gender-sensitive content in psychosocial treatments) might improve their access to physical healthcare services and to adequate support from perinatal services. This remains, however, to be investigated.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MD and JD carried out the literature review and drafted the article. Both authors contributed to and approved the final manuscript.

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REFERENCES

1. Hull L, Petrides KV, Mandy W. The female autism phenotype and camouflaging: a narrative review. *Rev J Autism Dev Disord*. (2020) 7:306–17. doi: 10.3389/frym.2019.00129
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM5), 5th ed*. Washington, DC: American Psychiatric Press (2013). doi: 10.1176/appi.books.9780890425596
3. Cooper K, Smith LGE, Russell AJ. Gender identity in autism: sex differences in social affiliation with gender groups. *J Autism Dev Disord*. (2018) 48:3995–4006. doi: 10.1007/s10803-018-3590-1
4. Strang JF, van der Miesen AI, Caplan R, Hughes C, daVanport S, Lai MC. Both sex- and gender-related factors should be considered in autism research and clinical practice. *Autism*. (2020) 24:539–543. doi: 10.1177/1362361320913192
5. Farkas M, Anthony WA. Psychiatric rehabilitation interventions: a review. *Int Rev Psychiatry*. (2010) 22:114–29. doi: 10.3109/09540261003730372
6. Franck N, Bon L, Dekerle M, Plasse J, Massoubre C, Pommier R, et al. Satisfaction and needs in serious mental illness and autism spectrum disorder: the REHABase psychosocial rehabilitation project. *Psychiatr Serv*. (2019) 70:316–23 doi: 10.1176/appi.ps.201800420
7. Dubreucq J, Plasse J, Gabayet F, Faraldo M, Blanc O, Chereau I, et al. Self-stigma in serious mental illness and autism spectrum disorder: results from the REHABase national psychiatric rehabilitation cohort. *Eur Psychiatry*. (2020) 63:e13. doi: 10.1192/j.eurpsy.2019.12
8. Dandil Y, Smith K, Kinnaird E, Toloza C, Tchanturia K. Cognitive remediation interventions in autism spectrum condition: a systematic review. *Front Psychiatry*. (2020) 11:722. doi: 10.3389/fpsyt.2020.00722
9. Mavranezouli I, Megnin-Viggars O, Cheema N, Howlin P, Baron-Cohen S, Pilling S. The cost-effectiveness of supported employment for adults with autism in the United Kingdom. *Autism*. (2014) 18:975–84. doi: 10.1177/1362361313505720
10. Keefer A, White SW, Vasa RA, Reaven J. Psychosocial interventions for internalizing disorders in youth and adults with ASD. *Int Rev Psychiatry*. (2018) 30:62–77. doi: 10.1080/09540261.2018.1432575
11. Spain D, Blainey SH. Group social skills interventions for adults with high-functioning autism spectrum disorders: a systematic review. *Autism*. (2015) 19:874–86. doi: 10.1177/1362361315587659

12. Hillier A, Campbell H, Mastriani K, Izzo MV, Kool-Tukcer A K, Cherry L, et al. Two-year evaluation of a vocational support program for adults on the autism spectrum. *Career Dev Transit Except Individ*. (2007) 30:35–47 doi: 10.1177/08857288070300010501
13. DaWalt LS, Taylor JL, Bishop S, Hall LJ, Steinbrenner JD, Kraemer B, et al. Sex differences in social participation of high school students with autism spectrum disorder. *Autism Res*. (2020) 13:2155–63. doi: 10.1002/aur.2348
14. Taylor JL, Henninger NA, Mailick MR. Longitudinal patterns of employment and postsecondary education for adults with autism and average-range IQ. *Autism*. (2015) 19:785–93. doi: 10.1177/1362361315585643
15. McVey AJ, Schiltz H, Haendel A, Dolan BK, Willar KS, Pleiss S, et al. Brief report: does gender matter in intervention for ASD? Examining the impact of the PEERS® social skills intervention on social behavior among females with ASD. *J Autism Dev Disord*. (2017) 47:2282–9. doi: 10.1007/s10803-017-3121-5
16. Sung C, Sánchez J, Kuo HJ, Wang CC, Leahy MJ. Gender differences in vocational rehabilitation service predictors of successful competitive employment for transition-aged individuals with autism. *J Autism Dev Disord*. (2015) 45:3204–18. doi: 10.1007/s10803-015-2480-z
17. Visser K, Greaves-Lord K, Tick NT, Verhulst FC, Maras A, van der Vegt EJM. A randomized controlled trial to examine the effects of the Tackling Teenage psychosexual training program for adolescents with autism spectrum disorder. *J Child Psychol Psychiatry*. (2017) 58:840–50. doi: 10.1111/jcpp.12709
18. Lai MC, Lombardo MV, Auyeung B, Chakrabarti B, Baron-Cohen S. Sex/gender differences and autism: setting the scene for future research. *J Am Acad Child Adolesc Psychiatry*. (2015) 54:11–24. doi: 10.1016/j.jaac.2014.10.003
19. Dubreucq J, Haesebaert F, Plasse J, Dubreucq M, Franck, N. A systematic review and meta-analysis of social skills training for adults with Autism Spectrum Disorder. *J Autism Dev Disord*. Revised.
20. Laugeson EA, Gantman A, Kapp SK, Orenski K, Ellingsen R. A Randomized controlled trial to improve social skills in young adults with autism spectrum disorder: the UCLA PEERS(®) program. *J Autism Dev Disord*. (2015) 45:3978–89. doi: 10.1007/s10803-015-2504-8
21. Cunningham A, Sperry L, Brady MP, Peluso PR, Pauletti RE. The effects of a romantic relationship treatment option for adults with autism spectrum disorder. *Counsel Outcome Res Eval*. (2016) 7:99–110. doi: 10.1177/2150137816668561
22. Tint A, Weiss JA. A qualitative study of the service experiences of women with autism spectrum disorder. *Autism*. (2018) 22:928–37. doi: 10.1177/1362361317702561
23. Urbano MR, Hartmann K, Deutsch SI, Bondi Polychronopoulos GM, Dorbin V. Relationships, sexuality, and intimacy in autism spectrum disorders. In: Fitzgerald M, editor. *Recent Advances in Autism Spectrum Disorders - Volume I*. IntechOpen (2013). Available online at: https://www.intechopen.com/books/recent-advances-in-autism-spectrum-disorders-volume-i/relationships-sexuality-and-intimacy-in-autism-spectrum-disorders (accessed January 12, 2021).
24. Pecora LA, Hancock GI, Mesibov GB, Stokes MA. Characterising the sexuality and sexual experiences of autistic females. *J Autism Dev Disord*. (2019) 49:4834–46. doi: 10.1007/s10803-019-04204-9
25. George R, Stokes MA. A quantitative analysis of mental health among sexual and gender minority groups in ASD. *J Autism Dev Disord*. (2018) 48:2052–63. doi: 10.1007/s10803-018-3469-1
26. Taylor JL, DaWalt LS. Working toward a better understanding of the life experiences of women on the autism spectrum. *Autism*. (2020) 24:1027–30. doi: 10.1177/1362361320913754
27. Pohl AL, Crockford SK, Blakemore M, Allison C, Baron-Cohen S. A comparative study of autistic and non-autistic women's experience of motherhood. *Mol Autism*. (2020) 11:3. doi: 10.1186/s13229-019-0304-2
28. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. (2015) 4:1. doi: 10.1186/2046-4053-4-1
29. Pluye P, Robert E, Cargo M, Bartlett G, O'Cathain A, Griffiths F, et al. *Proposal: A Mixed Methods Appraisal Tool for Systematic Mixed Studies Reviews*. (2011). Available online at: http://mixedmethodsappraisaltoolpublic.pbworks.com. Archived by WebCite® at http://www.webcitation.org/5tTRTc9yJ (accessed October 4, 2018).
30. Jamison TR, Schuttler JO. Overview and preliminary evidence for a social skills and self-care curriculum for adolescent females with autism: the girls night out model. *J Autism Dev Disord*. (2017) 47:110–25. doi: 10.1007/s10803-016-2939-6
31. Sundelin HE, Stephansson O, Hultman CM, Ludvigsson JF. Pregnancy outcomes in women with autism: a nationwide population-based cohort study. *Clin Epidemiol*. (2018) 10:1817–1826. doi: 10.2147/CLEP.S176910
32. Kanfiszer L, Davies F, Collins S. 'I was just so different': the experiences of women diagnosed with an autism spectrum disorder in adulthood in relation to gender and social relationships. *Autism*. (2017) 21:661–9. doi: 10.1177/1362361316687987
33. Sala G, Hooley M, Stokes MA. Romantic intimacy in autism: a qualitative analysis. *J Autism Dev Disord*. (2020) 50:4133–47. doi: 10.1007/s10803-020-04377-8
34. Bargiela S. Steward of late-diagnosed women with autism spectrum conditions: an investigation of the female autism phenotype. *J Autism Dev Disord*. (2016) 46:3281–94. doi: 10.1007/s10803-016-2872-8
35. Bejerot S, Eriksson JM. Sexuality and gender role in autism spectrum disorder: a case control study. *PLoS ONE*. (2014) 9:e87961. doi: 10.1371/journal.pone.0087961
36. Busch HH. Dimensions of sexuality among young women, with and without autism, with predominantly sexual minority identities. *Sex Disabil*. (2018) 37:275–92. doi: 10.1007/s11195-018-9532-1
37. Byers ES, Nichols S, Voyer SD, Reilly G. Sexual well-being of a community sample of high-functioning adults on the autism spectrum who have been in a romantic relationship. *Autism*. (2013) 17:418–33. doi: 10.1177/1362361311431950
38. Strang JF, Knauss M, van der Miesen A, McGuire JK, Kenworthy L, Caplan R, et al. A clinical program for transgender and gender-diverse neurodiverse/autistic adolescents developed through community-based participatory design. *J Clin Child Adolesc Psychol*. (2020) 6:1–16. doi: 10.1080/15374416.2020.1731817
39. Baldwin S, Costley D. The experiences and needs of female adults with high-functioning autism spectrum disorder. *Autism*. (2016) 20:483–95. doi: 10.1177/1362361315590805
40. Strunz S, Schermuck C, Ballerstein S, Ahlers CJ, Dziobek I, Roepke S. Romantic relationships and relationship satisfaction among adults with asperger syndrome and high-functioning autism. *J Clin Psychol*. (2017) 73:113–25. doi: 10.1002/jclp.22319
41. Smith R, Netto J, Gribble NC, Falkmer M. 'At the end of the day, it's love': an exploration of relationships in neurodiverse couples. *J Autism Dev Disord*. (2020). doi: 10.1007/s10803-020-04790-z. [Epub ahead of print].
42. Corona LL, Fox SA, Christodulu KV, Worlock JA. Providing education on sexuality and relationships to adolescents with autism spectrum disorder and their parents. *Sex Disabil*. (2015) 34:199–214. doi: 10.1007/s11195-015-9424-6
43. Hénault I. Programme d'éducation sociosexuelle. In: Hénault I, editor. *Sexualité et Syndrome d'Asperger, Éducation Sexuelle et Interventions Auprès de la Personne Autiste*. Louvain-la-Neuve: De Boeck (2010), p. 115–20.
44. Dubreucq M, Dubreucq J. Recovery-oriented program on sexuality and prevention of sexual abuse for women with Autism Spectrum Disorder (ASD): a new intervention based on a qualitative analysis. In preparation.
45. Pecora LA, Hancock GI, Hooley M, Demmer DH, Attwood T, Mesibov GB, et al. Gender identity, sexual orientation and adverse sexual experiences in autistic females. *Mol Autism*. (2020) 11:57. doi: 10.1186/s13229-020-00363-0
46. Gardner M, Suplee PD, Bloch J, Lecks K. Exploratory study of childbearing experiences of women with asperger syndrome. *Nurs Womens Health*. (2016) 20:28–37. doi: 10.1016/j.nwh.2015.12.001
47. Rogers C, Lepherd L, Ganguly R, Jacob-Rogers S. Perinatal issues for women with high functioning autism spectrum disorder. *Women Birth*. (2017) 30:e89–95. doi: 10.1016/j.wombi.2016.09.009
48. Donovan J. Childbirth experiences of women with autism spectrum disorder in an acute care setting. *Nurs Womens Health*. (2020) 24:165–74. doi: 10.1016/j.nwh.2020.04.001
49. Kassee C, Babinski S, Tint A, Lunsky Y, Brown HK, Ameis SH, et al. Physical health of autistic girls and women: a scoping review. *Mol Autism*. (2020) 11:84. doi: 10.1186/s13229-020-00380-z
50. Ames JL, Massolo ML, Davignon MN, Qian Y, Croen LA. Healthcare service utilization and cost among transition-age youth with autism

spectrum disorder and other special healthcare needs. *Autism*. (2020). doi: 10.1177/1362361320931268. [Epub ahead of print].
51. Milner V, McIntosh H, Colvert E, Happé F. A qualitative exploration of the female experience of autism spectrum disorder (ASD). *J Autism Dev Disord*. (2019) 49:2389–402. doi: 10.1007/s10803-019-03906-4
52. Sedgewick F, Hill V, Pellicano E. 'It's different for girls': gender differences in the friendships and conflict of autistic and neurotypical adolescents. *Autism*. (2019) 23:1119–32. doi: 10.1177/1362361318794930
53. Cage E, Troxell-Whitman Z. Understanding the reasons, contexts and costs of camouflaging for autistic adults. *J Autism Dev Disord*. (2019) 49:1899–911. doi: 10.1007/s10803-018-03878-x
54. Moody CT, Laugeson EA. Social skills training in autism spectrum disorder across the lifespan. *Child Adolesc Psychiatr Clin N Am*. (2020) 29:359–71. doi: 10.1016/j.chc.2019.11.001
55. Livingston LA, Happé F. Conceptualising compensation in neurodevelopmental disorders: Reflections from autism spectrum disorder. *Neurosci Biobehav Rev*. (2017) 80:729–42. doi: 10.1016/j.neubiorev.2017.06.005
56. Livingston LA, Colvert E, Social Relationships Study Team, Bolton P, Happé F. Good social skills despite poor theory of mind: exploring compensation in autism spectrum disorder. *J Child Psychol Psychiatry*. (2019) 60:102–10. doi: 10.1111/jcpp.12886
57. Livingston LA, Shah P, Happé F. Compensatory strategies below the behavioural surface in autism: a qualitative study. *Lancet Psychiatry*. (2019) 6:766–77. doi: 10.1016/S2215-0366(19)30224-X
58. Cassidy SA, Gould K, Townsend E, Pelton M, Robertson AE, Rodgers J. Is camouflaging autistic traits associated with suicidal thoughts and behaviours? Expanding the interpersonal psychological theory of suicide in an undergraduate student sample. *J Autism Dev Disord*. (2020) 50:3638–48. doi: 10.1007/s10803-019-04323-3
59. Tint A, Hamdani Y, Sawyer A, Desarkar P, Ameis SH, Bardikoff N, et al. Wellness efforts for autistic women. *Curr Dev Disord Rep*. (2018) 5:207–16. doi: 10.1007/s40474-018-0148-z
60. Schneid I, Raz AE. The mask of autism: social camouflaging and impression management as coping/normalization from the perspectives of autistic adults. *Soc Sci Med*. (2020) 248:112826. doi: 10.1016/j.socscimed.2020.112826
61. Dubreucq J, Plasse J, Franck N. Self-stigma in serious mental illness: a systematic review of frequency, correlates, and consequences. *Schizophr Bull*. (2021). doi: 10.1093/schbul/sbaa181. [Epub ahead of print].
62. Bachmann CJ, Höfer J, Kamp-Becker I, Küpper C, Poustka L, Roepke S, et al. Internalised stigma in adults with autism: a German multi-center survey. *Psychiatry Res*. (2019) 276:94–99. doi: 10.1016/j.psychres.2019.04.023
63. Turner D, Briken P, Schöttle D. Sexual dysfunctions and their association with the dual control model of sexual response in men and women with high-functioning autism. *J Clin Med*. (2019) 8:425. doi: 10.3390/jcm8040425
64. Barnett JP, Maticka-Tyndale E. Qualitative exploration of sexual experiences among adults on the autism spectrum: implications for sex education. *Perspect Sex Reprod Health*. (2015) 47:171–9. doi: 10.1363/47e5715
65. Yanos PT, Lysaker PH, Silverstein SM, Vayshenker B, Gonzales L, West ML, et al. A randomized-controlled trial of treatment for self-stigma among persons diagnosed with schizophrenia-spectrum disorders. *Soc Psychiatry Psychiatr Epidemiol*. (2019) 54:1363–78. doi: 10.1007/s00127-019-01702-0
66. Nagib W, Wilton R. Gender matters in career exploration and job-seeking among adults with autism spectrum disorder: evidence from an online community. *Disabil Rehabil*. (2020) 42:2530–41. doi: 10.1080/09638288.2019.1573936
67. Mulfinger N, Müller S, Böge I, Sakar V, Corrigan PW, Evans-Lacko S, et al. Honest, open, proud for adolescents with mental illness: pilot randomized controlled trial. *J Child Psychol Psychiatry*. (2018) 59:684–91. doi: 10.1111/jcpp.12853
68. Hauck Y, Rock D, Jackiewicz T, Jablensky A. Healthy babies for mothers with serious mental illness: a case management framework for mental health clinicians. *Int J Ment Health Nurs*. (2008) 17:383–91. doi: 10.1111/j.1447-0349.2008.00573.x
69. Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E, et al. Royal Australian and New Zealand college of psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Aust N Z J Psychiatry*. (2016) 50:410–72. doi: 10.1177/0004867416641195
70. Dubreucq M, Provasi A, Baudrant M, Dubreucq J. Development of a shared decision-making tool from preconception to post-partum care for women with serious mental illness: a qualitative analysis. In preparation.
71. Dolman C, Jones IR, Howard LM. Women with bipolar disorder and pregnancy: factors influencing their decision-making. *BJPsych Open*. (2016) 2:294–300. doi: 10.1192/bjpo.bp.116.003079

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New Technologies as Promising Tools for Assessing Facial Emotion Expressions Impairments in ASD: A Systematic Review

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The ability to recognize and express emotions from facial expressions are essential for successful social interactions. Facial Emotion Recognition (FER) and Facial Emotion Expressions (FEEs), both of which seem to be impaired in Autism Spectrum Disorders (ASD) and contribute to socio-communicative difficulties, participate in the diagnostic criteria for ASD. Only a few studies have focused on FEEs processing and the rare behavioral studies of FEEs in ASD have yielded mixed results. Here, we review studies comparing the production of FEEs between participants with ASD and non-ASD control subjects, with a particular focus on the use of automatic facial expression analysis software. A systematic literature search in accordance with the PRISMA statement identified 20 reports published up to August 2020 concerning the use of new technologies to evaluate both spontaneous and voluntary FEEs in participants with ASD. Overall, the results highlight the importance of considering socio-demographic factors and psychiatric co-morbidities which may explain the previous inconsistent findings, particularly regarding quantitative data on spontaneous facial expressions. There is also reported evidence for an inadequacy of FEEs in individuals with ASD in relation to expected emotion, with a lower quality and coordination of facial muscular movements. Spatial and kinematic approaches to characterizing the synchrony, symmetry and complexity of facial muscle movements thus offer clues to identifying and exploring promising new diagnostic targets. These findings have allowed hypothesizing that there may be mismatches between mental representations and the production of FEEs themselves in ASD. Such considerations are in line with the Facial Feedback Hypothesis deficit in ASD as part of the Broken Mirror Theory, with the results suggesting impairments of neural sensory-motor systems involved in processing emotional information and ensuring embodied representations of emotions, which are the basis of human empathy. In conclusion, new technologies are promising tools for evaluating the production of FEEs in individuals with ASD, and controlled studies involving larger samples of patients and where possible confounding factors are considered, should be conducted in order to better understand and counter the difficulties in global emotional processing in ASD.

Keywords: autism (ASD), facial expression, emotion, new technologies, automatic facial expression analysis

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INTRODUCTION

Non-verbal information extracted from facial expressions are crucial components of social functioning and impairments to such behavior have a strong impact on social interactions, since facial expressions provide a window to internal emotional state and are key to successful communication and social inclusion. In the general population, it is largely recognized that reciprocity and synchrony in facial expression production has an important social function and that atypical facial expressions are correlated with weaker social skills (1). Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by difficulties with social communication and interaction associated with stereotyped and repetitive behaviors, restricted interest and sensory abnormalities, according to the DSM-V (2). In ASD, the deficit observed in social skills represents one of the major and persistent characteristics of ASD's core symptoms and includes impairments in social and/or emotional reciprocity and in the use and understanding of verbal and non-verbal communication. These in turn lead to difficulties in modulating and maintaining adapted social behaviors, even in individuals with High Functioning Autism (HFA) who often struggle in social settings because of difficulty in interpreting and producing facial expressions. Therefore, Facial Emotion Recognition (FER) has been a topic of interest in autism research for more than three decades, although studies have generally documented mixed results that have failed to provide a consensus on these impairments in both children and adults with ASD (3). In addition to the deficit in FER (4), a deficit in the production of FEEs, which is part of non-verbal communication, is also a frequently reported symptom in ASD. FEEs are often perceived as awkward or atypical and are judged as clinically relevant measures in the Autism Diagnostic Observation Schedule - Second Edition (ADOS-2) (5) or the Autism Diagnostic Interview - Revised (ADI-R) (6), which are the most commonly used tools in the ASD diagnosis process.

The production of facial expressions has been proposed to be linked to a specific neural network corresponding to the Mirror Neuron System (MNS) that in humans includes the pre-motor cortex, the inferior parietal and frontal lobes and their interactions with the limbic system, the insula and the anterior cingulate cortex. In non-ASD individuals, this network is activated during the execution of a motor action as well as during the observation of a motor action performed by others (7). Evidence for MNS impairments in ASD has been taken to support the hypothesis that the MNS plays a role in higher order socio-cognitive functions that help us to understand another person's perspective and inner states, such as action understanding, theory of mind, emotion simulation and empathy (7, 8). Accordingly, it has been suggested that deficits in the production of FEEs may be related to a MNS dysfunction, particularly in ASD, in line with the general MNS dysfunction theory: the broken mirror theory (BMT) in ASD (9). However, despite the appealing simplicity of the BMT, evidence supporting the hypothesis is mixed, with a recent review distinguishing three variants of the BMT that highlight contradictory results in imitation, simulation and emotion recognition tasks (10). A MNS dysfunction limited to specific stimuli could better explain the abnormal modulation of social cues (10).

Related to the embodiment theory, the facial feedback hypothesis suggests that in non-ASD individuals, the experience of emotions is affected by feedback from facial muscle activation (11). Stel et al. demonstrated that automatic or voluntary facial expressions, modulated by holding a pen between the teeth, influenced corresponding emotions compared to non-pen holding in controls, while adolescents with ASD remained emotionally unaffected. The authors concluded that the facial feedback mechanism worked differently for individuals with ASD (12). Moreover, previous results reported that disrupting sensory feedback from the facial region of the somatosensory cortex using Transcranial Magnetic Stimulation (TMS) impaired the discrimination of facial expressions, but not the recognition of facial identity (13). Together, these studies suggest that perception and motor production may be linked through a common use of the motor system, in line with the perception-action coupling system theory. Similarly, it is recognized that people with ASD may also present atypical mental representations of their emotional experiences (14). A deficit in the perception-action coupling could, in ASD, partly explain both impairments: in sensory mental representations of emotion and motor programming of facial expression. The sensory-motor process plays an important role in the mentalization of one's internal states and intentions.

When engaged in a social interaction, typically developing individuals fail to interpret the facial expression of people with ASD (15), with difficulties to identify and discriminate the emotion expressed (e.g., not being able to discern a sad face from an angry face) (16). Furthermore, unfamiliar interlocutors judge individuals with ASD less favorably on the basis of their non-verbal cues, and are therefore less likely to engage in a social relationship because of an impression of "weirdness" (17). As a result, people with ASD are more likely to be judged more unfavorably by non-ASD peers, they develop less friendships and are more vulnerable to bullying, especially at school (18).

However, results concerning FEEs in ASD remain highly variable among traditional studies, without the use of new technology, partly due to both task and participant characteristic factors such as age and intellectual functioning (19). In addition, several clinical dimensional traits impact the production of FEEs, such as alexithymia [which involves difficulties in recognizing and distinguishing between different emotions and body sensations, difficulties in expressing emotions, lack of imagination or fantasy life, and thoughts focused on external rather than internal experiences (20)] (21), or depressive symptoms (22). Moreover, facial expressions have been studied through the employment of different tools. The Facial Action Coding System (FACS) (23), which was developed by Ekman in 1976, is the most frequently used tool in traditional research on FEEs. The FACS is a human rated system for objectively scoring facial expressions in terms of elemental movements, called action units (AUs), which correspond approximately to individual facial muscle movements. FACS provides a comprehensive description of facial expressions, imparting a greater specificity and diversity than emotion categories. Facial electromyography (EMG) is

another commonly used method that is proposed to measure selective facial muscle contractions during facial expression.

These conventional techniques have several disadvantages in addition to a lack of reliability. The FACS has been widely used for research on emotions, however it involves manual human coding and is therefore less reliable and objective. Moreover, it is likely to be difficult to apply to dynamic facial expressions. Particularly, human coding involves time and training requirements and above all cannot be used in real time or in an ecological social environment. EMG recordings are mainly limited to the two groups of muscles responsible for frowning (*corrugator supercilii*) and smiling (*zygomaticus major*) and does not allow detailed analysis of all regions of the human face. EMG analysis is also invasive and the required use of markers on the face can interfere with the natural facial expression of emotion. However, recent advances in automated facial expression recognition technology has opened new possibilities for the objective measurement of facial expressions, with both qualitative and quantitative advantages.

New technologies can be defined as the use of mechanical or electromechanical procedures that increase productivity and reduce or eliminate manual operations or operations performed by older technologies (24). They include mobile phones, video recording equipment, robotics, computers etc. The interest for the analysis of FEEs is multiple (25). First, the advent of automated facial expression analysis software and resultant reductions in analysis time allows researchers to obtain larger samples of individuals with ASD and collect in-depth information through real-time analysis of multiple and complex relevant characteristics. Second, the data obtained are recorded automatically, which makes distinguishing differences between participant groups more objective than those obtained with human observers and raters. Then, compared to studies based on human coders, it has been reported that automated FEE analysis were able to achieve high test–retest reliability across healthy, non-ASD participants (26).

The present systematic review therefore aims to report recent research using new technology based on automated facial expression recognition systems that allow a more objective and detailed characterization of quantitative and qualitative deficits of FEEs in individuals with ASD.

MATERIALS AND METHODS

This review focuses on the use of automated facial recognition technology to analyze facial expression in ASD subjects. We have not included either studies that examined only facial emotional recognition (FER) or other non-affective facial processing, nor studies based on observer rating of facial expressions or EMG monitoring (so called "traditional studies or literature"), but rather have focused uniquely on the automated evaluation of emotional facial expressions based on new technologies. This review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (27).

The data bases used were: PubMed database for medical sciences, the IEEE Xplore database for new technologies, computer science and engineering, and the Web of Science database using a combination of the following MESH terms or keywords: (asd OR Autism OR Asperger) AND (facial OR face) AND (emotion OR emotion expression OR emotion recognition OR expression OR production) AND (software OR technology OR comput* OR automat* OR technology-based intervention). A manual search was also performed by checking the list of References of the studies included in this review. Articles reporting experimental and clinical studies, literature reviews or meta-analyses were considered.

To be included in the systematic review, studies also had to meet the following criteria:

- the diagnosis of ASD must have been made formally by a specialist using the diagnostic criteria of the DSM-IV, DSM-IV-TR, DSM-V, or the International Classification of Diseases 10th Edition ICD-10 or ICD-11 to allow maximum generalizability to current practice,
- specification of the age or age category (child/adult) of the participants included.,
- specification of the type of stimuli used and the method of facial expression analysis,
- comparative studies that included a control group of participants without ASD
- studies written in English and published in scientific journals until August 2020.

In a first instance, 1,749 relevant results were found. After exclusion of duplicates ($n = 660$), the titles and abstracts of the remaining 1,089 articles were analyzed according to the above criteria.

Initially, two of this review's authors (KB, AA) evaluated the title and abstract of the selected articles to determine whether they met the inclusion and exclusion criteria. One thousand thirty-six articles were subsequently excluded and 53 were read in full. The studies selected from this first analysis were independently examined by the two authors, who read the full text. A further 33 articles were excluded because (1) they did not consider facial expression but recognition of emotion ($n = 15$), (2) they did not include a specific group of individuals without ASD ($n = 5$), (3) they included a number < 3 of subjects with ASD or were a case study ($n = 1$), (4) they were not an original study or a literature review or meta-analysis ($n = 5$), (5) they did not involve new technologies ($n = 4$), (6) the methodological description or description of the study population was too limited to ensure comparability with other studies ($n = 3$). Ultimately, 20 articles were included in our literature review. The associated flow chart is presented in **Figure 1**.

Each variable related to participant parameters, the methods used and the study results as presented in **Table 1** for clinical studies and in **Table 2** for reviews and meta-analysis. Participant parameters included were group size, age, gender, intellectual functioning, and method of ASD clinical assessment method. Methods of facial expression analysis included the type of stimulus provided (see **Figure 2** for a description), the type of measurement, and the type of expression (spontaneous or voluntary). Additional scales used were identified and a summary of the results was made. The quality of each study was evaluated using the score proposed by Bond et al. (45) that allowed

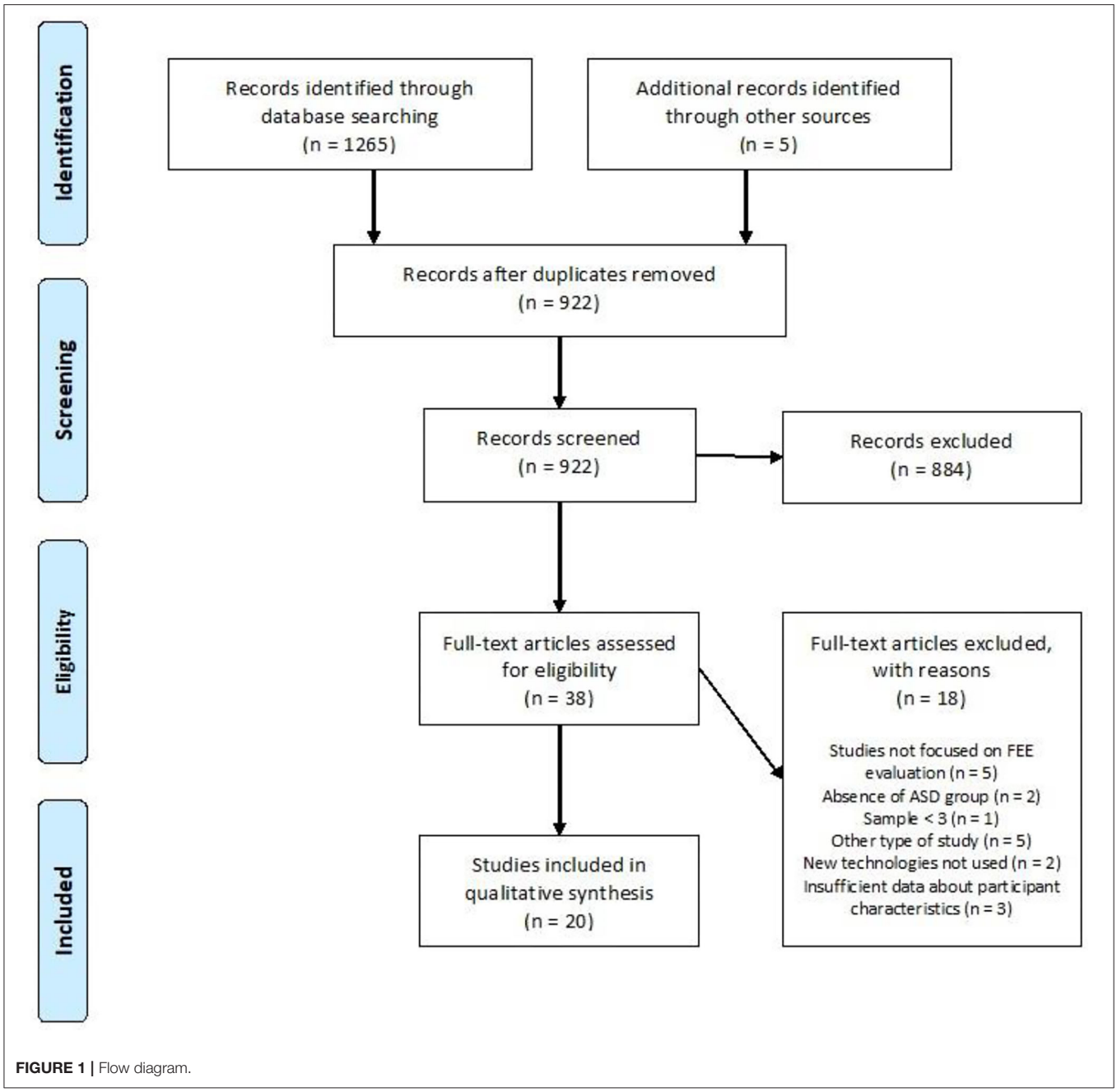

FIGURE 1 | Flow diagram.

classifying methodologies into three categories: high (score 5–7), medium (3–4) or low (0–2) quality (see **Table 1** and detailed quality score in **Supplementary Material**).

RESULTS

Analysis of Spontaneous Facial Expressions of Emotions

A recent meta-analytical review reported that autistic individuals display spontaneous facial expressions less frequently and for a shorter duration than in non-autistic individuals. Furthermore, they are less accurate and lower in quality (19). Only 7 studies were found to focus specifically on spontaneous FEEs in ASD using new technology.

Quantitative Analysis of Spontaneous FEEs in a Non-social Situation

Spontaneous facial expressions in people with ASD have been evaluated by designing various experimental conditions that are considered to provoke emotion, such as watching videos with

TABLE 1 | Parameter details in original studies.

Name	N (ASD/ control)	Gender (% males)	Age (mean ASD/ control)	Diagnostic method	Cognitive level	Stimuli	Measure	Skills assessed	Scales	Quality score	Results
Bangerter et al. (25)	124/41	75/65.85%	Children > 6 years old and adults (14.97 ± 8.19/16.27 ± 13.18)	ASD (ADOS-2)	IQ > 60 (KBIT-2) 99.25 ± 19.25	Funny videos (America's funniest home videos' library)	Automatic facial analysis software FACET (FACS)	Spontaneous expression of Joy	SRS-2 ABC ABI	High	Lower expression of joy in ASD group ($p < 0.05$). Correlation between the activation of AU12 and ABI impulsivity and hypersensitivity. Distinction between 2 subgroups: hypo-expressive (correlation with ABC social withdrawal) and hyper-expressive (correlation with ABI impulsivity)
Capriola-Hall et al. (28)	20/20	90/70%	Children 9–12 years old (10.20/10.81)	ASD (ADOS-2)	No intellectual deficit (WASI-II) 100.55/118.15	Dynamic human faces and cartoons, emotional scene with audio	Automatic facial analysis software FEET (Kinect VT-KFER)	Voluntary expression of joy, anger, fear, neutral		High	Differences in FEE accuracy ($p = 0.008$), mainly with human faces ($p < 0.05$). More errors in the ASD group for low-intensity cartoons and high-intensity human faces. Convergence between human and computer coding ($p < 0.001$)
Del Coco et al. (29)	5/5	No data	Children 4–6 years old (5.5 ± 1.3)	ASD (ADOS-2)	Development quotient between 92 and 42 (mean 70) (GMDS)	Videos from cartoons	Automatic computer analysis	Spontaneous expression of joy, fear, sadness		Low	Higher facial expression complexity in the control group both overall and when the upper and lower face are analyzed separately. More intra-group similarity than inter-group similarity. Statistics of data were not provided.
Grossard et al. (30)	36/157	75/52%	Children 6–12 years old 8.8 ±1.8/8.4 ± 1.4	ASD (ADOS and/or ADI-R)	WISC-IV 92.5 (±17.5)	Verbal request - Dynamic Avatar faces	Automatic facial analysis algorithm (random forest classifier)	Voluntary expression of joy, sadness, anger, neutral	ADI-R sub-scores	High	More ambiguous expressions in subjects with ASD requiring consideration of more facial markers. Anger confused with joy more frequently in the ASD group.
Guha et al. (31)	24/21	No data	Children 9–14 years old	ASD	No data	Dynamic human faces (Mind reading corpus)	Facial Motion Capture	Voluntary expression of joy, sadness, anger, fear, surprise, disgust		Medium	Difference between groups ($p = 0.024$), mostly for fear, disgust and sadness, especially in the eye area. Less facial symmetry, less variation in intensity.
Guha et al. (32)	20/19	90/95%	Children 9–14 years old 12.90 ± 3.19 /12.67 ± 2.34	ASD (ADOS)	HFA (Lieter-3/PPVT-4) 106.35 ± 15.38/108.74 ± 11.93	Dynamic human faces (Mind Reading corpus)	Facial Motion Capture (FACS)	Voluntary expression of joy, sadness, anger, fear, surprise, disgust		Medium	Less complexity of facial movements in the ASD group mainly from the eye area. Significant differences in joy, sadness, disgust ($p < 0.05$) mainly because of the eye area
Landowska et al. (33)	11/8	No data	Children	ASD	?	Interactions with a robot	Automatic facial analysis software Face Reader (FACS)	Spontaneous expression of joy, sadness, anger, fear, surprise, disgust		Low	Less expression of sadness ($p = 0.002$) and disgust ($p = 0.01$) in the ASD group during evaluation.

(Continued)

TABLE 1 | Continued

Name	N (ASD/ control)	Gender (% males)	Age (mean ASD/ control)	Diagnostic method	Cognitive level	Stimuli	Measure	Skills assessed	Scales	Quality score	Results
Manfredonia et al. (34)	144/41	77.8/65.9%	Children and adults 6–63 years old (14.6 ± 7.8/16.3 ± 13.18)	ASD (ADOS)	IQ > 60 (KBIT-2) 99.2 (±19.6)	Written request	Automatic facial analysis software FACET (FACS)	Voluntary expression of joy, sadness, anger, fear, surprise, disgust	ABI SRS-2	High	Difference in the use of joy, fear, surprise and disgust AUs ($p < 0.05$), but not sadness and anger AUs. Negative correlation between some FEEs and SRS and ABI social communication subscores (mainly < 13 years)
Metallinou et al. (35)	21/16	No data	Children 9–14 years old	ASD	HFA	Dynamic human faces	Facial Motion Capture	Voluntary expression of joy		Medium	More asynchronous movements between the different face regions and more variability and inaccuracy at the lower face in ASD children
Owada et al. (36)	18/17	100/100%	Adults 18–55 years old (32.2 ± 7/29.6 ± 4.3)	ASD (ADI-R and ADOS)	> 80 (WAIS) 105.8 ± 10.9	Semi-structured interview (ADOS)	Automatic facial analysis software Face Reader Noldus (FACS)	Spontaneous expression of joy, sadness, anger, fear, surprise, disgust, neutral	ADOS WHOQ-OL GAF AQ STAY-A CESD	Medium	More neutrality and less joy in the AD group with less variability ($p < 0.05$). Correlation between neutrality and higher ADOS social reciprocity subscore ($p = 0.042$).
Samad et al. (37)	8/8	No data	Children and young adults 7–20 years old (13 ± 4.4/16 ± 4.1)	ASD	No data	Static faces of 3D avatars	Facial imaging sensor 3D	Spontaneous expression of joy, sadness, anger, fear, surprise, disgust		Low	Asymmetrical facial muscle activation in ASD subjects compared to control group
Trevisan et al. (38)	17/17	76/76%	Children (10.21 ± 1.78/8.97 ± 1.30)	ASD (ADI-R and ADOS)	HFA (WASI vocabulary and matrix subtests)	Emotional videos	Automatic facial analysis software FACET (FACS)	Spontaneous expression: Positive (joy), negative: (sadness, anger, fear, surprise, disgust) neutral	AQ CAM	Medium	Negative correlation between alexithymia (CAM) and negative FEEs ($p = 0.03$), positive correlation with neutrality ($p = 0.012$) but not with positive FEE. No correlation between FEE and autistic symptoms (AQ). Difference in FEE scores between ASD and controls only for neutrality ($p = 0.024$) from univariate analysis.
Wieckowski et al. (39)	20/20	90/70%	Children 9–12 years old	ASD (ADOS-2)	HFA (WASI-II) 100.55/118.15	Dynamic cartoon and human faces Photo of emotional scene without face with audio	Automatic facial analysis software FEET (Kinect)	Voluntary expression of Joy, anger, fear, neutral	NEPSY-II	High	Children with ASD expressed accurate but more atypical FEE than controls in all conditions. Positive correlation between FEE on verbal request only and FER in the ASD group ($p = 0.01$), but not the control group.

(Continued)

TABLE 1 | Continued

Name	N (ASD/ control)	Gender (% males)	Age (mean ASD/ control)	Diagnostic method	Cognitive level	Stimuli	Measure	Skills assessed	Scales	Quality score	Results
Zampella et al. (40)	20/16	95/87.5%	Children 9–16 years old (13.8 ± 1.38/14.21 ± 2.03)	ASD (HFA) (ADOS-2 et ADI-R) SCQ	(WASI-II or WISC-IV) 108.5 ± 14.15/113.94 ± 12.68	Interactions during a conversation with a caregiver or a stranger	Automatic facial analysis software OpenFace (FACS)	Spontaneous expression of joy	SRS-2 Vineland II IRI	Medium	Children with ASD (p - 0.02) as well as their non-familiar interlocutor (p - 0.002) expressed less smiles than controls. Children with ASD showed less coordination in reciprocal smiles (p–0.02). Positive correlation between the coordination of smiles in ASD and social skills (SRS-2, IRI, Vineland-II).
Zane et al. (41)	19/18	89/94%	Children and adolescents 12.8/12.11	ASD (ADOS-2)	HFA (Lieter-R/PPVT-4) 105–108/110–119	Dynamic human faces (Mind Reading corpus)	Facial Motion Capture (FACS)	Voluntary expression of joy, sadness, anger, fear, surprise, disgust		Medium	Quantity of facial movements was dependent on intensity but independent of expression type (unlike the control group), and more jerky and fleeting.

ABC, Autism Behavior Checklist; ABI, Autism Behavior Interview; ADI-R, Autism Diagnosis Interview-Revised; ADOS-2, Autism diagnosis observation schedule; AQ, Autism Quotient; AU, Action Units; CAM, Children's Alexithymia Measure; CESD, Center for Epidemiologic Studies Depression Scale; FEE, Facial Emotion Expression; FACS, Facial action coding system; GAF, Global Assessment of Functioning; GMDS, Griffith Mental Development Scales; HFA, High Functioning Autism; IQ, Intelligence Quotient; IRI, Interpersonal Reactivity Index; KBIT-2, Kaufman Brief Intelligence Test 2; Lieter-R, Lieter International Performance Scale-Revised; N, number of subjects; p, p-value; %, percentage; PPVT-4, Peabody Picture Vocabulary Test 4; SCQ, Social Communication Questionnaire; SRS-2, Social Reciprocity Scale 2; STAY-A, State Trait Anxiety Inventory; Vineland II, Vineland Adaptive Behavior Scale 2; WAIS, Wechsler Adult Intelligence Scale; WASI-II, Wechsler Abbreviated Scale Intelligence 2; WHOQOL, World Health Organization Quality of Life; WISC-IV, Wechsler Intelligence Scale for Children.

emotional content (46), free play in children (47), using auditory (48) or olfactory (49) stimuli, or during social interaction (50). Studies using the FACS method, EMG or subjective human measures reported that subjects with ASD expressed less frequent and shorter FEEs (47, 51, 52).

The study conducted by Trevisan et al. (38) aimed to analyze automatically the quantity of spontaneous facial expressions in children with ASD using the FACS-based FACET software. In response to videos with emotional content without social interaction, the FEEs of 17 children with high functioning autism (HFA) were compared to 17 controls matched in gender and intellectual functioning. Comparisons between groups with and without ASD found differences in the production of FEEs only for neutrality ($p\eta^2 = 0.15$, $p = 0.024$) but not for either positive or negative expressions. ASD children expressed more "neutral faces" than their typical peers. In addition, alexithymia scores were measured using the CAM scale (Children's Alexithymia Measure) and correlation analyses were performed with FEEs scores using covariates such as age, gender, intellectual functioning and ASD severity [Autism Spectrum Quotient (AQ)]. It was found that only alexithymia scores were predictive of the variance of spontaneous FEEs scores ($p < 0.001$, $R^2 = 0.346$). The authors suggested that the rarer spontaneous facial expressions leading to more "neutral" facial expressions in children with ASD described clinically, was more related to concomitant alexithymia than to ASD feature severity, as proposed in a previous literature review of studies without using automated facial recognition technology (53). Alexithymia may therefore be partly responsible for deficits in both FER (54) and FEEs in ASD.

This independency of spontaneous facial expression production from ASD traits was partly replicated in a second study with a larger sample of participants conducted by Bangerter et al. (25) using the same FACET software. This study focused on the expression of joy (action units 6 and 12) in response to humorous videos in a sample of adults and children with ASD. One hundred and twenty-four subjects with ASD with an intellectual quotient (IQ) > 60 and 41 subjects without ASD were included. The authors identified an "over-reactive" ASD subgroup that statistically presented more facial expressions of joy than the control group ($p < 0.01$, $r = 0.31$) and an "hypo-reactive" subgroup that statistically presented fewer facial expressions of joy than the control group ($p < 0.01$, $r = 0.31$) ($p < 0.001$, $r = -0.36$). No differences were found between the two subgroups in terms of IQ, severity of autistic symptoms (as measured by ADOS-2) or social skills (as measured by SRS-2), but the "hyper-reactive" subgroup differed from the "hypo-reactive" subgroup by a significantly higher ABI impulsivity score ($p < 0.05$, $r = 0.21$), while the hypo-reactive group was associated with higher social withdrawal according to the results of the Aberrant Behavior Checklist ABC ($p < 0.01$, $r = -0.3$). Consequently, the authors suggested that internalizing and externalizing symptoms associated with ASD and especially emotional regulation impairments may be more involved in spontaneous FEE deficits than autistic traits, as suggested in a previous study without the use of facial recognition technology (55).

TABLE 2 | Relevant reviews and meta-analyses.

Review/meta-analysis	Objective	Number of studies about FEE in ASD included	Results	Commentaries
Davies et al. (22)	Review and meta-analysis of spontaneous FEE assessment in non-psychotic psychiatric disorders	6 out of 39 (including 0 using new technologies)	- Alterations of FEEs in included psychiatric disorders, except for anxiety disorders (depression, eating disorders). - Studies looking at ASD partially confirm the overall decrease in spontaneous facial expression in this group.	Review on FEEs, but is not focused on ASD or new technologies
Deutsch et al. (42)	Review of FEE assessment in people with ASD and neurobiological and clinical implications	2 Using new technologies	- Addresses the neurobiological, neuroanatomical and pathophysiological mechanisms potentially involved in ASD emotion-processing abnormalities. - Production of FERs discussed in an interventional section involving the use of new technologies.	Key considerations around recognition of FEEs and visual scanning in ASD
Keating et al. (43)	Review of FEE and FER assessment in people with ASD	17 of which 1 used new technologies	- Differences in FEEs are found between typically developing people and people with ASD, with less frequent expressions which are judged to be lower in quality by evaluators without ASD. - It seems that alexithymia can contribute to these differences in emotion expressions.	Few studies using new technologies included
Trevisan et al. (19)	Meta-analysis of studies about FEE assessment in ASD	39 out of 39 (including 1 using new technologies)	Participants with ASD produce FEEs less often and for less time. Involuntary mimicry and voluntary imitations are more often inaccurate. FEEs are also considered to be lower in quality and less precise. However, emotions are not expressed less intensely, and spontaneous reaction times are not slower.	Includes all methods of FEE analysis
Vivanti et Hamilton (44)	Review of imitation abilities assessment in ASD		- Evaluation of motor imitation skills: body, manual, language, facial. - This review suggests that most people with ASD have more difficulty in imitating unfamiliar actions and without a clear goal. In addition, imitation performance appears to be less good as social demands increase.	Reviews imitation data but not just FEEs, does not address the use of new technologies

ASD, Autism Spectrum Disorder; FEE, Facial Emotion Expression; FER, Facial Emotion Recognition.

Quantitative Analysis of Spontaneous FEEs in Social Interactions

In social interactions, it is often reported that individuals with ASD fail to orient their facial expressions toward their partners and have less communicative intentions. It is also frequently claimed that children with ASD tend to exhibit facial expressions less frequently in a social interaction, while other reports have suggested that these facial expressions would be less socially congruent, i.e., less appropriate to the social context. Several studies using observer ratings found that compared to a control group, children with ASD were less likely to express FEEs oriented to their mothers or other adults during interactions (39, 56, 57).

A study by Owada et al. (36) tested the use of automated emotional facial recognition technology during social interactions as part of the ASD diagnosis process. The amount of basic FEEs of 18 Japanese adult males with HFA were compared to a group of 17 non-ASD adults matched for age, gender, parental socioeconomic level, and intellectual functioning. Their spontaneous facial expressions were recorded with the FACS-based Face Reader software during a semi-structured social interaction situation extracted from the ADOS employed specifically in this study. More facial expressions of neutrality ($d = 1.02$, $p = 0.005$) and less facial expressions of joy ($d = -0.78$, $p = 0.038$) were reported in the ASD group compared to the control group. There was also less variability in the quantity of these two expressions during the transition periods between tasks in the ASD group ($p = 0.03$). This study therefore suggested a reduced facial expressiveness in social interactions, reproducing the results previously reported during a non-social situation. However, the emotional inner states and clinical characteristics of individuals were not accounted for in this study.

Beside these results, spontaneous expressions during an interaction between children with ASD and a robot were also evaluated by Landowska et al. (33) with the same Face Reader software. Interactions with a robot are supposed to be less complex and alarming than human interactions, and therefore more easily accepted by children with ASD (58). The basic facial expressions of 11 children with ASD and 8 controls were monitored to assess the amount of facial expressions recognized as valid by the software according to FACS during an interaction with the robot. The results indicated that the children with ASD expressed significantly less sadness ($p = 0.002$) and disgust ($p = 0.01$) compared to children without ASD, but the quality of the methodology in this study was considered to be low and the results need replicating.

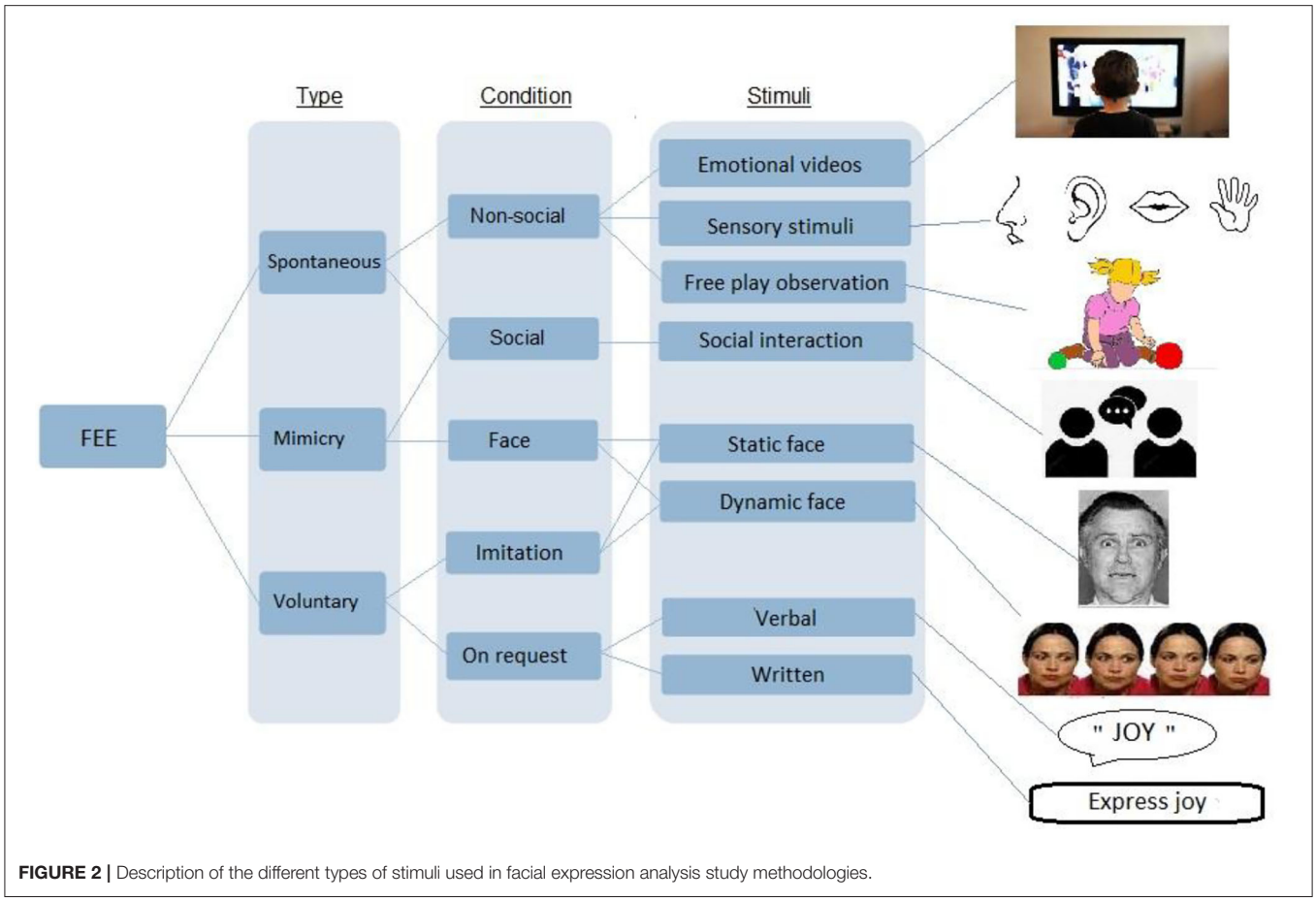

FIGURE 2 | Description of the different types of stimuli used in facial expression analysis study methodologies.

Taken together, the above findings are in favor of a greater neutrality of spontaneous facial expressions, corresponding to the clinical "amimia of the face" described in individuals with ASD in response to non-social and social environment. This spontaneous amimia seems to be partly more related to inner emotional states or the personal ability to identify these states rather than to the severity of ASD features.

Qualitative Analysis of Spontaneous FEEs

Studies that have evaluated the quality of spontaneous FEEs with traditional non-automated methods have found a decrease in the quality or precision of FEEs in subjects with ASD, leading to the notion that autistic and non-autistic faces may "speak a different language" when conveying emotion. In other words, a mismatch was suggested to occur between the emotion spontaneously produced by subjects with ASD and the emotion corresponding to the same situation that would be expressed by a subject without ASD. In line with this interpretation, numerous studies have reported that autistic individuals produce spontaneous expressions that are perceived as lower in quality, and rated as odd, stilted, or mechanical by non-autistic observers and experimenters (59–61). This would explain the feeling of strangeness or ambiguity reported by non-autistic individuals when interacting with an ASD peer. Although there is evidence that autistic and non-autistic individuals exhibit expressive differences, research has not yet identified what specifically is different about these facial expressions.

Several researchers have hypothesized that the final arrangement of facial features may have spatial differences between expressions produced by autistic and non-autistic individuals (e.g., one group might open their mouth further when smiling to express happiness). One can also ask whether there might be intergroup kinematic differences (e.g., when expressing happiness, one group might break into a smile more quickly or more briefly). Although autistic and non-autistic facial expressions could, in principle, differ in terms of spatial or kinematic features, to the best of our knowledge, traditional studies with human raters or EMG paradigms have not yet specifically aimed to assess the contributions of these two factors.

Our review of new technology literature found only one pilot study from Del Coco et al. published in 2017 that used a computer-based analysis of spontaneous facial expressions of joy, fear and sadness in 5 pre-school children with ASD compared to 5 age- and gender-matched controls in response to cartoon videos (29). The different action units mobilized during viewing were analyzed using a complex algorithm developed by the authors. The data were collected with a spatial analysis approach, in terms of "global mobilization" on one hand, and "hemi

part of the face mobilization" on the other (i.e., separating the upper and the lower part of the face) to compare the activation of the eye and mouth areas in both autistic and non-autistic individuals. The study concluded that non-ASD children express more complexity (calculated computationally with the average entropy) in the mobilization of their facial muscles in both the eye and mouth areas, compared to children with ASD, regardless of the emotion produced.

It was reported that facial expressions of individuals with ASD during a social interaction would also be less socially congruent, i.e., appropriate to the social context. To date, however, there is no study computing FEE quality during social interactions that reported consistent, non-subjective and accurate results. To our knowledge, no research based on new technologies has focused attention on the possible spatial and kinematic expressive differences between ASD and non-ASD individuals during a social interaction.

Automatic Facial Mimicry Analysis

The implicit, automatic and subconscious phenomenon of facial muscle activation in reaction to the observation of an emotional face is called "facial mimicry." This spontaneous facial behavior corresponds to an involuntary reproduction of interlocutor FEEs and is part of the global emotional contagion existing between partners during social interactions. It is supposed to facilitate both sharing and understanding of emotional signals (62). Studies of involuntary facial mimicry in ASD have mainly used electromyography. These have shown a delay (63) or a lower expression intensity (12), with undifferentiated muscle activation, when different types of emotions (anger or joy) are expressed (64, 65) or atypical and incongruent facial expression occurs in response to a presented stimulus (9, 66) in ASD individuals compared to TD peers.

According to our literature review, one pilot study, conducted by Samad et al. (37), used non-invasive 3D facial imaging technology to measure automatic facial mimicry in response to static Avatar faces presented on a computer screen. These authors proposed a new computer vision and data mining approach that was developed from curve-based geometric features of 3D facial data in order to discern the changes in facial muscle activations during mimicry. The program captured spatial information about the face that enabled detecting and quantifying subtle changes in facial expression based on the activation of different facial muscles. Eight participants with ASD and 8 controls aged 7 to 20 were included. In the group with ASD compared to the control group, a significant increase ($p = 0.049$) in the activation of the right *levator anguli oris* (lip elevator) muscle and a decreasing tendency ($p = 0.059$) in the activation of the left *levator anguli oris* were found to occur. These results should be interpreted with caution, however, because of the small size of the monitored sample, although the authors also noted an asymmetrical activation of the facial muscles of subjects with ASD that may contribute to the impression of oddity often reported during a social interaction. 3D imaging technology has the advantage of detecting facial muscle movements in a more detailed and subtle way. However, the analysis conducted in this study was on a static image of the participant and did not address dynamic aspects of FEEs.

Whereas, the phenomenon of facial mimicry is well-documented in non-ASD subjects, traditional studies without the use of new technologies that reported reduced mimicry in children and adults with ASD did not use paradigms based on "real time" social interactions or in ecological social contexts. This was due in part to a lack of the capability to measure dynamic facial expressions throughout the course of an interaction. On the other hand, automated facial analysis via new technologies provides a rapid, efficient and objective method for measuring in natural contexts the facial expressions and their coordination produced by participant partners during such interactions.

In 2020, Zampella et al. used computer-assisted automatic detection of FEEs to analyze more specifically the coordination of facial emotions during reciprocal social interaction (40). Twenty children with HFA and 16 matched controls participated in spontaneous conversations with their mothers and with non-familiar adults. Time-synchronized videos were analyzed, and the emotion of joy was recorded by the Open Face software for each of the interlocutors as well as the coordination of the child's expression of joy with that of the adult. Both child and adult partners exhibited less positive facial expressions during conversations when the younger participant had ASD compared with the same situation when the child participant did not have ASD ($p = 0.02$). Children with ASD also manifested a less effective coordination of facial expressions over the course of conversations ($p = 0.04$). The diminished coordination in ASD participants significantly predicted scores on measures of social skills, adaptive social skills, and empathy (Interpersonal Reactivity Index IRI, $p = 0.02$). The authors suggested that the weaker effective coordination and in particular the reduced smiling ability in children with ASD also affected the responses of the social partner, in particular when it was a stranger, therefore highlighting the impact of this interpersonal process in the success of social interaction. Moreover, these findings suggested that facial emotional reciprocity is linked to socio-emotional characteristics in ASD and suggests a promising novel method for the automated monitoring of facial expressions and emotional reciprocity during natural interactions.

Relationship Between Spontaneous FEE Production and Social Functioning in ASD

Research using traditional analytical paradigms have provided substantial evidence that spontaneous FEE capabilities are closely linked to successful social functioning (1), and have been reported as abnormal in frequency, duration and quality in individuals with ASD, whether performing social interaction tasks or not. Task-related factors (e.g., intensity, type of emotions or stimuli: statics or dynamics) and participant characteristics were reported to strongly influence facial expressions skills in both conditions: with and without social interaction (56).

Literature based on the use of new technologies has reported reduced spontaneous FEEs in tasks without social interactions and concluded that the deficits were related to clinical participant characteristics that were not linked to ASD symptoms. These

studies reported a qualitative and quantitative atypicality of FEEs that can be specified and detailed in ASD, in both spatial and kinematic aspects. This atypicality of autistic FEEs is associated with a greater expression of neutrality and asynchrony in facial expressions, which was also reported to occur during social interactions with a resultant impact on the latter' success.

It is possible that these atypical facial expressions are judged more negatively by an interlocutor and hinders the course of a social interaction or even the creation of social bonds, thereby worsening social experiences. In the study of Owada et al. (36), the intensity of the expression of neutrality was positively correlated with the reciprocal social interaction sub-score of the ADOS ($\rho = 0.48$, $p = 0.042$). This association in turn suggested that in ASD, a reduction in facial expressivity is associated with a deficit in *reciprocity* in social interaction skills. In the same idea, Zampella et al. reported significant correlations between poorer interaction coordination of FEEs in children with ASD during interactions and social reciprocity skills assessed by the SRS-2 score ($p = 0.02$) as well as in socio-adaptive skills assessed by the Vineland-II score ($p = 0.001$) (40). These correlations were maintained after adjusting for facial expressions intensity, indicating a relationship that is not only related to an overall reduction in facial expressivity in children with ASD. Their results further suggested that facial emotional coordination is an important process with implications for broader socio-emotional functioning in individuals with ASD and particularly for the reciprocity in social functioning. Deficits in spontaneous facial expression in people with ASD could thus be a major component of their deficit in reciprocity in social communication and interaction (19).

Analysis of Voluntary Facial Expression of Emotions

Studies of voluntary FEEs usually separate facial imitation (according to a model: photo, video, interlocutor) and the production of FEEs in response to verbal or written requests, with the latter involving the use of one's own mental representations of each emotion. Previous studies on the developmental course of imitation skills in children with ASD reported mixed evidences for imitation impairments in children (67), although a preserved production of voluntary FEEs, particularly in adults was observed, in contrast to the impairments in spontaneous facial expressions (9, 19, 63). The authors then suggested that voluntary facial expression imitation skills may improve with age in ASD, due to social experiences. According to our review of studies using new technologies, eight studies of voluntary FEE production have been identified.

Voluntary Facial Imitation

Facial imitation is the ability to reproduce the facial expression presented by another in a model. In most traditional studies including adults and children with ASD, FEEs were described as less "natural" or more "mechanical" or "weird" than the FEEs of individuals without ASD, although FEEs of autistics' were still recognizable by observers (15, 59, 68). ASD individuals had more difficulty in reproducing FEEs if the stimulus was dynamic (67), and no deficit was reported when ASD individuals were asked to imitate pictures of static emotional faces (9). The quality of the FEEs were also reported to be better in adults than in children with ASD (69).

Capriola-Hall et al. (28) using automated methods analyzed voluntary FEEs production in children with ASD in response to several types of dynamic stimuli. The FEET (Facial Emotion Expression Training) software used aimed at analyzing facial information in 3D using the Kinect system and automated facial emotion recognition was conducted in real-time to provide immediate corrective feedback. Three different types of stimuli were used, involving 3 "levels": videos of "cartoon faces" (level 1), videos of "human faces" (level 2) and finally, scenes without face, but eliciting emotion in participants (level 3). For each type of stimulus, the participant was instructed to imitate "With your face, show what I am feeling," to produce the expected emotion. The authors hypothesized that, depending on the different type of stimulus, children with ASD produce less accurate FEEs compared to their TD peers. An overall difference in the production of FEEs was found between both groups with and without ASD ($p = 0.008$). Children with ASD produced facial emotions more often classified as "error" than the control group. This difference ($p < 0.05$) was mainly observed when the stimuli were human faces, implying that people with ASD had more difficulties in reproducing dynamic real human faces, which are more complex than cartoon representations. However, the quality of the FEEs was not assessed in this study and none of the clinical characteristics were considered to adjust the results.

The same software and method (FEET) were used in a higher quality study conducted by Wiekowski et al. (39) among 20 children with HFA compared with 20 controls aged from 9 to 12 and included a procedure with human observers/raters to determine "proof of concept" of this interactive computer-assisted program. This study's aim was to analyze both facial emotion recognition (FER) scores (assessed with the NEPSY-II Facial Affect Recognition Test) and voluntary FEE productions, then to compare the two skills in ASD. The authors reported "atypical"- but "recognizable" - FEEs, in children with ASD for both cartoon and human stimuli. When comparing automated evaluation of FEE accuracy between groups, it was found that children with ASD were as accurate as their peers when they were asked to produce a specific, named emotion ($p = 0.54$, partial $\eta^2 = 0.01$). Children with ASD were also comparable to their TD peers when expressing emotions in response to both types of stimuli: a cartoon ($p = 0.27$, partial $\eta^2 = 0.03$) or a human face ($p = 0.59$, partial $\eta^2 = 0.01$). Children with ASD seemed to be less accurate at expressing an expected emotion in response to a scene without faces when the emotion was neither labeled nor modeled, although the difference was not significant ($p = 0.09$, partial $\eta^2 = 0.08$). The authors concluded that FEEs production appeared to have deteriorated in children with ASD when facial stimuli were removed, or when the cues were less obvious. In addition, on the basis of raters' measures, the authors reported a group difference in atypicality of FEEs, since the ASD group appeared to display more atypicality in expression across all levels of the stimulus presentations ($p < 0.01$). However, even though emotion recognition scores were lower in the group of children

with ASD as expected, no relationship was found between FER score and facial imitation scores.

Voluntary Emotional Facial Production on Request

Several conventional studies have suggested that individuals with ASD produce better voluntary FEEs when using an external model than on request, i.e., based on internal/mental representations (69, 70). Similarly, FEEs were less accurate when children with ASD were asked to display a facial expression without visual feedback, than with a mirror (71), thus providing evidence indicating that individuals with ASD rely on rule-based strategy when perceiving facial expression of emotions (72). In the absence of faces, children with ASD are no longer able to rely on such a rule-based strategy for emotional perception, resulting in a lowered accuracy (15, 59, 61, 68).

In 2019, Manfredonia et al. conducted a study including a large sample of both children and adults with HFA to evaluate their ability to produce FEEs specifically in response to a written request that did not involve a model (34). The FACET automatic facial expression analysis software was used to measure the *quality* of basic FEEs in 144 participants with ASD compared with 41 non-ASD participants. The activation of the two most representative Action Units (AU) for each emotion was recorded. Statistical analyses found significant differences ($p < 0.05$) between groups in the use of AU 12 (which mainly involves the expression of joy), AU 5 (mainly involved in fear and surprise), and AU 9 (involved in the expression of disgust). It should be noted, however, that the software's treatment of such a small number of action units could not accurately reflect either the accuracy of the FEEs or the quality itself, although potential atypicality or abnormality in voluntary activation of global facial muscle in ASD could be revealed.

Quality of Voluntary FEEs in ASD: What Is Atypical?

Traditional observer-based studies have failed to identify specific differences in autistic FEEs from the norm and the characteristics of FEEs responsible of the "atypicality" perceived by observers. However, through the use of new technology for motion capture with facial markers, Metallinou et al. (35) investigated more precisely the atypicality of autistic FEEs. Specifically, this study focused on the global synchronization of facial movements (35) through a facial imitation task with dynamic human faces in 21 children with HFA and 16 non-ASD children. The stimuli used were human faces expressing basic emotions taken from the Mind Reading Corpus, a video database for facial expression recognition training. The activation of a facial region, that can be measured by the intensity of movement that a given region undergoes during a facial expression, was analyzed and compared between the two groups. The results indicated a significantly reduced synchronization of motion between the upper and lower regions of the face ($p < 0.05$), and between each left/right hemiface in individuals with ASD (mouth: $p = 0.02$, eyebrow: $p = 0.01$) compared to non-ASD children. In this study, moreover, children with ASD were found to express rougher facial and head movements and especially in the lower face regions compared to typically developing (TD) children ($p < 0.02$). Complex statistical analysis also reported that children with ASD display a wider *variability* in motion intensity across facial regions compared to their TD peers, leading to idiosyncratic facial gestures that were mostly for complex expressions, such as the manifestation of joy.

These results were partly replicated in 2015 and then in 2018 by Guha et al. using motion capture analysis with the same stimuli (video clips of the six basic emotions) in a facial imitation task (31, 32). The 2015 study included 24 children with HFA and 21 controls (31). Facial Motion Capture software analyzed the whole face and eight facial sub-regions. As expected, the ASD group exhibited less efficient imitations than the control group ($p = 0.024$), especially for sadness, fear and disgust. The results also indicated differences ($p < 0.001$) in dynamic facial motions between the two groups, arising primarily from movements of the eyes. In addition, the symmetry between the right and left regions tended to be less, although this difference was not statistically significant ($p = 0.055$). Participants with ASD also produced less variability across facial regions in terms of strength of activation, leading to the conclusion that ASD subjects appear to have a less complex underlying mechanism generating facial expressions than their TD peers. This lack of complexity could at least partially explain the idiosyncratic facial motions in ASD, as perceived by TD observers. The overall differences were found to be more pronounced for negatively valenced emotions (fear, disgust, sadness), which are more likely to induce a higher perception of atypicality by observers.

In 2018 (32), the same authors questioned the clinical characteristics of their sample (20 Children with ASD and 19 TD children) and so to ensure a better group homogeneity they verified that each of the children included did not have cognitive and language disabilities, nor neurological, psychiatric or genetic co-morbidities. Differences between groups remained significant for the expressions of joy, sadness and disgust ($p < 0.05$), again observed specifically in the eye region, which exhibited most variability and complexity in the control group. The authors interpreted these findings in the context of the "eye avoidance" symptom that has been widely reported as an ASD clinical feature. They hypothesized that children with ASD may be unable to produce complex movements in the eye region, partly because of the lack of experience in perceiving and processing complex dynamic information from this region.

In 2019, Zane et al. also used Facial Motion Capture technology and the same stimuli to describe features concerning the intensity of facial expressions of emotions in individuals with ASD (41). Global facial muscle activations were recorded and subsequently analyzed using statistical growth curve analysis, in two groups of 19 children and adolescents with HFA and their TD peers, matched for age, gender, and verbal and non-verbal IQ. The authors tested whether the expression sub-type or clinical group could predict the patterns of muscle activation recorded. However, significant data were not found, and analysis failed to establish inter-group differences in terms of intensity of the FEEs produced. Contrary to previous findings, a higher variability in global muscle activations was reported in children with ASD compared to their non-ASD peers ($p < 0.0001$). Furthermore, in direct contrast to the control TD group where the pattern of facial muscle movement was positively correlated

with the valence of the imitated emotion, valence provided no indication of the activation pattern of the facial muscles in the ASD group.

Significantly also, a detailed analysis of global facial motion shape showed exaggerated peaks or short apexes in the motion pattern of the ASD group, suggesting the occurrence of extreme changes in facial configuration, marked by frequent, brief spurts of large displacement, which were not observed in TD facial expressions. The authors concluded that individuals with ASD had "rougher" FEEs than their peers without ASD. Short periods of large amplitude motion may then be one of the characteristics of idiosyncratic autistic facial expressions and could contribute to negative observer judgments of facial expression quality in ASD.

From the findings of Metallinou, Guha and Zane, it could be concluded that the patterns of facial activation by individuals with ASD are more abrupt and desynchronized, involving more peaks of motion while those of the control group are more subtle and variable, implying greater complexity. It should be noted, however, that a major limitation of motion capture technology relates to the use of facial markers that can inhibit or interact with voluntary facial expressions.

Grossard et al. (30) proposed a non-invasive method for characterizing facial movements during FEE production in a large sample of 37 children with ASD and 157 typically developing children aged from 6 to 12 year old, when performing various tasks (e.g., imitation of a dynamic Avatar face and production on verbal request), while controlling several potentially confusing variables. The latter included age, sex, intellectual functioning, cultural background and the emotion subtypes (joy, sadness, anger or neutral). The automated emotion recognition processing involved the tracking and pre-processing of 49 facial landmarks that encoded geometric deformations of the face. The facial landmarks selected corresponded to strategic points such as the mouth, corners of the eyes and nose tip. The automated tracking of these landmarks and analysis (measurement of distances between markers and their orientation) generated a set of features that were distinguishable from geometric (spatial distances between markers) and appearance ones (gradients of marker orientation). A learning machine approach using Random forest (RF) classifiers was then applied.

When training and testing were performed on ASD children, the model proposal led to a poorer performance than in TD children. The FEEs produced by children with ASD were reported to be more ambiguous than those of TD children, and according to the algorithm, TD and ASD individuals did not perform similarly, except for the expression of joy. For the latter, the RF classifier needed more facial landmarks to achieve the best classification in children with ASD compared to TD children, in particular for the mouth area. This requirement was related to a hypo-activation and a higher degree of variance in motion production recorded in the eye area of children with ASD. Consequently, the algorithm essentially used the mouth to identify joy in this group, which was then categorized along with the control group, although the apparent autistic features involved less activations of the eye area muscles and a greater asymmetry. Resolving this issue therefore requires more information (via additional markers) to ensure unambiguous feature extraction and classification.

In addition, the algorithm had further difficulties in distinguishing between positive and negative expressions and confused anger and joy, classifying anger as joy more frequently in children with ASD, indicating that they had difficulties in producing FEEs with clear emotional cues, leading to ambiguity. The authors highlighted the lack of a significant effect of age or gender, but there was a significant effect of IQ on the quality of children FEE productions. Children with ASD and a lower IQ produced less accurate FEEs than those with a normal IQ, in accordance with previous findings (19).

Consequences for Social Functioning

Negative correlations were found by Wieckowski et al. between face activation during the voluntary production of FEEs (number and type of AUs) and socio-communicative impairments, as assessed by social communication sub-scores of SRS-2 and ABI, after adjustment for age and IQ, which was especially relevant in the case of the youngest sample participants (<13 years old) (39). The authors advocated for early specific interventions targeting an improvement of the voluntary production of FEEs in young individuals with ASD, which could potentially impact their subsequent development of social and communication skills. However, caution should be taken when interpreting these findings, that have not been replicated from now and because null results may get unreported by other authors, the link between altered FEE and social deficit in ASD should be studied more specifically.

DISCUSSION

The Relevance of New Technology to Research on FEEs in ASD

The idea that people with ASD spontaneously express less frequent FEEs and of lower quality than their TD peers is widely accepted, and many screening and diagnostics tools for ASD include the items: "range of facial expression" or "inappropriate facial expressions," as one of the early signs of ASD (e.g., the Social Communication Questionnaire, Modified Checklist for Autism in Toddlers, Childhood Autism Rating Scale, Autism Diagnostic Interview). In the line of Owada et al. (36) protocol, who tested the use of automated emotional facial recognition technology during social interactions extracted from the ADOS protocol, automated assessment of FEE algorithms could improve the (early) detection of ASD and be part of standardized diagnosis protocols for children (during social interactions between young children and clinicians extracted from the ADOS protocol for Children and toddlers, or during free interaction sessions between young children with alert signs of ASD, for example). This more automatic assessment is not supposed to confirm diagnosis but could be an interesting tool to integrate into the protocols for a more standardized and quantitative diagnosis process. It is specifically interesting in young children presenting in clinical center before the age of 5 years with various symptoms of delay or deviance in general development, communication and language, social interaction, attention and activity level,

usually signaling an underlying neurodevelopmental disorder. New technology could participate to the effort of differentiate ASD, ADHD or complex and mixed NDDs, as facial expressions impairments (in contrary to facial recognition) seems to be unaffected in ADHD (73). Furthermore, it is important to promote future studies to assess the specific value of automated FEE analysis and to directly compare the accuracy of using manual human coding and computer-assisted analysis in early stage of screening process, in infants with high risk of ASD (siblings), as identification of potential prodromal symptoms of ASD.

However, research using new technologies aiming to more specifically characterize atypical autistic FEEs have reported quantitative and qualitative differences. Such approaches have found that individuals with ASD spontaneously manifest more neutral expressions (36, 38) and less expressions of joy (25, 36) than non-ASD subjects. This is consistent with the results from traditional FEEs studies, with the idea that people with ASD display less facial expressions than their peers, described as "amimia" in clinical reports (19). However, studies using new technology have highlighted factors that potentially influence spontaneous FEE productions in ASD individuals, specifically including symptoms of alexithymia (38), depression (22), and impulsivity (40), in addition to traditional factors such as age and IQ that have been usually reported in earlier studies (19). Alexithymia is characterized by difficulties in identifying, expressing, and naming emotions. Recent evidence suggests that, among both autistic and non-autistic populations, alexithymia may be implicated in a decrease in production of facial expressions. Approximately 50% of the autistic population experiences co-occurring alexithymia (56) compared to 14% of the non-ASD population (56), which is in line with the "alexithymia hypothesis" that postulates that most difficulties in emotion processing in ASD are caused by co-occurring alexithymia, rather than ASD itself (53). These results are also consistent with findings reported in populations without ASD (74).

Moreover, the literature based on the use of new technologies suggests that although a reduction in spontaneous FEE seems to be related to non-ASD clinical characteristics, a qualitative atypicality of FEEs can be identified and detailed in ASD concerning both spatial and kinematic aspects. More precisely, spontaneous FEEs in autistic individuals were found to be less complex (29), more asymmetrical (37) and less coordinated with interlocutor expressions (40). These qualitative characteristics are in part responsible for the judgment of ambiguity or oddity frequently reported by non-ASD observers and seems to worsen specifically the reciprocity component of social interaction, although these findings were obtained from relatively small samples. Future research is therefore needed to more fully characterize the spatial and kinematic expressive differences between ASD and non-ASD individuals in order to better train clinicians to "read" autistic facial expressions and to facilitate more successful social interactions early in development.

Data in the traditional literature reported that voluntary FEEs are less congruent with expected emotions or considered as less natural and odder (19) in ASD. Using computer-based emotion recognition approaches, more recent studies have objectively demonstrated FEE atypicality during various tasks such as facial imitation (28, 30, 39) or facial production without a model (34) in children with ASD. Thus far, however, research on FEE production in ASD has been almost exclusively being oriented to group comparisons between individuals with and without ASD, but the mechanisms and characteristics of FEEs that contributing to the observer's judgment of abnormality, atypicality or ambiguity have received less attention. Facial Motion Capture technologies have led to advances in the description of spatial and kinematic characteristics of atypical FEEs, revealing an asynchrony (31, 35) and a decreased degree of complexity of facial muscle activations in individuals with ASD (35, 41), particularly significant in the eye area (31, 32). This is consistent with the "eye contact avoidance hypothesis," whereby children with ASD make rarer eye contact compared to TD peers, and therefore experience limited access to the "good model" of FEEs. The specific role of the eye region in the screening strategy on human faces has been mainly documented in TD individuals and concerns all domains of face recognition (e.g., emotions, gender or familiarity recognition) as well as its strong implication in ASD recognition impairments (75, 76). In light of these recent results, therefore, the eye avoidance hypothesis has provided a plausible explanation, not only for face recognition deficits (77, 78) but also for facial emotional production abnormalities in ASD.

Recent findings have also highlighted the role of specific action units such as AU 12, AU 5, and AU 9 in the judgment of ambiguity or the specificity of the emotion of joy, which is responsible for a high level of variability in the corresponding production of FEEs in children with ASD (34). New approaches based on the global and local analysis of facial motion have reported exaggerated peaks or short apexes in patterns of facial activation that lead to more abrupt and desynchronized expressions. These extreme changes in facial configuration, marked by frequent, brief spurts over large distances and mostly observed in the eye area, seem to be closely involved in the idiosyncrasy of autistic FEEs. These new results were replicated by Grossard et al. (30) with a mixed approach that included human raters and an innovative computerized method based on machine learning. The findings supported the hypothesis that people with ASD do not share a specific way to produce FEEs, but produce numerous variable patterns that account for the difficulty of non-ASD observers to recognize autistic facial expressions (15).

This variability in facial motion in ASD is consistent with a body of current literature that indicates a high heterogeneity in the general movement and motor profiles of individuals with ASD (79), suggesting that they move quite differently from both non-autistic individuals and other individuals with ASD. An interpretation of movement (either facial or global) can only be formulated when our interaction partner is someone who usually moves in a similar way to ourselves. Thus, movement interpretation and the resulting social interaction in autistic-autistic peers may not be any better than between autistic and non-ASD peers. This suggests that the "social deficits" in individuals with ASD could reflect, or be a consequence

of, a *mismatch* in movement profiles between ASD and non-ASD (or other ASD) individuals (43). The "non-consistency" in facial motion of individuals with ASD therefore prevents the interlocutor from inferring emotional states and intentions on the basis of FEEs during social interactions.

In line with these findings, some authors have argued that impairments in voluntary FEEs in ASD indicates a degree of dysfunction in the sensorimotor processing that allows the coupling between perception and action. This coupling underlies embodied representations of emotions, the mechanistic basis of empathy in humans that relies on the human mirror neuron system (MNS) (10, 62). The human MNS is defined as a network of brain regions which are active both when participants perform an action and when they observe another person performing the same action (7). From numerous fMRI studies using emotional stimuli, the dominant theory of MNS function is based on a direct-matching model in which observed actions are directly mapped onto the observers own motor system (80). This broader mirror neuron network incorporates the somatosensory and premotor cortex and possibly the anterior insula [for a review see Hamilton (10)]. A dysfunction of the MNS may be a causal factor in poor social cognition in ASD and is commonly called the broken mirror theory (BMT) of autism. The simulation version of the broken mirror theory derives from the idea that the MNS provides the basis for simulating other people. Such simulation could apply to actions, but also to emotions and mental states. The second version of the BMT, called the chaining version, is a more subtle hypothesis based solely on the idea that some mirror neurons represent action chains or sequences, and suggests that the comprehension and production of action and emotional expression sequences is abnormal in ASD (81). Automated assessment of voluntary FEEs in ASD has provided new evidence for abnormality in the sequence of muscle activation (spatial and kinematic chain motion dysfunctions) (31, 32, 35) and for an impact on interlocutor behavior during social interaction. This is in line with both versions of the BMT in ASD, even though over two decades of research the broken mirror theory of autism is still debated.

Until now, FMRI studies that have examined mirroring responses to emotional stimuli in ASD on the basis of emotional facial viewing tasks, have provided a mixed picture, with some results suggesting a clear deficit (82), whereas others have shown normal responses under neutral or instructed task conditions (83). Group differences emerged in brain regions associated with theory of mind, but not in the inferior frontal cortex, the core component of the human MNS. In particular, both autistic and non-autistic participants engaged the inferior frontal gyrus (IFG) of the left hemisphere when instructed to attend to their own emotions, and the authors concluded that participants with ASD can engage their MNS when the task requires latter. The chaining broken mirror theory claims that these simple actions do not require chaining, whereas the production and comprehension of more complex action sequences, such as facial emotion, does require chaining which would be abnormal in ASD. Evidence relevant to the chaining theory can also be found in studies of motor control and action understanding. Individuals with autism often present comorbid dyspraxia or other motor control difficulties (84, 85), and these could be accounted for by difficulties in action chaining. Together, these findings from cognitive neuroscience and psychology suggest that perceptual systems for facial expression recognition are linked with motor as well as somatosensory feedback systems, with motor production playing an important role in the development of perceptual recognition abilities (86, 87).

Some hypothesized that atypical FEEs could also be attributable to global neuromuscular dysfunctions (i.e., not just facial muscle coordination problem) as evidences of muscles tones abnormalities in ASD were reported in the literature (88), or directly linked to face recognition deficit and/or global Biological Motion (BM) perception impairment in ASD, in line with the Mirror Neuron System (MNS) impairment theory in ASD. This hypothesis is in accordance to various studies that reported reduced ability in extracting social information from global Biological Motion, in ASD (89, 90). More recent results of a meta-analysis on global motion perception in ASD reported as well overall differences between ASD and non-ASD individuals in global motion processing with a general decreased performance in detecting or recognizing global motion patterns in perception paradigms including social but also non-social stimuli (91). Future studies, in line with Yeung et al. (92) should focus on relation between FEE, Facial Emotion Recognition (FER), global facial perception (part of BM) and global motion perception.

New Technology for Clinical Practice

Advances in automated facial expression recognition technology should open new avenues toward clinical interventions that target these deficits. The development of such interventions based on facial expression production would be further enhanced by extending expression recognition technology to provide real-time feedback from to a subject's own facial expressions. On the basis of recent findings using this new technology, evidence suggests that practice with expression production may not only influence production itself, but may also influence perception due to possible associations between recognition and motor production, as illustrated by rare previous results obtained in non-ASD children (93, 94). Only a few studies have focused on the relationship between learning in facial motor production and learning in facial expression perception, challenging the hypothesis that motor production contributes to perceptual improvement. Further work is now necessary to test the perception-action learning and action chaining theories. Advances in these areas will lead to a better understanding of what is really different about action systems in autism, which in turn should lead to more productive interventions that help individuals with autism to imitate and interact with the social world.

Overall, this review highlights the finding that automated facial expression analysis has an efficiency equivalent to human observation rating or EMG measurements (28, 30) while being more objective, precise and less consuming in time, material, and human constraints. This has direct implications in clinical practice through this technology's potential participation with FEE computer-based analysis in the ASD diagnosis process, in line with Owada's approach (36).

ASD is an heterogeneous condition, with significant risks of added co-morbidities (95) that in call for individualization both in the initial evaluation process and in terms of socio-emotional supports. Additionally, a voluntary adaptation of facial expressions is reported to be frequently used in daily life by individuals with ASD, mainly in subjects without intellectual deficits and females (96). Self-training of their own voluntary FEEs is reported to be a strategy for compensating ("social camouflage") for associated socio-communicational deficits. However, this requires significant effort, which could be at the origin of increased stress levels and higher levels of anxiety in subjects with ASD (97).

From our literature review, it is evident that machine learning technology may provide promising advances to individualized care (30), and offer a promising tool to support the learning process related to emotion production and correction. The inclusion of individualized computer feedback could be part of a global support strategy that could be proposed as early as possible to children with ASD, in order to diminish stress and emotional co-morbidity in later adulthood (95).

In addition, until recently, studies on the field seemed "to ignore the fact that social interactions are exactly that, an interaction between individuals," as reported by Keating, in his recent review (43). This review focused on the "bidirectional" approach to evaluate social interactions that leads to a consideration of both sides of the interaction and discussed the small amount of research investigating non-ASD individuals' recognition of autistic expressions of emotion. Evidences that non-ASD individuals shown difficulties in recognizing ASD facial expressions are recent and rare (15, 59), but as proposed by some authors (43, 98) as social interaction is bi-directional, non-ADS individuals' recognition of autistic expressions may contribute to social interaction deficit and could be a target for future interventions. 3D sensor cameras such as Microsoft Kinect™ and the newer Intel RealSense™ received recently, much attention due to its advantages in capturing fine-grained skeleton and facial landmark data in contexts closer to real-life, providing motion facial data for more accurate analysis (35) than human observers (98). Some new recent findings and a pilot study proposed the integration of a naturalistic multi-sensory environment through the use of portable technologies including automatic facial expression recognition to help non-ASD individuals to read the emotions of children with ASD (99). Authors focused on training individuals without ASD to recognize the expressions posed by 6 children with ASD, with the use of a Kinect camera and the programmable and portable RealSense camera when viewing cartoons. More research, which formally uses a control group in their statistical comparisons, is necessary to develop this interesting approach.

Limitations of the Review

Even though there is consensual interest in the use of new technologies for research on individuals with ASD, this review has highlighted the current limited number of studies, which have mostly been pilot studies or with small sample sizes. Moreover, the methodologies and tools employed in these studies were highly heterogeneous, with results rarely replicated and the quality relatively low (low or medium scores for 66% of the studies), making the conclusions difficult to generalize. It is therefore necessary to replicate these results with larger samples, including matched control groups (in terms of age, IQ, gender and alexithymia). However, the increasing number of studies, mostly published in the last 2 years, suggests that new valid proposals and data will emerge in the near future.

In addition, future studies need to consider participant characteristics factors. First, intellectual functioning has not been consistently assessed, with studies to date having mostly included individuals with high functioning autism only. Accordingly, the majority of the findings reviewed may not be generalizable to individuals with ID. Secondly, as widely reported and relative to the neurodevelopmental aspect of ASD, age is a factor that strongly influences the ability to produce FEE (19). Studies have often chosen to include only children or adults, but it would be instructive to conduct longitudinal studies to better address the developmental course of FEE skills and capability. Furthermore, gender differences in emotional expression have been reported in typically developing children (100) and the effect of gender on autistic symptomatology is an issue raised by many authors (101), and is therefore a factor which also needs to be considered in studies of FEEs in individuals with ASD. Moreover, only a few studies considered symptoms of depression, alexithymia, level of empathy and emotional regulation abilities, despite an impact of these participant characteristics on FEEs (22, 25, 38, 40). Thus, the identification of subgroups of individuals with ASD, as proposed in recent studies using automatic FEE detection (25, 41), may help to explain some of the conflicting findings in the traditional literature. The inherent heterogeneity of ASD and expression of autistic symptoms, including the idiosyncratic production of FEEs, must be taken into account to better interpret the results of clinical research.

Moreover, most studies in the field of new technologies have focused on the technological development of software rather than on their clinical application, and have tended to be reported in journals specializing in computer science or engineering, which perhaps does not promote accessibility to the wider experimental research and clinical community. Although several recent studies have found that individuals with ASD display a good acceptance and interest in technology-based interventions (102), there is still little proof of concept, and only a few researchers have tested their approaches and the efficacy of computer-based FEE training on social and perceptual clinical functions. Translational approaches must also be further developed to convince clinicians, and promising tools should be tested using methodologies that are accepted by both clinicians and researchers alike, so that they can be more widely applied.

Limitations in the Use of New Technology

The use of new technologies to analyze the production of FEEs in people with ASD is a promising avenue, both in terms of gaining fundamental neurobiological knowledge of emotion processing and also in the study of learning and plasticity in perception and production systems. Such innovative technology could contribute not only to potential new therapeutic approaches to support social impairments in ASD, but also to train and support

caregivers and clinicians to "read the language" of autistic facial expressions that might be lead to a reduction in bidirectional socio-communicative difficulties.

Nevertheless, the ethical question of computer and robotic usage arises in the field of health care, particularly regarding automated facial recognition. The protection of private data represents a challenge in the health field and more particularly when data requiring subject identification is involved, as with facial recognition measures (103). Consequently, the employment of these approaches requires special attention to be paid to ensuring patient information confidentiality and consent, as well as the implementation of rigorous procedures to ensure the security of computerized health data storage.

CONCLUSION

Most research focusing on facial emotion processing in ASD has emphasized facial emotion recognition differences, and only a few studies have addressed features of the actual production of FEEs in individuals with ASD, despite its major role in social functioning (1, 12). Most traditional studies conducted over the past few decades have agreed that ASD individuals exhibit more atypical or less frequent spontaneous and voluntary FEEs (19). Recent studies using new technologies have proposed advances in the categorization and description of "what is abnormal" in autistic FEEs, through spatial and kinematic computer-based analytical approaches. Current results indicate (i) that participant characteristics are strongly implicated in spontaneous FEE production, as age, IQ, but also symptoms of alexithymia depression, and impulsivity (ii) that asynchrony and deficits in eye region activation could be specifically involved in the abnormal production of voluntary FEEs and feelings of "strange faces" in non-ASD individuals, contributing to deficit in social reciprocity, (iii) that atypical FEEs may be attributable or linked to global Face Recognition deficit and/or global Biological Motion (BM) perception impairment in ASD as well as sensorimotor processing impairments in line with the Mirror Neuron System (MNS) impairment theory in ASD. Some new recent findings based on portable technologies that permit the integration of a naturalistic multi-sensory environment recording, including automatic facial expression recognition, are promising tool to address the issue of FEEs impairments in ASD, in a global, bidirectional approach that leads to a consideration of both sides of the interaction to explore also how non-ASD individuals may be trained to the ASD atypical affective expressions recognition.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

KB and AA: conception of the review, analysis and interpretation of data for the work. AP and MB: contributed to manuscript revision and provided approval for publication of the content. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.634756/full#supplementary-material

REFERENCES

1. Nowicki S, Duke MP. Individual differences in the nonverbal communication of affect: the diagnostic analysis of nonverbal accuracy scale. *J Nonverbal Behav.* (1994) 18:9–35. doi: 10.1007/BF02169077
2. American Psychiatric Association, American Psychiatric Association, éditeurs. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. Washington, D.C: American Psychiatric Association (2013). 947 p.
3. Harms MB, Martin A, Wallace GL. Facial emotion recognition in autism spectrum disorders: a review of behavioral and neuroimaging studies. *Neuropsychol Rev.* (2010) 20:290–322. doi: 10.1007/s11065-010-9138-6
4. Uljarevic M, Hamilton A. Recognition of emotions in autism: a formal meta-analysis. *J Autism Dev Disord.* (2013) 43:1517–26. doi: 10.1007/s10803-012-1695-5
5. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule—generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord.* (2000) 30:205–23. doi: 10.1023/A:1005592401947
6. Rutter M, Le Couteur A, Lord C. *ADI-R: Autism Diagnostic Interview-Revised : Manual*. Los Angeles, CA: Western Psychological Services (2008).
7. Rizzolatti G, Craighero L. The mirror-neuron system. *Annu Rev Neurosci.* (2004) 27:169–92. doi: 10.1146/annurev.neuro.27.070203.144230
8. Singer T, Leiberg S. Sharing the emotions of others: the neural bases of empathy. In: Gazzaniga MS, editor. *The Cognitive Neurosciences IV*. Cambridge, MA: MIT Press (2009). p. 971–84.
9. McIntosh DN, Reichmann-Decker A, Winkielman P, Wilbarger JL. When the social mirror breaks: deficits in automatic, but not voluntary, mimicry of emotional facial expressions in autism. *Dev Sci.* (2006) 9:295–302. doi: 10.1111/j.1467-7687.2006.00492.x
10. Hamilton AF de C. Reflecting on the mirror neuron system in autism: a systematic review of current theories. *Dev Cogn Neurosci.* (2013) 3:91–105. doi: 10.1016/j.dcn.2012.09.008
11. Coles N, Larsen J, Lench H. A meta-analysis of the facial feedback literature: effects of facial feedback on emotional experience are small and variable. *Psychol Bull.* (2019) 145:610–51. doi: 10.1037/bul0000194
12. Stel M, van den Heuvel C, Smeets RC. Facial feedback mechanisms in autistic spectrum disorders. *J Autism Dev Disord.* (2008) 38:1250–8. doi: 10.1007/s10803-007-0505-y
13. Pitcher D, Garrido L, Walsh V, Duchaine BC. Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *J Neurosci.* (2008) 28:8929–33. doi: 10.1523/JNEUROSCI.1450-08.2008
14. Losh M, Capps L. Understanding of emotional experience in autism: insights from the personal accounts of high-functioning children with autism. *Dev Psychol.* (2006) 42:809–18. doi: 10.1037/0012-1649.42.5.809
15. Brewer R, Biotti F, Catmur C, Press C, Happé F, Cook R, et al. Can neurotypical individuals read autistic facial expressions? Atypical production of emotional facial expressions in autism spectrum disorders. *Autism Res.* (2016) 9:262–71. doi: 10.1002/aur.1508
16. Love SR. *Recognition and production of facial emotion by autistic children* (LSU Historical Dissertations and Theses). (1993). p. 227. Available online at: https://digitalcommons.lsu.edu/gradschool_disstheses/5527

17. Sasson NJ, Faso DJ, Nugent J, Lovell S, Kennedy DP, Grossman RB. Neurotypical peers are less willing to interact with those with autism based on thin slice judgments. *Sci Rep.* (2017) 7:40700. doi: 10.1038/srep40700
18. Paul A, Gallot C, Lelouche C, Bouvard MP, Amestoy A. Victimisation in a French population of children and youths with autism spectrum disorder: a case control study. *Child Adolesc Psychiatry Ment Health.* (2018) 12:48. doi: 10.1186/s13034-018-0256-x
19. Trevisan DA, Hoskyn M, Birmingham E. Facial expression production in autism: a meta-analysis. *Autism Res.* (2018) 11:1586–601. doi: 10.1002/aur.2037
20. Nemiah JC. Alexithymia. Theoretical considerations. *Psychother Psychosom.* (1977) 28:199–206. doi: 10.1159/000287064
21. Wagner H, Lee V. Alexithymia and individual differences in emotional expression. *J Res Pers.* (2008) 42:83–95. doi: 10.1016/j.jrp.2007.04.001
22. Davies H, Wolz I, Leppanen J, Fernandez-Aranda F, Schmidt U, Tchanturia K. Facial expression to emotional stimuli in non-psychotic disorders: a systematic review and meta-analysis. *Neurosci Biobehav Rev.* (2016) 64:252–71. doi: 10.1016/j.neubiorev.2016.02.015
23. Ekman P, Friesen WV. Measuring facial movement. *J Nonverbal Behav.* (1976) 1:56–75. doi: 10.1007/BF01115465
24. Goldsmith T, Leblanc L. Use of technology in interventions for children with autism. *J Early Intens Behav Interv.* (2004) 1:166. doi: 10.1037/h0100287
25. Bangerter A, Chatterjee M, Manfredonia J, Manyakov NV, Ness S, Boice MA, et al. Automated recognition of spontaneous facial expression in individuals with autism spectrum disorder: parsing response variability. *Mol Autism.* (2020) 11:31. doi: 10.1186/s13229-020-00327-4
26. Doveling K, Scheve C von, Konijn EA (editors). *The Routledge Handbook of Emotions and Mass Media*. New York, NY: Routledge (2010). p. 437. doi: 10.4324/9780203885390
27. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097
28. Capriola-Hall NN, Wieckowski AT, Swain D, Tech V, Aly S, Youssef A, et al. Group differences in facial emotion expression in autism: evidence for the utility of machine classification. *Behav Ther.* (2019) 50:828–38. doi: 10.1016/j.beth.2018.12.004
29. Del Coco M, Leo M, Carcagnì P, Spagnolo P, Mazzeo PL, Bernava M, et al. A computer vision based approach for understanding emotional involvements in children with autism spectrum disorders. In: *2017 IEEE International Conference on Computer Vision Workshops (ICCVW)*. (2017). p. 1401–7.
30. Grossard C, Dapogny A, Cohen D, Bernheim S, Juillet E, Hamel F, et al. Children with autism spectrum disorder produce more ambiguous and less socially meaningful facial expressions: an experimental study using random forest classifiers. *Mol Autism.* (2020) 11:5. doi: 10.1186/s13229-020-0312-2
31. Guha T, Yang Z, Ramakrishna A, Grossman RB, Hedley D, Lee S, et al. On quantifying facial expression-related atypicality of children with autism spectrum disorder. In: *2015 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*. (2015). p. 803–7.
32. Guha T, Yang Z, Grossman RB, Narayanan SS. A computational study of expressive facial dynamics in children with autism. *IEEE Trans Affect Comput.* (2018) 9:14–20. doi: 10.1109/TAFFC.2016.2578316
33. Landowska A, Robins B. Robot eye perspective in perceiving facial expressions in interaction with children with autism. In: Barolli L, Amato F, Moscato F, Enokido T, Takizawa M, editors. *Web, Artificial Intelligence and Network Applications*. Cham: Springer International Publishing (2020). p. 1287–97. (Advances in Intelligent Systems and Computing). doi: 10.1007/978-3-030-44038-1_117
34. Manfredonia J, Bangerter A, Manyakov NV, Ness S, Lewin D, Skalkin A, et al. Automatic recognition of posed facial expression of emotion in individuals with autism spectrum disorder. *J Autism Dev Disord.* (2019) 49:279–93. doi: 10.1007/s10803-018-3757-9
35. Metallinou A, Grossman RB, Narayanan S. Quantifying atypicality in affective facial expressions of children with autism spectrum disorders. In: *2013 IEEE International Conference on Multimedia and Expo (ICME)*. (2013). p. 1–6.
36. Owada K, Kojima M, Yassin W, Kuroda M, Kawakubo Y, Kuwabara H, et al. Computer-analyzed facial expression as a surrogate marker for autism spectrum social core symptoms. *PLoS ONE.* (2018) 13:e0190442. doi: 10.1371/journal.pone.0190442
37. Samad MD, Bobzien JL, Harrington JW, Iftekharuddin KM. Analysis of facial muscle activation in children with autism using 3D imaging. In: *2015 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*. (2015). p. 337–42.
38. Trevisan DA, Bowering M, Birmingham E. Alexithymia, but not autism spectrum disorder, may be related to the production of emotional facial expressions. *Mol Autism.* (2016) 7:46. doi: 10.1186/s13229-016-0108-6
39. Wieckowski AT, Swain DM, Abbott AL, White SW. Task dependency when evaluating association between facial emotion recognition and facial emotion expression in children with ASD. *J Autism Dev Disord.* (2019) 49:460–7. doi: 10.1007/s10803-018-3712-9
40. Zampella CJ, Bennetto L, Herrington JD. Computer vision analysis of reduced interpersonal affect coordination in youth with autism spectrum disorder. *Autism Res.* (2020) 13:2133–42. doi: 10.1002/aur.2334
41. Zane E, Yang Z, Pozzan L, Guha T, Narayanan S, Grossman RB. Motion-capture patterns of voluntarily mimicked dynamic facial expressions in children and adolescents with and without ASD. *J Autism Dev Disord.* (2019) 49:1062–79. doi: 10.1007/s10803-018-3811-7
42. Deutsch S, Raffaele C. Understanding facial expressivity in autism spectrum disorder: an inside out review of the biological basis and clinical implications. *Progr Neuro Psychopharmacol Biol Psychiatry.* (2018) 88:401–17. doi: 10.1016/j.pnpbp.2018.05.009
43. Keating CT, Cook JL. Facial expression production and recognition in autism spectrum disorders: a shifting landscape. *Child Adolesc Psychiatr Clin N Am.* (2020) 29:557–71. doi: 10.1016/j.chc.2020.02.006
44. Vivanti G, Hamilton A. Imitation in autism spectrum disorders. In: Volkmar FR, Paul R, Rogers SJ, Pelphrey KA, editors. *Handbook of Autism and Pervasive Developmental Disorders*. Vol. 1. Hoboken, NJ: John Wiley & Sons, Inc. (2014). p. 278–301. doi: 10.1002/9781118911389.hautc12
45. Bond C, Woods K, Humphrey N, Symes W, Green L. Practitioner review: the effectiveness of solution focused brief therapy with children and families: a systematic and critical evaluation of the literature from 1990-2010. *J Child Psychol Psychiatry.* (2013) 54:707–23. doi: 10.1111/jcpp.12058
46. Weiss EM, Rominger C, Hofer E, Fink A, Papousek I. Less differentiated facial responses to naturalistic films of another person's emotional expressions in adolescents and adults with high-functioning autism spectrum disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* (2019) 89:341–6. doi: 10.1016/j.pnpbp.2018.10.007
47. Czapinski P, Bryson S. 9. Reduced facial muscle movements in Autism: Evidence for dysfunction in the neuromuscular pathway? *Brain Cogn.* (2003) 51:177–9. doi: 10.1016/S0278-2626(02)00541-9
48. Sterling L, Munson J, Estes A, Murias M, Webb SJ, King B, et al. Fear-potentiated startle response is unrelated to social or emotional functioning in adolescents with autism spectrum disorders. *Autism Res.* (2013) 6:320–31. doi: 10.1002/aur.1289
49. Legiša J, Messinger DS, Kermol E, Marlier L. Emotional responses to odors in children with high-functioning autism: autonomic arousal, facial behavior and self-report. *J Autism Dev Disord.* (2013) 43:869–79. doi: 10.1007/s10803-012-1629-2
50. Kasari C, Sigman M, Mundy P, Yirmiya N. Affective sharing in the context of joint attention interactions of normal, autistic, and mentally retarded children. *J Autism Dev Disord.* (1990) 20:87–100. doi: 10.1007/BF02206859
51. Snow ME, Hertzig ME, Shapiro T. Expression of emotion in young autistic children. *J Am Acad Child Adoles Psychiatry.* (1987) 26:836–8. doi: 10.1097/00004583-198726060-00006
52. Capps L, Kasari C, Yirmiya N, Sigman M. Parental perception of emotional expressiveness in children with autism. *J Consult Clin Psychol.* (1993) 61:475–84. doi: 10.1037/0022-006X.61.3.475
53. Bird G, Cook R. Mixed emotions: the contribution of alexithymia to the emotional symptoms of autism. *Transl Psychiatry.* (2013) 3:e285. doi: 10.1038/tp.2013.61
54. Cook R, Brewer R, Shah P, Bird G. Alexithymia, not autism, predicts poor recognition of emotional facial expressions. *Psychol Sci.* (2013) 24:723–32. doi: 10.1177/0956797612463582
55. Richey JA, Damiano CR, Sabatino A, Rittenberg A, Petty C, Bizzell J, et al. Neural mechanisms of emotion regulation in autism spectrum

disorder. *J Autism Dev Disord.* (2015) 45:3409–23. doi: 10.1007/s10803-015-2359-z
56. Berthoz S, Hill EL. The validity of using self-reports to assess emotion regulation abilities in adults with autism spectrum disorder. *Eur Psychiatry.* (2005) 20:291–8. doi: 10.1016/j.eurpsy.2004.06.013
57. Salminen JK, Saarijärvi S, Äärelä E, Toikka T, Kauhanen J. Prevalence of alexithymia and its association with sociodemographic variables in the general population of Finland. *J Psychosom Res.* (1999) 46:75–82. doi: 10.1016/S0022-3999(98)00053-1
58. Pennisi P, Tonacci A, Tartarisco G, Billeci L, Ruta L, Gangemi S, et al. Autism and social robotics: a systematic review. *Autism Res.* (2016) 9:165–83. doi: 10.1002/aur.1527
59. Faso DJ, Sasson NJ, Pinkham AE. Evaluating posed and evoked facial expressions of emotion from adults with autism spectrum disorder. *J Autism Dev Disord.* (2015) 45:75–89. doi: 10.1007/s10803-014-2194-7
60. Grossman RB, Edelson LR, Tager-Flusberg H. Emotional facial and vocal expressions during story retelling by children and adolescents with high-functioning autism. *J Speech Lang Hear Res.* (2013) 56:1035–44. doi: 10.1044/1092-4388(2012/12-0067)
61. Macdonald H, Rutter M, Howlin P, Rios P, Conteur AL, Evered C, et al. Recognition and expression of emotional cues by autistic and normal adults. *J Child Psychol Psychiatry.* (1989) 30:865–77. doi: 10.1111/j.1469-7610.1989.tb00288.x
62. De Jaegher H. Embodiment and sense-making in autism. *Front Integr Neurosci.* (2013) 7:15. doi: 10.3389/fnint.2013.00015
63. Oberman LM, Winkielman P, Ramachandran VS. Slow echo: facial EMG evidence for the delay of spontaneous, but not voluntary, emotional mimicry in children with autism spectrum disorders. *Dev Sci.* (2009) 12:510–20. doi: 10.1111/j.1467-7687.2008.00796.x
64. Beall PM, Moody EJ, McIntosh DN, Hepburn SL, Reed CL. Rapid facial reactions to emotional facial expressions in typically developing children and children with autism spectrum disorder. *J Exp Child Psychol.* (2008) 101:206–23. doi: 10.1016/j.jecp.2008.04.004
65. Rozga A, King TZ, Vuduc RW, Robins DL. Undifferentiated facial electromyography responses to dynamic, audio-visual emotion displays in individuals with autism spectrum disorders. *Dev Sci.* (2013) 16:499–514. doi: 10.1111/desc.12062
66. Mathersul D, McDonald S, Rushby JA. Automatic facial responses to briefly presented emotional stimuli in autism spectrum disorder. *Biol Psychol.* (2013) 94:397–407. doi: 10.1016/j.biopsycho.2013.08.004
67. Yoshimura S, Sato W, Uono S, Toichi M. Impaired overt facial mimicry in response to dynamic facial expressions in high-functioning autism spectrum disorders. *J Autism Dev Disord.* (2015) 45:1318–28. doi: 10.1007/s10803-014-2291-7
68. Volker MA, Lopata C, Smith DA, Thomeer ML. Facial encoding of children with high-functioning autism spectrum disorders. *Focus Autism Other Dev Disabl.* (2009) 24:195–204. doi: 10.1177/1088357609347325
69. Beadle-Brown JD, Whiten A. Elicited imitation in children and adults with autism: is there a deficit? *J Intellect Dev Disabil.* (2004) 29:147–63. doi: 10.1080/13668250410001709494
70. Loveland KA, Tunali-Kotoski B, Pearson DA, Brelsford KA, Ortegon J, Chen R. Imitation and expression of facial affect in autism. *Dev Psychopathol.* (1994) 6:433–44. doi: 10.1017/S0954579400006039
71. Langdell T. *Face Perception: An Approach to the Study of Autism* (Doctoral thesis). University of London (1981). Available online at: https://discovery.ucl.ac.uk/id/eprint/1317720/ (accessed September 15, 2020).
72. Rutherford MD, McIntosh DN. Rules versus prototype matching: strategies of perception of emotional facial expressions in the autism spectrum. *J Autism Dev Disord.* (2007) 37:187–96. doi: 10.1007/s10803-006-0151-9
73. Deschamps P, Munsters N, Kenemans L, Schutter D, Matthys W. Facial mimicry in 6–7 year old children with disruptive behavior disorder and ADHD. *PLoS ONE.* (2014) 9:e84965. doi: 10.1371/journal.pone.0084965
74. Rasting M, Brosig B, Beutel ME. Alexithymic characteristics and patient-therapist interaction: a video analysis of facial affect display. *PSP.* (2005) 38:105–11. doi: 10.1159/000085772
75. Falck-Ytter T, von Hofsten C. How special is social looking in ASD: a review. *Prog Brain Res.* (2011) 189:209–22. doi: 10.1016/B978-0-444-53884-0.00026-9
76. Amestoy A, Guillaud E, Bouvard MP, Cazalets J-R. Developmental changes in face visual scanning in autism spectrum disorder as assessed by data-based analysis. *Front Psychol.* (2015) 6:989. doi: 10.3389/fpsyg.2015.00989
77. Tanaka JW, Sung A. The "eye avoidance" hypothesis of autism face processing. *J Autism Dev Disord.* (2016) 46:1538–52. doi: 10.1007/s10803-013-1976-7
78. Yi L, Fan Y, Quinn PC, Feng C, Huang D, Li J, et al. Abnormality in face scanning by children with autism spectrum disorder is limited to the eye region: evidence from multi-method analyses of eye tracking data. *J Vis.* (2013) 13:5. doi: 10.1167/13.10.5
79. Edey R, Cook J, Brewer R, Johnson MH, Bird G, Press C. Interaction takes two: typical adults exhibit mind-blindness towards those with autism spectrum disorder. *J Abnorm Psychol.* (2016) 125:879–85. doi: 10.1037/abn0000199
80. Rizzolatti G, Sinigaglia C, Rizzolatti G, Sinigaglia C. The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. *Nat Rev Neurosci.* (2010) 11:264–74. doi: 10.1038/nrn2805
81. Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. Parietal lobe: from action organization to intention understanding. *Science.* (2005) 308:662–7. doi: 10.1126/science.1106138
82. Dapretto M, Davies MS, Pfeifer JH, Scott AA, Sigman M, Bookheimer SY, et al. Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nat Neurosci.* (2006) 9:28–30. doi: 10.1038/nn1611
83. Schulte-Rüther M, Otte E, Adigüzel K, Firk C, Herpertz-Dahlmann B, Koch I, et al. Intact mirror mechanisms for automatic facial emotions in children and adolescents with autism spectrum disorder. *Autism Res.* (2017) 10:298–310. doi: 10.1002/aur.1654
84. Fournier KA, Hass CJ, Naik SK, Lodha N, Cauraugh JH. Motor coordination in autism spectrum disorders: a synthesis and meta-analysis. *J Autism Dev Disord.* (2010) 40:1227–40. doi: 10.1007/s10803-010-0981-3
85. Gowen E, Hamilton A. Motor abilities in autism: a review using a computational context. *J Autism Dev Disord.* (2013) 43:323–44. doi: 10.1007/s10803-012-1574-0
86. Heberlein AS, Adolphs R. Neurobiology of emotion recognition: current evidence for shared substrates. In: Harmon-Jones E, Winkielman P, editors. *Social Neuroscience: Integrating Biological and Psychological Explanations of Social Behavior*. New York, NY: The Guilford Press (2007). p. 31–55.
87. Niedenthal PM, Mermillod M, Maringer M, Hess U. The Simulation of Smiles (SIMS) model: embodied simulation and the meaning of facial expression. *Behav Brain Sci.* (2010) 33:417–33. Discussion 433-480. doi: 10.1017/S0140525X10000865
88. Paquet A, Olliac B, Golse B, Vaivre-Douret L. Evaluation of neuromuscular tone phenotypes in children with autism spectrum disorder: an exploratory study. *Clin. Neurophysiol.* (2017) 47:261–8. doi: 10.1016/j.neucli.2017.07.001
89. Kaiser MD, Shiffrar M. The visual perception of motion by observers with autism spectrum disorders: a review and synthesis. *Psychon Bull Rev.* (2009) 16:761–77. doi: 10.3758/PBR.16.5.761
90. Todorova GK, Hatton REM, Pollick FE. Biological motion perception in autism spectrum disorder: a meta-analysis. *Mol Aut.* (2019) 10:49. doi: 10.1186/s13229-019-0299-8
91. Van der Hallen R, Manning C, Evers K, Wagemans J. Global motion perception in autism spectrum disorder: a meta-analysis. *J Autism Dev Disord.* (2019) 49:4901–18. doi: 10.1007/s10803-019-04194-8
92. Yeung MK, Lee TL, Chan AS. Impaired recognition of negative facial expressions is partly related to facial perception deficits in adolescents with high-functioning autism spectrum disorder. *J Autism Dev Disord.* (2020) 50:1596–606. doi: 10.1007/s10803-019-03915-3
93. Deriso D, Susskind J, Krieger L, Bartlett M. Emotion mirror: a novel intervention for autism based on real-time expression recognition. In: Fusiello A, Murino V, Cucchiara R, editors. *Computer Vision – ECCV 2012 Workshops and Demonstrations*. Berlin, Heidelberg: Springer (2012). p. 671–4. (Lecture Notes in Computer Science).
94. Oberman LM, Winkielman P, Ramachandran VS. Face to face: blocking facial mimicry can selectively impair recognition of emotional expressions. *Soc Neurosci.* (2007) 2:167–78. doi: 10.1080/17470910701391943

95. Lai M-C, Kassee C, Besney R, Bonato S, Hull L, Mandy W, et al. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *Lancet Psychiatry.* (2019) 6:819–29. doi: 10.1016/S2215-0366(19)30289-5
96. Lai M-C, Lombardo MV, Ruigrok AN, Chakrabarti B, Auyeung B, Szatmari P, et al. Quantifying and exploring camouflaging in men and women with autism. *Autism.* (2017) 21:690–702. doi: 10.1177/1362361316671012
97. Cage E, Troxell-Whitman Z. Understanding the reasons, contexts and costs of camouflaging for autistic adults. *J Autism Dev Disord.* (2019) 49:1899–911. doi: 10.1007/s10803-018-03878-x
98. Tang TY, Winoto P, Chen G. Emotion recognition via face tracking with realsense(TM) 3D camera for children with autism. In: *Proceedings of the 2017 Conference on Interaction Design and Children.* (IDC '17). New York, NY, USA: Association for Computing Machinery (2017). p. 533–9.
99. Tang TY. Helping neuro-typical individuals to ≪ read ≫ the emotion of children with autism spectrum disorder: an internet-of-things approach. In: *Proceedings of the the 15th International Conference on Interaction Design and Children* (IDC '16). New York, NY, USA: Association for Computing Machinery (2016). p. 666–71.
100. Chaplin TM, Aldao A. Gender differences in emotion expression in children: a meta-analytic review. *Psychol Bull.* (2013) 139:735–65. doi: 10.1037/a0030737
101. Lai M-C, Lombardo MV, Auyeung B, Chakrabarti B, Baron-Cohen S. Sex/gender differences and autism: setting the scene for future research. *J Am Acad Child Adolesc Psychiatry.* (2015) 54:11–24. doi: 10.1016/j.jaac.2014.10.003
102. White SW, Abbott L, Wieckowski AT, Capriola-Hall NN, Aly S, Youssef A. Feasibility of automated training for facial emotion expression and recognition in autism. *Behav Ther.* (2018) 49:881–8. doi: 10.1016/j.beth.2017.12.010
103. Martinez-Martin N. What are important ethical implications of using facial recognition technology in health care? *AMA J Ethics.* (2019) 21:E180–7. doi: 10.1001/amajethics.2019.180

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Automatic Classification of Adult Males With and Without Autism Spectrum Disorder by Non-contact Measurement of Autonomic Nervous System Activation

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People with autism spectrum disorder (ASD) exhibit atypicality in various domains of behavior. Previous psychophysiological studies have revealed an atypical pattern of autonomic nervous system (ANS) activation induced by psychosocial stimulation. Thus, it might be feasible to develop a novel assessment tool to evaluate the risk of ASD by measuring ANS activation in response to emotional stimulation. The present study investigated whether people with ASD could be automatically classified from neurotypical adults based solely on physiological data obtained by the recently introduced non-contact measurement of pulse wave. We video-recorded faces of adult males with and without ASD while watching emotion-inducing video clips. Features reflective of ANS activation were extracted from the temporal fluctuation of facial skin coloration and entered into a machine-learning algorithm. Though the performance was modest, the gradient boosting classifier succeeded in classifying people with and without ASD, which indicates that facial skin color fluctuation contains information useful for detecting people with ASD. Taking into consideration the fact that the current study recruited only high-functioning adults who have relatively mild symptoms and probably developed some compensatory strategies, ASD screening by non-contact measurement of pulse wave could be a promising assessment tool to evaluate ASD risk.

Keywords: ASD, autonomic nervous system, emotion, non-contact measurement, digital phenotyping, pulse wave, color

INTRODUCTION

Autism spectrum disorder (ASD) is a group of closely related developmental disabilities characterized by a collection of symptoms including persistent deficits in social communication and reciprocal interaction, repetitive behavior, and restricted interest (1). Although genetics is considered to play major role in the development of ASD, despite years of effort by researchers, the exact cause of ASD still remains elusive (2). As such, there exists no definitive cure for ASD.

Public awareness of ASD has risen significantly in recent years (3), but several surveys suggest the possibility that a significant portion of the ASD population remains undiagnosed (4). Importantly, some of them remain undiagnosed well into adulthood and experience great distress due to failure in adaptation to occupational and social environments (5–7). The difficulty in detecting ASD risk in adults is attributable to several causes. First, adults with milder cases of ASD can sometimes compensate for their atypicality to some degree by adjusting their behavior with deliberate effort. Second, misdiagnosis is prone to be made because of the comorbidity of other psychiatric conditions.

One promising way to reduce the number of undiagnosed adults with ASD is to develop a supplementary assessment tool for ASD. The currently accepted protocol for ASD diagnosis requires hours of interviews and assessment by clinicians and is quite labor-intensive. Such strict protocols are relevant from the perspective of suppressing overdiagnosis of ASD. At the same time, it is also necessary to establish a convenient and handy assessment tool for primary screening to broadly catch those who "might" have ASD.

Recent studies on digital phenotyping (8) have pointed to the potential of semiautomated quantification of behavioral phenotypes in the primary screening of ASD. In these studies, behavioral features of people with ASD were captured by information technology, such as video analysis of facial movement by computer vision (9–11) and bodily movement analysis using cost-effective sensors [Kinect sensors and touch sensors implemented in tablet computers; (12, 13)]. Some studies have entered the extracted features into machine learning and succeeded in classifying ASD and neurotypical counterparts (11–13).

Classical theories of ASD have claimed that atypicality in emotional function causes ASD-like behaviors (14, 15). Although not in its original form, some of these theories have gained support from studies showing poor performance in emotion recognition (16, 17) and atypical patterns of neural activation and morphology in emotion-associated regions such as the amygdala (14, 18). In addition to atypical development of emotion-related neural regions, a number of studies indicate that people with ASD, especially pediatric patients, show poor ability of emotional regulation (19) as can be seen in occurrences of sudden burst of emotion, so-called "meltdown." Taken together, people with ASD have atypicality in both the induction of emotion and emotional regulation, which leads to an atypical pattern of emotional responses.

Taking such atypical emotional responses in ASD people into consideration, measurement of emotional response might be useful in screening adults with ASD. Emotional response can be objectively quantified by measuring the activation of the autonomic nervous system (ANS), which comprises the sympathetic and parasympathetic nervous system. Psychophysiological studies have linked the relative increase of sympathetic over the parasympathetic nervous system to a high arousal state (20). In addition, several studies have found atypical patterns of ANS activation in people with ASD, especially in response to social situations. For example, studies have revealed reduced sympathetic activation in adults with ASD in response to social interaction (21) and psychosocial stress (22). Similar atypicality has also been observed in pediatric samples (23), although the exact pattern of atypicality differs among studies (24, 25). Previous studies on ANS activation in people with ASD also revealed increased heart rate and reduced respiratory sinus arrhythmia during rest (26, 27) and sleep (28) in individuals with ASD.

Currently, measurement using a polygraph system is deemed the gold standard for ANS activity measurement. However, polygraph systems are relatively expensive and thus difficult to introduce in many facilities. In addition, attachment of sensors onto the skin surface makes people with ASD, especially those with hypersensitivity to tactile stimulation (29), uncomfortable. A recently introduced method of non-contact measurement of pulse waves (30, 31), an index of ANS activation, could be an alternative technique to a polygraph. In this method, the timing of the pulse wave is detected by analyzing a slight change in facial skin coloration. Immediately after cardiac pulsation, arterial blood rich in fresh-red oxygenated hemoglobin circulates through the blood vessels. Hemoglobin pigmentation on the skin surface is slightly intensified synchronously with this event. The temporal interval between neighboring peaks of pigmentation intensity reveals the balance between sympathetic and parasympathetic nervous system activations (32, 33) and, thus, certain aspects of emotional response.

The present study examined whether this non-contact measurement of ANS activation is assistive in distinguishing between neurotypical adults and adults with ASD. We extracted features reflective of ANS activation from video-recorded images of the participant's face while experiencing film-induced emotions (34, 35). These features were fed to machine-learning algorithms to ascertain whether pulse waves extracted from video-recorded images contain enough information to distinguish ASD adults from neurotypical ones. We focused on the phasic change of ANS activation during emotion-inducing film viewing from baseline.

METHOD

Participants

A total of 21 typically developed (TD) adult males ($M = 31.7$ years old; SD = 6.03) and 17 adult males with ASD ($M = 31.5$ years old; SD = 5.2) participated in the present study after giving written informed consent. We excluded female participants so as not to increase variance in responses in the ASD group because previous studies have found phenotypic differences between males and females with ASD (36, 37). The TD participants were recruited by word of mouth and recruitment agency. They had no ties or relations with the ASD participants. The average age did not differ significantly between the ASD and TD groups, $t_{(36)} = 0.07$, $p = 0.94$. All participants with ASD were referred to Showa University Hospital by physicians from other clinics. The inclusion criteria of the present study were as follows: males, Wechsler Adult Intelligence Scale-III, full intelligence ≥70 (high functioning evaluated by WAIS), and a formal diagnosis of ASD based on DSM-5 (1). The exclusion

criteria were comorbid personality disorders. Three of them had a comorbidity of mood disorders. Out of 17 ASD participants, nine were on medication (antidepressant, $n = 5$; anxiolytic, $n = 4$; soporific, $n = 3$; antipsychotic, $n = 4$; anticonvulsant, $n = 3$). None was taking behavioral therapy. A psychiatrist made a diagnosis according to the diagnostic criteria of the DSM-5 for ASD based on a consensus among a team comprised of experienced psychiatrists and a clinical psychologist who carried out clinical interviews. All participants satisfied the Autism Diagnostic Observation Schedule diagnostic criteria at the time of the interview ($M = 11.4$, SD $= 2.8$). The diagnosis was reconfirmed after at least a 2-month follow-up period. The protocol of this research was approved by the ethical committees of the Graduate School of Biomedical Sciences in Nagasaki University and the Graduate School of Engineering in Chiba University, according to the Declaration of Helsinki.

Apparatus and Stimuli

The stimuli included six video clips with lengths of about 1.5–4.5 min intended to induce happy, sad, fearful, and neutral emotional states. These video clips were taken from a TV show or films to induce these emotional states, the details of which are described in **Table 1**. Four of the video clips depicted social interactions among several people. Two more video clips, that is, popular line drawing animation and a video clip of factory machines without human figures, were included in the stimulus set because previous studies have indicated that some people with ASD are prone to show interest in these contents (38, 39). Due to the scarcity of studies on emotion induction by films in Japanese samples, a new set of emotion-inducing films was created for the present study. We first screened Asian films (most of them, Japanese ones) that seemed suitable for emotion induction. Scenes including graphic content and violence were avoided so as not to elicit shock from the participants. Then, a small pilot study was carried out in which our lab members (one female and five males) evaluated 13 Asian films[1] intended to induce sad (two films), fear (three films), happy (two films), and neutral (two films) emotions and two machine factory scenes (two films). Based on the selectivity and intensity of emotional state evaluation, we chose the six films summarized in **Table 1**.

The participants viewed a 19-inch monitor with their head stabilized on a chin rest. Their faces were lit up using two fluorescent lights. The viewing distance was 75 cm. An LED light located near the participant's chin lit up at the start and the end of each video clip. The participants' faces and the LED lights were recorded by an RGB camera (situated between the monitor and the chin rest) for industrial use (ARGO Corporation, Suita, Osaka, Japan). A picture of the experimental setup is shown in **Figure 1A**.

[1]The 13 films tested included "*Lullaby of Narayama* (1983)" (sad), "*Dark Water* (Japanese Version, 2002)" (fear), "*A Tale of Two Sisters* (2003)" (fear), "*Gottu-Ee-Kanji* (Japanese TV comedy show)" (an episode other than the one used in the experiment; happy), and "*Maboroshi* (1995)" (neutral) and a video of machine factory (other than the one used in the experiment) in addition to six clips selected.

Procedure

Face Movie Recording

At the start of each trial, a black background was shown for 40 s. Then, a video clip was presented. The video clip included 10 s presentation of a brief explanation about the context of the scene. The participants were instructed to view the video clip without overt movement quietly. Immediately after the end of the video clip, seven track bars with 11 tics were presented on the screen. The participants' task was to answer their emotional states, that is, the levels of happiness, anger, sadness, fear, disgust, unpleasantness, and arousal, using the track bar. After the completion of the subjective evaluation of emotional state, the next trial started. Six video clips were separated into three blocks with interblock rest intervals. The order of the video clips was determined randomly.

Self-Administered Questionnaires

After the completion of the facial movie recording, the participants answered a battery of self-administered paper-and-pencil questionnaires in front of the experimenter. The questionnaires included Japanese translations of the IRI [Interpersonal Reactivity Index; (40)] and TAS-20 [The 20-item Toronto Alexithymia Scale; (41)]. The IRI measures empathic tendencies, and it comprises four subscales: perspective-taking, fantasy, empathic concern, and personal distress (42), while TAS measures the level of difficulty in identifying feelings, difficulty in describing feelings, and externally oriented thinking (41, 43).

Image Processing

Recorded movies of the participants' faces were analyzed offline according to the algorithm described by Fukunishi et al. (31, 44). The skin color of the small facial region near the cheekbone was analyzed. First, skin coloration in each frame was separated into hemoglobin pigmentation, melanin pigmentation, and shade information by independent component analysis (45). Because shade information is separated from hemoglobin intensity, the intensity of hemoglobin pigmentation can be assessed independently of lighting condition. Then, the temporal fluctuation of hemoglobin intensity across video frames was analyzed.

The temporal course of hemoglobin pigmentation intensity shows pulsatile fluctuation as shown in **Figure 1B**. From the temporal course of hemoglobin pigmentation fluctuation, 20 indices of ANS activation were computed for each video clip for each participant. The details of the extracted indices are summarized in **Table 2**. These indices were measured during 30 s baseline just before video clip presentation and during video clip viewing. We used Kubios-HRV software (46) for computing some of the indices. The phasic change in these indices from baseline was calculated by subtracting index values during baseline from those during video clip viewing. Thus, six change-from-baseline values were obtained for each of the 20 indices, yielding a total of 120 features for machine learning.

TABLE 1 | Detailed descriptions of scenes in stimulus video clips.

Clip	Film title	Scene description
Happy	Gottu Ee Kanji (Japanese TV comedy show)	A female police officer expresses her intention to resign from the police force, but her boss refuses to accept the resignation. Their colleagues dressed in flamboyant costumes make a fuss of the situation.
Fear	The EYE (1995)	A female takes an elevator. She sees an old man in the elevator, but his image is not captured in the security camera. As the elevator ascends, the man, floating on the floor, moves toward the female.
Sad	A Cicada of the Eighth Day (2011)	A female fugitive is trying to escape an island by ferry with a hostage child, whom she brought up as her daughter. After realizing that they are surrounded by police officers, she tells the child to leave. Police officers arrest her and the child cries out for her.
Neutral	A Scene at the Sea (1991)	A couple boards a bus, but the driver cautions the man not to bring a surfboard into the bus. The bus leaves and the female keeps watching his boyfriend, who is standing in the bus stop with his surfboard, through the window of the bus.
Line drawing animation	Pendulum (2014)	A pendulum clock is drawn as a motif. Together with the pendulum swing, the animation shows snippets of the life of a couple. When the couple reaches the end of their life, the husband tries to reverse the swing of the pendulum, but the wife gently stops him. All the objects and people are drawn in a thick black line on a white background in this animation.
Machine factory	None	This video describes the movements of various factory machines and mechanical tools. No images of humans are included.

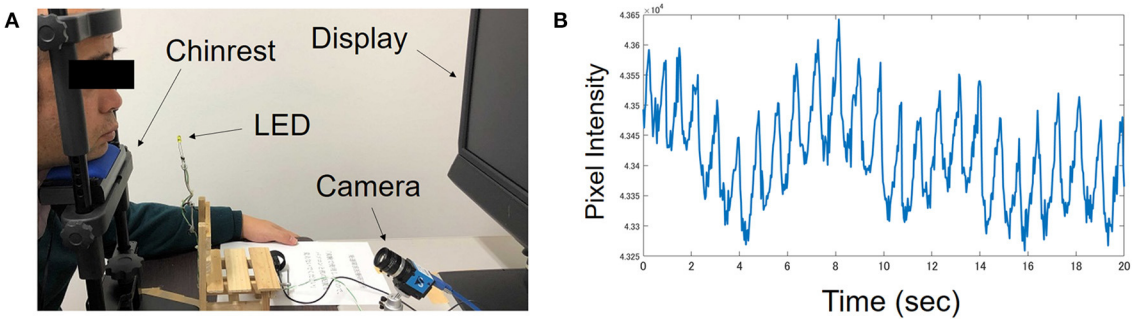

FIGURE 1 | (A) A picture of experimental setting taken during preparation. The man in the picture is one of the authors, not a participant. During the actual experiment, participant held a keypad with their head stabilized on a chin rest. **(B)** Typical pattern of pulsatile fluctuation in hemoglobin intensity recorded from one ASD participant.

Group Classification by Machine Learning

To ascertain whether participants with and without ASD can be automatically classified by 120 features reflective of ANS activation obtained by non-contact measurement, data were analyzed using a supervised machine-learning algorithm. First, 120 features were standardized and then compressed to principal components (PCs) by principal component analysis (PCA). Then, the scores of PCs were fed into a gradient boosting (GB) classifier. GB is one of the ensemble learning algorithms, which is known to show good prediction performance and generalizability, i.e., the ability of the classifier to predict the class of unknown data, over the other types of machine learning algorithms in many classification problems. In ensemble learning, a set of weak predictors with limited prediction ability is created, instead of a single strong predictor with high prediction ability. Then, the final prediction is made by aggregating the predictions of these weak predictors. Intuitively, in GB, weak predictors are added sequentially to the decision trees so that the addition of a new predictor gradually minimizes the discrepancy between observed data and prediction. There are two popular ensemble learning algorithms, GB and random forest. Though random forest excels at generalizability in some cases, GB can show superior performance when its hyperparameters are tuned appropriately.

The GB classifier was cross-validated by a leave-one-out procedure. Specifically, data from one participant were used as the unknown test data, and the data of the remaining 37 participants were used to train the classifier. After training, the classifier predicted which group, i.e., TD or ASD, the unknown test data belonged to. The performance indicators, i.e., accuracy, sensitivity, specificity, precision, and F1 score, were calculated according to the formula below after repeating this procedure 38 times by using the data of every participant as test data.

$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{FP} + \text{TN} + \text{FN}}$$

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

$$\text{Precision} = \frac{\text{TP}}{\text{TP} + \text{FP}}$$

$$\text{F1 Score} = \frac{2 \times \text{Sensitivity} \times \text{Precision}}{\text{Sensitivity} + \text{Precision}}$$

TABLE 2 | Summary of extracted ANS activation indices.

Index no.	Description
1	LF/HF by the FFT spectrum: ratio between LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz) band power evaluated by Fourier transformation (FFT)
2	LF/HF by the AR spectrum: ratio between LF and HF band power evaluated by autocorrelation (AR)
3	Normalized LF power by FFT: LF band power normalized by total power minus very low frequency (VLF) band power evaluated by FFT
4	Normalized HF power by FFT: HF band power normalized by total power minus very low frequency (VLF) band power evaluated by FFT
5	Normalized LF power by the AR spectrum: LF band power normalized by total power minus very low frequency (VLF) band power evaluated by AR
6	Normalized HF power by the AR spectrum: HF band power normalized by total power minus very low frequency (VLF) band power evaluated by AR
7	Relative LF power against total power by the FFT spectrum: ratio between LF band power and total power evaluated by FFT
8	Relative HF power against total power by the FFT spectrum: ratio between HF band power and total power evaluated by FFT
9	Relative LF power against total power by the AR spectrum: ratio between LF band power and total power evaluated by AR
10	Relative HF power against total power by the AR spectrum: ratio between HF band power and total power evaluated by AR
11	Mean of RRI: mean of RR interval
12	Mean of HR: mean heart rate
13	RMSSD: root mean square of differences of successive RR intervals
14	pNN50: number of successive RR intervals that differ more than 50 ms divided by the total number of RR intervals
15	HRV triangular index: area covered by RR interval histogram divided by the height of the histogram
16	TINN: bottom width of RR interval histogram
17	SD1 of Poincaré plot: standard deviation of data points along the line of identity of an ellipsoid approximating the Poincaré plot (a scatter plot with n-th RR interval as horizontal axis and $n+1$-th RR interval as vertical axis)
18	SD2 of Poincaré plot: standard deviation of data points in the direction perpendicular to the line of identity of an ellipsoid approximating the Poincaré plot
19	Ratio between SD1 and SD2: ratio between SD1 and SD2 in the Poincaré plot
20	Mean of hemoglobin intensity: mean pixel value of hemoglobin image

The definitions summarized above are partly taken from the site of Kubios software (https://www.kubios.com/downloads/Kubios_HRV_Users_Guide.pdf).
FFT, Fourier transformation; LF, low frequency; HF, high frequency; AR, autoregression; RRI, RR interval; HR, heart rate; RMSSD, root mean square of successive differences between heartbeats; pNN50, percentage of neighboring NN intervals (interval between normal heartbeats) that differ from each other by more than 50 ms; HRV, heart rate variability; TINN, triangular interpolation of RR intervals; SD, standard deviation.

where TP (true positive), FP (false positive), TN (true negative), and FN (false negative) represent the frequencies with which the ASD participant was correctly identified as ASD, the TD participant was misclassified as ASD, the TD participant was correctly classified as TD, and the ASD participant was misclassified as TD, respectively.

To obtain a robust estimate of performance, we repeated this process 20 times by changing the random number seed.

Basic Emotion Classification by Machine Learning

Among the six video clips, happy, fear, sad, and neutral clips are intended to induce a particular emotional state. In order to examine whether these four clips induced differential physiological states in ASD and neurotypical adults, a GB classifier was trained to discriminate these four clips based on the 20 ANS indices. The features were first compressed by PCA, and then the GB classifier was trained for the TD and ASD groups separately.

In the ASD group, there were emotional category (4) × participant (17) = 68 data. In the leave-one-out procedure, one of the 68 data was treated as unknown test data and the GB classifier was trained on the basis of the remaining 67 data. Accuracy rate and confusion matrix were computed after repeating this procedure 68 times using every one of the 68 data as the test data. Accuracy and confusion matrix were computed in the TD group according to essentially the same procedure using emotional category (4) × participant (21) = 84 data. Computation of accuracy and confusion matrix was repeated 20 times by changing the random seed.

In the next step of analysis, we tested whether emotional states are less clearly differentiated in ASD than TD participants (47). If this hypothesis is correct, the pairwise similarities among physiological responses induced by the four emotion-inducing clips should be higher in the ASD group than in the TD group. To examine this possibility, the cosine similarity of physiological states induced by the four video clips was calculated based on the confusion matrices. The cosine similarity between emotion j and emotion k, CS_{jk}, is computed according to the following formula where N_{ij} represents the frequency with which emotion j was classified as emotion i (happy, fear, sad, neutral).

$$CS_{jk} = \frac{\sum_{i=1}^{4} N_{ij} \times N_{ik}}{\sqrt{\sum_{i=1}^{4} N_{ij}^2} \times \sqrt{\sum_{i=1}^{4} N_{ik}^2}}$$

Statistical Analysis

Subjective ratings of emotional states were entered into an analysis of variance (ANOVA) with the between-participant factor of group (2; TD, ASD) and the within-participant factors of clip (6; happy, fear, sad, neutral, line drawing, machine) and emotional state (7; happiness, anger, fear, sadness, disgust, surprise, unpleasantness, arousal). When an interaction reached significance, simple main effect analysis was conducted to clarify its source.

In leave-one-out, the GB classifier gives the probability estimate that the test data belong to the ASD class. In the present study, leave-one-out cross-validation was repeated 20 times, yielding 20 probability values for each participant. We tested whether the average probabilities assigned to ASD participants were higher than those assigned to TD participants as expected by the Mann–Whitney U-test. The chi-squared test was used to examine if the proportions of participants classified into the ASD

group differed between the ASD and TD groups. It was tested whether the mean accuracy of classification was significantly above chance (50%) by two-tailed *t*-test.

Group difference in subscores of IRI and TAS-20 was tested by two-tailed *t*-tests. To see if these traits are associated with classification results by the GB classifier, Spearman's rank-order correlation was tested between averaged probabilities and the scores of IRI and TAS-20.

RESULTS

Group Difference in Subjective Emotional States

The mean and standard deviation of the subjective ratings in each condition are shown in **Figure 2**.

The ANOVA revealed significant main effects of clip, $F_{(5,180)} = 14.53$, $p < 0.0001$, $\eta_p^2 = 0.29$, and emotional state, $F_{(6,216)} = 30.53$, $p < 0.0001$, $\eta_p^2 = 0.46$. There were also significant interactions between group and emotional state, $F_{(6,216)} = 4.08$, $p < 0.001$, $\eta_p^2 = 0.10$, and between clip and emotional state, $F_{(30,1,080)} = 35.04$, $p < 0.0001$, $\eta_p^2 = 0.49$. All these main effects and interactions were further qualified by a significant three-way interaction between group, clip, and emotional state, $F_{(30,1,080)} = 1.56$, $p = 0.028$, $\eta_p^2 = 0.042$. No other effects reached significance, Fs < 1.0, ps > 0.4. In order to clarify the source of the significant three-way interaction, two-way ANOVA with the between-participant factor of group (2) and within-participant factor of emotional state (7) was carried out for each clip.

Happy Clip

The ANOVA revealed a significant main effect of emotional state, $F_{(6,216)} = 59.67$, $p < 0.0001$, $\eta_p^2 = 0.62$, and a significant interaction between group and emotional state, $F_{(6,216)} = 4.48$, $p = 0.0003$, $\eta_p^2 = 0.11$. The main effect of group failed to reach significance, $F_{(1,36)} = 0.03$, $p = 0.85$, $\eta_p^2 < 0.001$. Simple main effect analysis revealed significantly higher "happy" rating in TD than in the ASD group, $F_{(1,36)} = 5.72$, $p = 0.02$, $\eta_p^2 = 0.14$. People with ASD also gave higher "unpleasantness" ratings than TD people, $F_{(1,36)} = 4.87$, $p = 0.034$, $\eta_p^2 = 0.12$. A simple main effect of group failed to reach significance in the other emotional states, Fs < 3.4, ps > 0.07.

Fear Clip

The main effect of emotional state reached significance, $F_{(6,216)} = 36.34$, $p < 0.0001$, $\eta_p^2 = 0.50$. The main effect of group failed to reach significance, $F_{(1,36)} = 0.39$, $p = 0.53$, $\eta_p^2 = 0.01$. The interaction between group and emotional state failed to reach significance either, $F_{(6,216)} = 1.88$, $p = 0.086$, $\eta_p^2 = 0.05$.

Neutral Clip

The main effect of emotional state reached significance, $F_{(6,216)} = 13.43$, $p < 0.0001$, $\eta_p^2 = 0.27$. Neither the main effect of group, $F_{(1,36)} = 0.20$, $p = 0.66$, $\eta_p^2 = 0.006$, nor the interaction between group and emotional state, $F_{(6,216)} = 0.29$, $p = 0.94$, $\eta_p^2 = 0.01$, reached significance.

Sad Clip

The main effect of emotional state, $F_{(6,216)} = 36.45$, $p < 0.0001$, $\eta_p^2 = 0.50$, and the interaction between group and emotional state reached significance, $F_{(6,216)} = 3.36$, $p = 0.0035$, $\eta_p^2 = 0.085$. The main effect of group failed to reach significance, $F_{(1,36)} = 0.93$, $p = 0.34$, $\eta_p^2 = 0.025$. Simple main effect analysis revealed a significantly higher "fear" rating in the ASD than in the TD group, $F_{(1,36)} = 9.12$, $p = 0.005$, $\eta_p^2 = 0.20$. A simple main effect of group reached significance for no other emotional state, Fs < 1.9, ps > 0.17.

Line Drawing Animation

The main effect of emotional state reached significance, $F_{(6,216)} = 34.37$, $p < 0.0001$, $\eta_p^2 = 0.49$. This main effect was qualified by a significant interaction between group and emotional state, $F_{(6,216)} = 2.62$, $p = 0.018$, $\eta_p^2 = 0.07$. The main effect of group failed to reach significance, $F_{(1,36)} = 0.06$, $p = 0.80$, $\eta_p^2 = 0.002$. Simple main effects of group failed to reach significance, Fs < 3.5, ps > 0.07.

Machine Factory Clip

Only the main effect of emotional state was significant, $F_{(6,216)} = 22.34$, $p < 0.0001$, $\eta_p^2 = 0.38$. Neither the main effect of group, $F_{(1,36)} = 0.61$, $p = 0.45$, $\eta_p^2 = 0.017$, nor the interaction between group and emotional state reached significance, $F_{(6,216)} = 0.095$, $p = 0.99$, $\eta_p^2 = 0.003$.

Automatic Group Classification

We first tested whether the performance of the GB classifier was dependent on the number of PCs used as features. Thus, GB classifiers were trained and tested by using scores of 1–10 PCs as features. The PCs were entered into the classifier in descending order of the amount of variance explained. For example, when the number of PCs was two, the PCs with the first and second largest variance explained were used as the features. The performance of GB classifiers was compared by the accuracy and F1 score as performance indicator. The classifier showed its best performance when the number of PCs was eight.

The Mann–Whitney *U*-test revealed a significantly higher probability of being classified into ASD by the classifier in the ASD than in the TD group, $U = 117$, $p = 0.037$. When the threshold was set to 0.5, 13 out of 17 (76.4%) ASD participants and 8 out of 21 (38.1%) TD participants were classified into the ASD group. The proportions of participants classified into the ASD group differed significantly between the ASD and TD groups, $\chi_(1) = 5.59$, $p = 0.018$.

Mean accuracy across 20 repetitions of cross-validation was 0.68 (SD = 0.015). Accuracy was significantly higher than chance (0.5), $t_(19) = 54.46$, $p < 0.001$. Averages of sensitivity, specificity, precision, and F1 score were 0.76 (SD = 0.021), 0.63 (SD = 0.021), 0.63 (SD = 0.016), and 0.68 (SD = 0.015).

Feature importance of each PC is shown in **Figure 3**. As can be seen in this figure, the fourth and sixth PCs contributed most to the classification followed by the first and second PCs. For completeness, we compared scores of the eight PCs between the ASD and TD groups. No group difference was found, ts < 1.7, ps > 0.10.

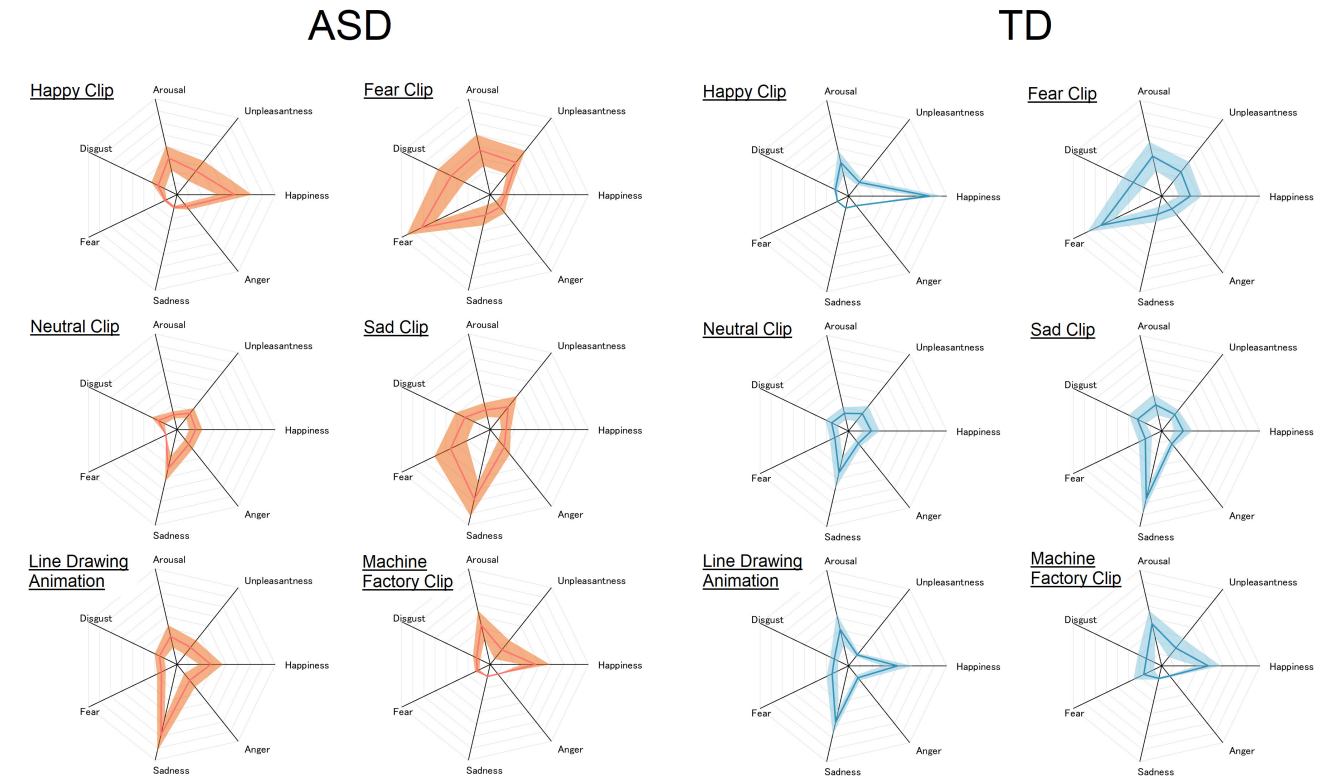

FIGURE 2 | Subjective rating of each emotional state given to each of the six video clips in the ASD **(left)** and TD **(right)** groups. The center of the radar chart is zero, and the outermost point of each axis is eight. The thick line and the width of the shaded area along each axis represent mean and standard deviation, respectively.

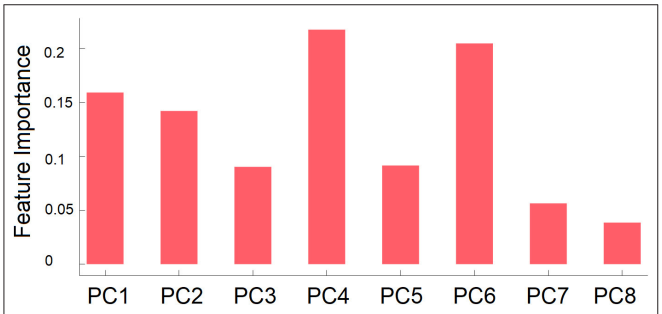

FIGURE 3 | Mean feature importance of the right PCs used as features in group classification by GB classifier. PC*n* is the PC that explained the *n*-th largest amount of variance.

Relationship Between Classification Results and Scores of IRI and TAS-20

The average and standard deviations of IRI and TAS-20 are summarized in **Table 3**. Two ASD participants failed to complete TAS-20. In IRI, adults with ASD showed lower perspective-taking and higher personal distress scores than their neurotypical counterparts. The results also revealed a higher score in every factor of TAS-20 in the ASD than in the TD group.

The results of correlation coefficients between questionnaire results and the probabilities of being classified as ASD assigned by the GB classifier are summarized in **Table 4**. After significance threshold correction by Bonferroni's procedure, there was no significant correlation.

Automatic Classification of Emotional States Within Each Group

The performance of the GB classifier was dependent on the number of PCs. Thus, we evaluated the performance of the GB classifier by changing the number of PCs in the same manner as described above. In the TD groups, the best performance was achieved when the number of PCs was six, while one in the ASD group. Thus, the number of PCs was set to these values.

The averaged accuracy was 0.34 in the TD group and 0.31 in the ASD group. The confusion matrix for each group is shown in **Table 5** together with the hit rate, i.e., the probability that the classifier made a correct classification of each emotion.

The cosine similarities between each pair of emotional states are listed in **Table 6**. As can be seen in this table, cosine similarities between happy and neutral, and between happy and sad, were relatively low compared with the other pairwise combinations in both ASD and TD groups.

DISCUSSION

Recent advances in image processing technology have enabled the quantification of ANS activation by non-contact measurement of

TABLE 3 | Mean and standard deviation of IRI and TAS-20 scores in each group, and the results of group comparison of each score by two-tailed *t*-test.

	IRI				TAS-20		
	Perspective-taking	**Empathic concern**	**Fantasy**	**Personal distress**	**Difficulty in identifying feelings**	**Difficulty in describing feelings**	**Externally oriented thinking**
ASD ($N = 17$)	18.0*	19.8	18.6	21.7**	19**	16.1*	21.7**
	(3.7)	(3.6)	(3.8)	(4.3)	(6.4)	(4.0)	(4.2)
TD ($N = 21$)	21.3	20.4	19.6	15.4	12.1	13.0	17.8
	(4.5)	(3.7)	(3.8)	(3.8)	(3.8)	(3.6)	(4.3)
t-value	−2.43	−0.5	−0.75	4.79	4.03	2.4	2.75
df	36	36	36	36	34	34	34
p	0.02	0.618	0.46	<0.001	<0.001	0.022	0.009

In parenthesis are the standard deviations.
**p < 0.05; **p < 0.01.*

TABLE 4 | Spearman's rank-order correlation coefficients between averaged probability and scores of IRI and TAS-20.

		IRI				TAS-20		
		Perspective-taking	**Empathic concern**	**Fantasy**	**Personal distress**	**Difficulty in identifying feelings**	**Difficulty in describing feelings**	**Externally oriented thinking**
All	Rho	−0.20	0.08	0.14	0.08	0.18	0.20	0.23
	p-value	0.236	0.634	0.414	0.643	0.287	0.235	0.182
ASD ($N = 17$)	Rho	−0.38	0.27	0.19	−0.11	−0.34	−0.25	0.54
	p-value	0.132	0.304	0.474	0.669	0.213	0.362	0.038
TD ($N = 21$)	Rho	0.13	−0.01	0.29	0.02	0.28	0.44	−0.10
	p-value	0.581	0.971	0.209	0.937	0.211	0.046	0.673

TABLE 5 | Confusion matrix of emotion categorization in each group.

Group	**Clip**	**Prediction**				**Hit rate (%)**
		Happy	**Fear**	**Neutral**	**Sad**	
ASD ($N = 17$)	Happy	**3**	8	2	4	17.6
	Fear	6	**6**	3	2	35.3
	Neutral	4	4	**7**	2	23.5
	Sad	5	2	5	**5**	29.4
TD ($N = 21$)	Happy	**10**	4	2	5	47.6
	Fear	5.1	**6.9**	4.4	4.6	24.3
	Neutral	4.8	2.6	**6.85**	6.75	22.9
	Sad	4.8	2.85	8.25	**5.1**	22.9

The number in each cell represents averaged frequency. Hit rates are also shown in the rightmost column. The numbers along the diagonal line (bold) represent averaged frequency of hit.

TABLE 6 | Mean cosine similarity between emotional states in each group.

		Happy	**Fearful**	**Neutral**	**Sad**
ASD	Happy	1	0.9	0.74	0.71
	Fearful		1	0.86	0.82
	Neutral			1	0.89
	Sad				1
TD	Happy	1	0.85	0.79	0.75
	Fearful		1	0.87	0.85
	Neutral			1	0.97
	Sad				1

The number in each cell represents averaged cosine similarity.

pulse waves from images of the skin surface (30, 31, 44). Here, we used this technology to measure ANS activity in adults with ASD in response to six types of video clips.

At the behavioral level, ASD people gave lower "happy" rating (for happy clip) and higher "fear" (for sad clip) and "unpleasant" (for happy clip) ratings than TD people. The overall pattern indicates a stronger negativity bias in emotional reactions to video clips in ASD individuals. Anxiety disorder is a common comorbidity of ASD (24, 48) and sometimes leads to misdiagnosis of patients with mood disorders as ASD (7). The present finding of negativity bias in individuals with ASD is in line with this clinical observation. At the same time, the present results tell nothing about the cause of this bias. This could be due to hyperactivation in neural centers of emotion induction, such as the amygdala and anterior cingulate cortex (49), or the atypical interpretation of the physiological state induced by video clips.

We tried a semiautomatic classification of TD and ASD groups by submitting the features reflective of ANS activation into a gradient boosting classifier. The classifier succeeded in classifying

unknown participants into either the TD or ASD group above the chance level. Furthermore, the probability of belonging to the ASD group estimated by the best performance classifier was significantly higher in the ASD group than in the TD group, which further supports the proposition that non-contact measurement of pulse waves captures atypical responses useful for classifying ASD from TD adults.

At the same time, we have to point out that our success was only modest. Although the accuracy rate was significantly above chance, the values of performance indicators were far from being acceptable for practical use. The relatively poor performance of the classifier is not surprising considering the fact that we focused on a single facet of peripheral nervous system activation, i.e., pulse wave. Needless to say, faces covey abundant information, and some of the previous studies on digital phenotyping of ASD made efficient use of facial information in automatic discrimination of ASD and TD samples (10, 11, 50). Thus, a combination of the other sources of facial information together with non-contact measurement of pulse waves might lead to the establishment of a classifier with better prediction performance.

The relatively low performance of our classifier is also attributable to heterogeneity in ASD participants. It is now well-acknowledged that people with ASD are a heterogeneous group and the symptomatic profiles differ greatly among patients (51). This observation gained further support from the emerging view that each symptom of ASD derives from a different set of etiological factors (52, 53). Given this, it is highly possible that participants in our ASD group had heterogeneous characteristics, which might have yielded a variance in ANS responses to emotional clips. Of particular relevance to the present study, it is possible that participants with hypersensitivity to visual and auditory stimulation might have shown different responses to the video clips from those without hypersensitivity in the present study. Unfortunately, the sample size of the present study is not large enough to examine the effects of symptomatic heterogeneity on physiological responses to emotional clips. This point is surely an important topic for future study.

The results of self-administered questionnaires revealed lower perspective-taking in ASD. Considering that the vicarious experience of the characters' emotion is at the core of emotional experience in film viewing, one might conceive that a lower tendency of perspective-taking might explain a different pattern of ANS activation in ASD compared with TD participants. However, the results of correlation analysis do not support this view; correlation analyses did not show a reliable association between IRI scores and averaged probability belonging to the ASD group generated by the classifier. All of the three scores measured by TAS-20 were higher in the ASD group, which is consistent with the reported strong alexithymic tendency in ASD (54).

The classification results of basic emotional states revealed comparable accuracy in the classification of four emotional states by gradient boosting classifier in the TD and ASD groups. The averaged accuracy rate of classification across all the emotional categories was numerically low in the ASD than in the TD group, but this is probably because the sample size of adults with ASD was smaller than that of TD adults; the classifier for ASD was disadvantaged due to the smaller size of the training dataset. In both ASD and TD groups, cosine similarity was high for the combination between happy and fear, but was relatively low for the combinations of happy and two low arousal emotions (neutral, sad). This indicates that indices extracted from pulse wave are sensitive to arousal level, consistent with previous studies that show the association between arousal state and ANS activation (20). Interestingly, hit rate for happy emotion was drastically lower in the ASD than in the TD group. Actually, the pattern of ANS activation induced by the happy clip was more likely to be confused with that induced by the fearful clip in the ASD than in the TD group. This might indicate a less clear differentiation of emotional state in ASD (47). This finding also dovetails with the proposal that people with ASD show atypical pattern of activation in fear-related neural circuits (18, 55) by emotional stimulation. However, definitive conclusion awaits further empirical studies. An alternative explanation for this result is that the film set used in the present study was not optimized to induce discrete emotional states in ASD participants. Given the prevalent use of films for emotion induction (34, 56) in TD population, it is desirable to establish a standardized set of emotion-inducing films suitable for people with ASD.

The present study showed the potential of non-contact ANS measurement in the automatic classification of adult males with and without ASD. The number of studies reporting the successful application of affordable non-contact measurement to digital phenotyping of atypical behavior in ASD has increased recently (8, 11–13). Combined with these previously established methodologies, the current technique could serve as an assessment tool to screen hitherto undiagnosed or misdiagnosed adults with ASD (5–7). However, there are several limitations that qualify our conclusion. First, many of the relevant studies, including the current one, fail to include participants with other psychiatric conditions, and as such, it remains uncertain whether non-contact measurement of pulse wave can discriminate ASD from patients with other psychiatric conditions. Second, the present study recruited only adult males with and without ASD. Thus, it is unclear whether the current technology could contribute to the classification of females or pediatric samples with ASD from their neurotypical counterparts. Third, the distribution of ASD and TD people in the present study does not mirror the prevalence of ASD in the population. The prevalence of ASD among males is estimated to be around 1 in 50–60 (57), though the reported number varies widely among studies. Given the relatively low prevalence rate, the sensitivity/specificity of our classifier is unclear when it is applied to actual clinical settings. Fourth, we used a video camera with a 30-Hz frame rate for cost-effectiveness. The use of a low frame rate might have made the estimation of some of the ANS activation indicators somewhat unreliable. In other words, the performance of the classifier might be improved by integrating video cameras with a higher frame rate. Considering these, it would be desirable to test the reliability of the current technique by recruiting a more diverse population and using more suitable equipment in future studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The ethical committee of Graduate School of Biomeidcal Sciences in Nagasaki University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HD, NT, and CK conceived of the research. HD, CK, KM, RM, and TN collected data. NT, KM, RM, and TN carried out the analysis of video images. HD analyzed the data and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 5th ed. Arlington, VA: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596
2. Anderson GM. Autism biomarkers: challenges, pitfalls and possibilities. *J Autism Dev Disord.* (2015) 45:1103–13. doi: 10.1007/s10803-014-2225-4
3. Matson J, Kozlowski AM. The increasing prevalence of autism spectrum disorders. *Res Autism Spectr Disord.* (2011) 5:418–25. doi: 10.1016/j.rasd.2010.06.004
4. Baron-Cohen S, Scott FJ, Allison C, Williams J, Bolton P, Matthews FE, et al. Prevalence of autism-spectrum conditions: UK school-based population study. *Br J Psychiatry.* (2009) 194:500–9. doi: 10.1192/bjp.bp.108.059345
5. Foran LL. Identifying autism spectrum disorder in undiagnosed adults. *The Nurse Pract.* (2018) 43:14–8. doi: 10.1097/01.NPR.0000544285.02331.2c
6. van Niekerk ME, Groen W, Vissers CT, van Driel-de Jong D, Kan CC, Oude Voshaar RC. Diagnosing autism spectrum disorders in elderly people. *Int Psychogeriatr.* (2011) 23:700–10. doi: 10.1017/S1041610210002152
7. Stagg SD, Belcher H. Living with autism without knowing: receiving a diagnosis in later life. *Health Psychol Behav Med.* (2019) 7:348–61. doi: 10.1080/21642850.2019.1684920
8. Washington P, Park N, Srivastava P, Voss C, Kline A, Varma M, et al. Data-driven diagnostics and the potential of mobile artificial intelligence for digital therapeutic phenotyping in computational psychiatry. *Biol Psychiatry Cogn Neurosci Neuroimaging.* (2019) 5:759–69. doi: 10.1016/j.bpsc.2019.11.015
9. Dawson G, Campbell K, Hashemi J, Lippmann SJ, Smith V, Carpenter K, et al. Atypical postural control can be detected via computer vision analysis in toddlers with autism spectrum disorder. *Sci Rep.* (2018) 8:17008. doi: 10.1038/s41598-018-35215-8
10. Grossard C, Dapogny A, Cohen D, Bernheim S, Juillet E, Hamel F, et al. Children with autism spectrum disorder produce more ambiguous and less socially meaningful facial expressions: an experimental study using random forest classifiers. *Mol Autism.* (2010) 11:5. doi: 10.1186/s13229-020-0312-2
11. Drimalla H, Scheffer T, Landwehr N, Baskow I, Roepke S, Behnia B, et al. Towards the automatic detection of social biomarkers in autism spectrum disorder: introducing the simulated interaction task (SIT). *NPJ Digit Med.* (2020) 3:25. doi: 10.1038/s41746-020-0227-5
12. Anzulewicz A, Sobota K, Delafield-Butt JT. Toward the autism motor signature: gesture patterns during smart tablet gameplay identify children with autism. *Sci Rep.* (2016) 6:31107. doi: 10.1038/srep31107
13. Ardalan A, Assadi AH, Surgent OJ, Travers BG. Whole-body movement during videogame play distinguishes youth with autism from youth with typical development. *Sci Rep.* (2019) 9:20094. doi: 10.1038/s41598-019-56362-6
14. Bachevalier J. Medial temporal lobe structures and autism: a review of clinical and experimental findings. *Neuropsychologia.* (1994) 32:627–48. doi: 10.1016/0028-3932(94)90025-6
15. Bachevalier J. Brief report: medial temporal lobe and autism: a putative animal model in primates. *J Autism Dev Disord.* (1996) 26:217–20. doi: 10.1007/BF02172015
16. Doi H, Fujisawa TX, Kanai C, Ohta H, Yokoi H, Iwanami A, et al. Recognition of facial expressions and prosodic cues with graded emotional intensities in adults with asperger syndrome. *J Autism Dev Disord.* (2013) 43:2099–113. doi: 10.1007/s10803-013-1760-8
17. Loth L, Garrido L, Ahmad J, Watson E, Duff A, Duchaine B. Facial expression recognition as a candidate marker for autism spectrum disorder: how frequent and severe are deficits? *Mol Autism.* (2018) 30:9:7. doi: 10.1186/s13229-018-0187-7
18. Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SCR. The amygdala theory of autism. *Neurosci Biobehav Rev.* (2000) 24:355–64. doi: 10.1016/S0149-7634(00)00011-7
19. Mazefsky CA, Herrington J, Siegel M, Scarpa A, Maddox BB, Scahill L, et al. The role of emotion regulation in autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry.* (2013) 52:679–88. doi: 10.1016/j.jaac.2013.05.006
20. Kreibig SD. Autonomic nervous system activity in emotion: a review. *Biol Psychol.* (2010) 84:394–421. doi: 10.1016/j.biopsycho.2010.03.010
21. Smeekens I, Didden R, Verhoeven EW. Exploring the relationship of autonomic and endocrine activity with social functioning in adults with autism spectrum disorders. *J Autism Dev Disord.* (2015) 45:495–505. doi: 10.1007/s10803-013-1947-z
22. Jansen LM, Gispen-de Wied CC, Wiegant VM, Westenberg HG, Lahuis BE, van Engeland H. Autonomic and neuroendocrine responses to a psychosocial stressor in adults with autistic spectrum disorder. *J Autism Dev Disord.* (2006) 36:891–9. doi: 10.1007/s10803-006-0124-z
23. Watson LR, Roberts JE, Baranek GT, Mandulak KC, Dalton JC. Behavioral and physiological responses to child-directed speech of children with autism spectrum disorders or typical development. *J Autism Dev Disord.* (2012) 42:1616–29. doi: 10.1007/s10803-011-1401-z
24. Kushki A, Drumm E, Pla Mobarak M, Tanel N, Dupuis A, Chau T, et al. Investigating the autonomic nervous system response to anxiety in children with autism spectrum disorders. *PLoS ONE.* (2013) 8:e59730. doi: 10.1371/journal.pone.0059730
25. Louwerse A, Tulen JH, van der Geest JN, van der Ende J, Verhulst FC, Greaves-Lord K. Autonomic responses to social and nonsocial pictures in adolescents with autism spectrum disorder. *Autism Res.* (2014) 7:17–27. doi: 10.1002/aur.1327
26. Guy L, Souders M, Bradstreet L, DeLussey C, Herringto JD. Brief report: Emotion regulation and respiratory sinus arrhythmia

in autism spectrum disorder. *J Autism Dev Disord.* (2014) 44:2614–20. doi: 10.1007/s10803-014-2124-8
27. Matsushima K, Matsubayashi J, Toichi M, Funabiki Y, Kato K, Awaya T, et al. Unusual sensory features are related to resting-state cardiac vagus nerve activity in autism spectrum disorders. *Res Autism Spectr Disord.* (2016) 25:37–46. doi: 10.1016/j.rasd.2015.12.006
28. Harder R, Malow BA, Goodpaster RL, Iqbal F, Halbower A, Goldman SE, et al. Heart rate variability during sleep in children with autism spectrum disorder. *Clin Auton Res.* (2016) 26:423–32. doi: 10.1007/s10286-016-0375-5
29. Schaffler MD, Middleton LJ, Abdus-Saboor I. Mechanisms of tactile sensory phenotypes in autism: current understanding and future directions for research. *Curr Psychiatry Rep.* (2019) 21:134. doi: 10.1007/s11920-019-1122-0
30. Poh MZ, McDuff DJ, Picard RW. Non-contact, automated cardiac pulse measurements using video imaging and blind source separation. *Opt Express.* (2010) 18:10762–74. doi: 10.1364/OE.18.010762
31. Fukunishi M, Kurita K, Yamamoto S, Tsumura N. Non-contact video based estimation of heart rate variability spectrogram from hemoglobin composition. *Artif Life Robot.* (2017) 22:457–63. doi: 10.1007/s10015-017-0382-1
32. Porges SW. The polyvagal perspective. *Biol Psychol.* (2007) 74:116–43. doi: 10.1016/j.biopsycho.2006.06.009
33. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. *Front Public Health.* (2017) 5:258. doi: 10.3389/fpubh.2017.00258
34. Gross JJ, Levenson RW. Emotion elicitation using films. *Cogn Emot.* (1995) 9:87–108. doi: 10.1080/02699939508408966
35. Samson AC, Kreibig SD, Soderstrom B, Wade AA, Gross JJ. Eliciting positive, negative and mixed emotional states: a film library for affective scientists. *Cognit Emot.* (2016) 30:827–56. doi: 10.1080/02699931.2015.1031089
36. Werling DM, Geschwind DH. Sex differences in autism spectrum disorders. *Curr Opin Neurol.* (2013) 26:146–53. doi: 10.1097/WCO.0b013e32835ee548
37. Van Wijngaarden-Cremers PJM, van Eeten E, Groen WB, Van Deurzen PA, Oosterling IJ, Van der Gaag RJ. Gender and age differences in the core triad of impairments in autism spectrum disorders: a systematic review and meta-analysis. *J Autism Dev Disord.* (2014) 44:627–35. doi: 10.1007/s10803-013-1913-9
38. Parsons OE, Bayliss AP, Remington A. A few of my favorite things: circumscribed interests in autism are not accompanied by increased attentional salience on a personalized selective attention task. *Mol Autism.* (2017) 8:20. doi: 10.1186/s13229-017-0132-1
39. Brosnan M, Johnson H, Grawmeyer B, Chapman E, Benton L. Emotion recognition in animated compared to human stimuli in adolescents with autism spectrum disorder. *J Autism Dev Disord.* (2015) 45:1785–96. doi: 10.1007/s10803-014-2338-9
40. Himichi T, Osanai H, Goto T, Fujita H, Kawamura Y, Davis MH, et al. Development of a Japanese version of the interpersonal reactivity index. *Japan J Psychol.* (2017) 88:61–71. doi: 10.4992/jjpsy.88.15218
41. Komaki G, Maeda M, Arimura T, Nakata A, Shinoda H, Ogata I, et al. The reliability and factorial validity of the Japanese version of the 20-item toronto alexithymia scale (TAS-20). *Jpn J Psychosom Med.* (2003) 43:839–46. doi: 10.1016/S0022-3999(03)00360-X
42. Davis MH. Measuring individual differences in empathy: Evidence for a multidimensional approach. *J. Pers. Soc. Psychol.* (1983) 44:113–26. doi: 10.1037/0022-3514.44.1.113
43. Bagby RM, Taylor GJ, Parker JDA. The twenty-item toronto alexithymia scale: II. Convergent, discriminant, concurrent validity. *J Psychosom Res.* (1994) 38:33–40. doi: 10.1016/0022-3999(94)90006-X
44. Fukunishi M, Kurita K, Yamamoto S, Tsumura N. Video Based measurement of heart rate and heart rate variability spectrogram from estimated hemoglobin information. In: *2018 IEEE/CVF Conference on Computer Vision and Pattern Recognition Workshops (CVPRW)*. Salt Lake City, UT. (2018). doi: 10.1109/CVPRW.2018.00180
45. Tsumura N, Haneishi H, Miyake Y. Independent-component analysis of skin color image. *J Opt Soc Am A Opt Image Sci Vis.* (1999) 16:2169–76. doi: 10.1364/JOSAA.16.002169
46. Tarvainen MP, Niskanen JP, Lipponen JA, Ranta-Aho PO, Karjalainen PA. Kubios HRV–heart rate variability analysis software. *Comput Methods Programs Biomed.* (2014) 113:210–20. doi: 10.1016/j.cmpb.2013.07.024
47. Erbas Y, Ceulemans E, Boonen J, Noens I, Kuppens P. Emotion differentiation in autism spectrum disorder. *Res Autism Spectr Disord.* (2013) 7:1221–7. doi: 10.1016/j.rasd.2013.07.007
48. Cath DC, Ran N, Smit JH, van Balkom AJLM, Comijs HC. Symptom overlap between autism spectrum disorder, generalized social anxiety disorder and obsessive-compulsive disorder in adults: A preliminary case-controlled study. *Psychopathology.* (2008) 41:101–10. doi: 10.1159/000111555
49. Hartley CA, Phelps EA. Changing fear: the neurocircuitry of emotion regulation. *Neuropsychopharmacology.* (2010) 35:136–46. doi: 10.1038/npp.2009.121
50. Metallinou A, Grossman RB, Narayanan S. Quantifying atypicality in affective facial expression of children with autism spectrum disorders. *Proc.* (2013) 2013:1–6. doi: 10.1109/ICME.2013.6607640
51. Lenroot RK, Yeung PK. Heterogeneity within autism spectrum disorders: what have we learned from neuroimaging studies? *Front Hum Neurosci.* (2013) 7:733. doi: 10.3389/fnhum.2013.00733
52. Doi H, Fujisawa TX, Iwanaga R, Matsuzaki J, Kawasaki C, Tochigi M, et al. Association between single nucleotide polymorphisms in estrogen receptor 1/2 genes and symptomatic severity of autism spectrum disorder. *Res Dev Disabil.* (2018) 82:20–6. doi: 10.1016/j.ridd.2018.02.014
53. Asif M, Martiniano HFMC, Marques AR, Santos JX, Vilela J, Rasga C, et al. Identification of biological mechanisms underlying a multidimensional ASD phenotype using machine learning. *Transl Psychiatry.* (2020) 10:43. doi: 10.1038/s41398-020-0721-1
54. Kinnaird E, Stewart C, Tchanturia K. Investigating alexithymia in autism: a systematic review and meta-analysis. *Eur Psychiatry.* (2019) 55:80–9. doi: 10.1016/j.eurpsy.2018.09.004
55. Top DN, Stephenson KG, Doxey CR, Crowley MJ, Kirwan CB, South M. atypical amygdala response to fear conditioning in autism spectrum disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging.* (2016) 1:308–15. doi: 10.1016/j.bpsc.2016.01.008
56. Hewig J, Hagemann D, Seifert J, Gollwitzer M, Naumann E, Bartussek D. A revised film set for the induction of basic emotions. *Cogn Emot.* (2005) 19:1095–109. doi: 10.1080/02699930541000084
57. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 years — Autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *MMWR Surveil Summaries.* (2018) 67:1–23. doi: 10.15585/mmwr.ss6706a1

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Considerations and Perspectives on Interventions to Improve Social Cognition in Adolescents With ASD Without ID: Involving Parents in Social Skills Groups

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Improving social cognition and social skills is a challenge faced by individuals with Autism Spectrum Disorder without Intellectual Disability at any age. This process is particularly critical during late adolescence (15–18 years), a developmental phase generally characterized by rich social experiences that usually foster the development of friendships. Nevertheless, for youth with ASD, lingering difficulties in social cognition often hinder their ability to generate responses considered socially appropriated. These social deficits can contribute to isolation that has a detrimental effect on mental health. In adulthood, deficits of social skills are strongly associated with an overall lack of support, characterized by a failure to integrate into the labor market, a high unemployment rate, social isolation, and a higher suicide rate. In clinical settings, social skills groups are well-established therapeutic means to improve social cognition and social skills. Nevertheless, these interventions vary greatly regarding their objectives, contents and duration. Moreover, few have been validated and replicated by research. Our aim is to bring certain perspectives to a type of intervention that are widely used in care settings. After reviewing its positive aspects for increasing social cognition, and its limitations, we will discuss strategies to facilitate the generalization of social skills in an ecological context. In particular, we will base our reflection on our clinical experience and on our current project to adapt the PEERS© model for adolescents into French. We will consider the current trend of involving parents as "social coaches" to generalize the social knowledge acquired in the social skills groups.

Keywords: Autism Spectrum Disorder without intellectual disability, adolescents, parents, evidence-based interventions, social skills groups

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INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by social communication deficits with the presence of stereotypical behaviors, sensory atypicalities, and restricted interests. The clinical presentations of ASD are heterogeneous, with various levels of intellectual and motor functioning and verbal skills (1). ASD is often associated with comorbid disorders such as anxiety or ADHD that have a significant impact on a person's

functioning and, consequently, on their quality of life (2–4). ASD's prevalence globally increases and is now estimated at 18.5/1,000 (i.e., 1/54) in children of 8 years of age in the United States (5, 6).

In the case of individuals with ASD without intellectual disabilities (ID), it appears that improving social skills has long been considered as a main challenge throughout their development, particularly during adolescence and the transition to adulthood (7). Indeed, this critical period is characterized by a phase generally rich in social experiences that foster the development of friendly relationships with peers (8–10). These naturally learned behaviors and attitudes contribute to acceptance by peers and usually avoid marginalization. For adolescents with ASD without ID, difficulties often persist in social communication. This includes, for example, proposing topics for discussion or repetitive conversations based on their specific interests not always shared by peers (11, 12). Difficulties in the acquisition of social skills in ASD have been linked to deficits in social cognition. Based on the cognitive and emotional processes that underlie the understanding and prediction of others' behaviors, social cognition is a concept that encompasses several skills, ranging from basic recognition of emotions to more complex processes such as perspective taking, also known as theory of mind (12–14). These cognitive, affective, and behavioral skills form the basis of social skills and thus social behavior. Deficits in social cognition impact social skills and interfere with the production of responses considered socially appropriate. In a neurotypical world, these social challenges are, at any age, an isolating and exclusion factor from peers (15). Rejection also affects ASD youth's mental health and is a risk factor for developing depression or anxiety disorders (7, 10, 16). These difficulties continue in the access to employment in adulthood (17, 18). Social relationships remain a major factor in job rejection and a source of stress for workers with autism (19). Deficit of social skills are accompanied by an overall lack of support characterized by a failure to integrate into the labor market and a high unemployment rate (17, 19, 20). In fact, studies on adults with ASD without ID report psychiatric co-morbidities and increased social isolation with a higher suicide rate for this population (21).

In recent years, researchers and clinicians have focused on the development of interventions aimed at supporting youth with ASD without ID to better understand social situations and respond with appropriate social behaviors (22). To this end, over the past two decades, social skills groups emerged as a natural attempt to extend learning in an individual setting by grouping participants with common difficulties. Nevertheless, this common practice in health care settings has led to very variable support in terms of objectives, content and duration. For adolescents, the contribution of parents or other significant caregivers as "social coaches" and generalization agents was considered later (23, 24). Moreover, perceptions about people with autism are changing. Under a new vision of neurodiversity, their differences are beginning to be increasingly recognized as strengths rather than the sum of social deficits. We need then to look at these groups with new perspectives. The feedbacks of people with autism and their families appear to be an essential prerequisite for improving and redefine them. In this paper, our objective is, first of all, to review the elements validating the effectiveness of social skills groups and the limits to consider. We will then discuss on the active contribution of parents. Finally, we will conclude on new reflexions on these groups to best meet the current needs and expectations of young people with ASD.

SOCIAL SKILLS GROUPS FOR ADOLESCENTS: KNOWN BENEFITS AND LIMITATIONS

First, how a social intervention can be considered "efficient"? In social skill group, we speak of effectiveness, when the objectives of acquiring new social skills are achieved (e.g., the adolescent can start and follow a reciprocal conversation with peers). Generalization refers to new skills that are reused appropriately outside the group in more natural contexts. One of the most important benefits of participating in a social skill group is the improvement of social knowledge and the quality of friendship relationships (25). Then, participation in a social skill group can also bring benefits in terms of improved emotional skills and social communication (26). Young people would have more opportunities to spend time with friends and would demonstrate a reduction in inappropriate social behaviors in favor of more adapted social behaviors (7, 27). Finally, this type of intervention is generally appreciated by participants for the sense of belonging and mutual support that the group provides in experiencing positive social interactions in a secure setting (28). Despite their popularity in clinical settings, the overall benefits of these interventions remain modest, with a small number of meta-analyses reporting improvements in social skills with average overall effect sizes (25, 29). In addition, a significant portion of validation studies has focused on evidence-based practices for preschool-age children and elementary school-age children (15, 30). Only a minority of the randomized controlled trials (RCT) identified in the most recent meta-analyses targeted social skills groups for adolescents (25, 29).

It is important to recognize that social skills are complex, context-related, and therefore subject to variation among different informants who observe change and on the instruments used to measure it (29, 31, 32). Most of the measures gathered in the literature are based on pre- and post-test questionnaires filled out by parents, adolescents, and in some cases by teachers and external observers (33). A high level of variability is then encountered in the results. The parental questionnaires most commonly used in programs are the Social Responsiveness Scale (SRS) and the Social Skills Rating System (SSRS) (34). The meta-analysis by Gates et al. (29) highlights a significant self-reported effect among youth in the overall improvement of their skills while parents do not report the same progress. This discrepancy in outcomes can be attributed to adolescents' bias to overestimate their skills (35). This effect would be enhanced by their sense of satisfaction after group participation (29, 33). In addition, the authors call for caution on outcomes. Indeed, a distinction must be drawn between "social knowledge" and "social performance," two measures that are often analyzed conjointly (35, 36). When

this distinction is taken into account, the results indicate a significant improvement in social knowledge among adolescents, but no benefits in terms of overall social performance (25, 29, 37).

Some other limitations about the social skills groups' effectiveness study must also be taken into account. Social skills groups are also heterogeneous in terms of curriculum content. Some intervention formats present the content and the behaviors to be adopted with a structured didactic approach and behavior rehearsals, designed as "social knowledge training," while others, known as "social performance training" will rather focus into the experimentation of positive exchanges, where the skills are implicitly taught (29, 33, 38). Of the 25 manualized interventions identified by Hall et al. (39), only five programs offer an effectiveness study and only three consider generalization aspects. This is the case of Skillstreaming (40) aimed at teaching emotional and prosocial skills for adolescent with common social needs, Social Competence Intervention, a curriculum that combines cognitive-behavioral and applied behavior analysis principals to enhance specific social competences (27) and Program for the Education and Enrichment of Relational Skills, (PEERS©) which focuses on improving friendship for Adolescents with ASD without ID (41). This latter program, with the most research published, will be discussed below.

For adolescents with ASD without ID, transferring new knowledge of social rules into various contexts and maintaining it over time remains a challenge (29, 37, 42). To date, few studies include follow-up measures for groups of adolescents with ASD without ID (24), especially since research findings are inconsistent in measuring generalization and skill maintenance (43).

INVOLVEMENT OF PARENTS AS COACHES AND GENERALIZATION AGENTS

Clinicians observe that one of the most recurring requests from parents of adolescents with ASD without ID is precisely to target social skills work. They are very often worried about the social gap between their child and peers. Indeed, the differences experienced by adolescents can lead to a drop in self-esteem, anxiety, and depressive symptoms or manipulating conducts for the young person's social entourage (e.g., bullying). A recent review has identified the most effective components to generalize the skills acquired through participation in a social skills group (44). It appears that the individualization of objectives and the constant links with the adolescent's natural environment are precisely significant predictors of the effectiveness of these interventions. The presence of typical peers, the regular practice of the skills learned alongside them and the active involvement of parents also help to improve their effectiveness. Indeed, social skills groups that include groups of parents are those that obtain the most promising results with larger effect sizes (32).

For this reason, some programs involve parents as active support agents in the intervention. This is the case of PEERS©, that our team has translated into French and is currently experimenting in a French-speaking context (French-speaking Switzerland) with adolescents with ASD without ID aged 15–18. PEERS© is based on the joint involvement of adolescents and their parents with the common goal of learning and developing friendships (41). It emerges as one of the most research-validated manualized programs that has been replicated in different cultural backgrounds with a durability of these gains over time (39). Indeed, follow-up measures over 1–5 years have shown that social skills were maintained and improved, including social responsiveness, better social knowledge, and a higher level of social reciprocity with an increased number of get together with peers (24, 45). The maintenance of its effects could be explained by the participation of the parents who would have acted as agents of reinforcement and generalization of the acquired knowledge (24). This program includes 14 weekly 90-min social skills training sessions for adolescents with ASD without ID, while their parents attend parallel coaching sessions to teach them how to help their child to generalize these skills. In small groups (6–8 participants), the teaching of adolescents is based on learning practical rules governing social codes and skills that are ecologically valid, i.e., applicable in different contexts of adolescents' daily lives (e.g., developing friendships, knowing the rules of reciprocal communication, the etiquette of social networks and electronic communications, dealing with conflict and rejection, etc.). It is complemented by demonstrations of appropriate or bad social behavior models (video-modeling), role-playing and exercises for which adolescents receive feedback from facilitators and peers. The youth are given small homework assignments, which present gradual challenges to practice and generalize what they have learned between sessions. These cognitive-behavioral components are the ones that have been mainly found to be the most effective way to improve social skills (25, 46, 47).

During this time, parents work together on the same topic as their child. Another facilitator begins by talking with them about their child's successes and challenges related to the previous session, raising any difficulties in completing homework assignments, and finding new ways to accomplish them successfully. These sessions are not seen here as classic support sessions such as a support group because their objective is clearly to provide parents with tools related to a social theme (e.g., finding an appropriate group of friends, and managing rumors). Nevertheless, the atmosphere is generally warm between parents who share their experiences and are invited to propose solutions to the other participants. At the end of each session, teenagers and parents meet to agree on their roles and tasks for the next session. Outside of the sessions, parents take over to support the homework assigned to their child in order to repeat these teachings in a natural social context and to continue to generalize the skills discussed.

PEERS© combines a didactic approach and social rehearsal. Its originality lies particularly in the involvement of parents. It appears that general participation in a psychoeducational parenting skills training program has a positive impact on their children's development as well as on their own well-being (48). In the PEERS© model, their involvement can give them a sense of control over the difficulties they face and reduce significantly their stress (49). PEERS© has been validated and replicated in

other cultural backgrounds as Israel or Asian countries (50–53). In Europe, a Dutch team is currently conducting a RCT to compare their results with those of an active control group (54). At this stage, our experience remains very modest but our goal is to adapt it in a francophone RCT. Nevertheless, our preliminary observations are in line with results of larger samples, particularly in terms of increasing knowledge of social conventions. Overall, adolescents and their parents shared positive experiences with the program and the relevance of the new skills learned. As Mirzaei et al. (44) point out, active parental involvement thus brings an added value between what is learned in the rather limited context of the social skills group and the adolescent's life with peers and family in his or her daily life. The fact that parents are equipped and have access to the same lessons and content as their children, allows them to go beyond what is taught in a 14-session program.

GOING FURTHER: PERSPECTIVES

With 20 years of hindsight in the field of social skills groups, researchers, and clinicians in all countries are now facing several observations but also questions to ensure that this type of intervention continues to gain in effectiveness. We will end here by addressing some practical aspects and raising more general questions.

First of all, due to the complexity of social skills, the characteristics of each participant and the variability of the available outcomes, the measurement of the effectiveness of social skills programs still needs to be improved. While self-report questionnaires remain an effective measure for improvements in social knowledge (32), more refined tools are needed to objectively measure adolescents' progress, especially since the questionnaires used have not been developed to specifically assess social skill groups (33). A valuable measure would be the involvement in programs of trained blind observers who could thus assess the ability of the participants to generalize their learning in different ecological settings (33, 55). However, access to and training of these observers involves a significant financial and time investment (24). In a recent study, Keifer et al. (31) support the importance of using different types of measures to observe changes in social cognition and social behavior. They point out that the general concept of social cognition needs to be further decomposed with the less studied measure of implicit social cognition defined by "processes that are fast, spontaneous, and primarily unconscious" (56). Yet, it is precisely these processes that would predict outcomes on social awareness and are observed through changes in young people's social behavior. The authors combined electrophysiological measures with other types of data such as the number of creative solutions proposed or the reaction time taken to solve a problematic social situation. Keifer et al. (31) recommend that it is therefore crucial that implicit social cognition be targeted by future interventions but also better measured as a marker of change in social skills.

Second, adolescents' motivation to participate in this type of program is an important question and may differ from their parents' motivation. Parents see or anticipate their children's difficulties, while teens do not necessarily see the benefits and claim their right to a certain social singularity. Their reticence is often explained by years of negative experiences that have led them to withdraw from the social world or to apprehend it through internalized or externalized disorders. It is important that adolescents feel fully free to accept or refuse to participate in a group despite certain well-intentioned pressures from those around them. Here, the fact that their parents are actively involved and block this time to support them in a concrete way may be a facilitating factor. Joint participation in the group can then be more easily accepted as a joint attempt to find solutions rather than another "extra-curricular" activity that rests solely on the adolescent's shoulders. It should be emphasized that this transition period to adulthood is often accompanied by a high level of anxiety experienced at the academic level (revisions, exams and preparation for team work) in addition to being associated with all the decisive questions of school and career orientation.

These questions about motivation and improvement of the effectiveness social skills groups finally lead us to take a step back and ask about the social objectives targeted solutions that we propose to try to overcome the "core deficits" of ASD. At present, the questions of camouflage, defined as behaviors used to hide or mask "autistic" aspects of one's personality, and social compensation strategies are more and more reported by adolescents and adults with ASD, who very generally name the exhaustion that the application of social rules engenders on their mental health (57). More than ever, it is a matter of working with autistic individuals themselves to determine their expectations, their needs and jointly establish the best tools to best navigate the complexities of the social world while recognizing their singularity and the right to neurodiversity. Bottema-Beutel et al. (37) thus warn of the risk that participation in a social skills group restricts the authenticity of its participants without diminishing the risks of stigmatization.

In a recent editorial on the issue of camouflage, Fombonne (58) "note[s] incidentally that most behaviors discussed in camouflage commentaries are precisely those skills that are actively targeted for scaffolding in social skill treatment interventions" (p.737). This perspective on the issue of teaching neurotypical social rules leads to the idea of continuing to improve the quality of our social skills groups by tailoring its objectives to the particular needs of its participants (27, 44). One proposal would be to revisit the experiences of those who have participated in these groups. In this way, qualitative research could clarify in greater detail how their participation met their needs or if group participation had contributed to feeling more stigmatized and anxious.

These ideas of close partnership have been taken up in different countries such as the United Kingdom, which encourages people with ASD to be active and paid consultants to help clinical teams to adapt medical interventions to their particular needs (59). In the social skills groups, participating youth and their parents could then become consultants whose experience would be valuable in improving the design of these groups, identifying the components that have been most helpful to them and the variables that remain impediments. Their subsequent participation as "mentors" and their testimonials

about their progress after participating in such a group could also be a form of mentoring that would encourage their younger peers and their parents.

To conclude, social skills groups constantly lead us to question our tools. More broadly, they also lead us to reflect on our social rules, the behaviors defined by the group as socially appropriate and those that, on the contrary, are a source of rejection. We must then discuss together the bases governing life in the community in order to facilitate exchanges and to better understand behaviors that autistic and neurotypical people may each consider as "bizarre." What are the social rules considered indispensable by all and which "battles" should we prioritize? On which rules should society be more tolerant and inclusive? These are all ethical questions that deserve to be tackled together and should guide the foundations of the implementation of future social skills groups.

AUTHOR CONTRIBUTIONS

DV and DC reviewed the available evidence and took the lead in writing the manuscript. NC provided critical feedback. All authors agree with the content of this manuscript.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th edn. Washington, DC (2013).
2. Moss P, Mandy W, Howlin P. Child and adult factors related to quality of life in adults with autism. *J Autism Dev Disord.* (2017) 47:1830–7. doi: 10.1007/s10803-017-3105-5
3. Khanna R, Jariwala-Parikh K, West-Strum D, Mahabaleshwarkar R. Health-related quality of life and its determinants among adults with autism. *Res Autism Spectrum Disord.* (2014) 8:157–67. doi: 10.1016/j.rasd.2013.11.003
4. Tobin MC, Drager KDR, Richardson LF. A systematic review of social participation for adults with autism spectrum disorders: support, social functioning, and quality of life. *Res Autism Spectrum Disord.* (2014) 8:214–29. doi: 10.1016/j.rasd.2013.12.002
5. Maenner MJ, Shaw KA, Baio J, Washington A, Patrick M, DiRienzo M, et al. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2016. *Morb Mortal Weekly Rep.* (2020) 69:1–12. doi: 10.15585/mmwr.ss6904a1
6. Chiarotti F, Venerosi A. Epidemiology of Autism Spectrum Disorders: A Review of Worldwide Prevalence Estimates Since 2014. (2020) 10:274. PubMed PMID: doi: 10.3390/brainsci10050274
7. Volkmar FR, Reichow B, McPartland JC. Autism spectrum disorder in adolescents and adults: an introduction. In: Volkmar FR, Reichow B, McPartland JC, editors. *Adolescents and Adults With Autism Spectrum Disorders*. New York, NY: Springer New York (2014). p. 1–13.
8. Ke F, Whalon K, Yun J. Social skill interventions for youth and adults with autism spectrum disorder: a systematic review. *Rev Educ Res.* (2018) 88:3–42. doi: 10.3102/0034654317740334
9. Humphrey N, Symes W. Peer interaction patterns among adolescents with autistic spectrum disorders (ASDs) in mainstream school settings. *Autism.* (2011) 15:397–419. doi: 10.1177/1362361310387804
10. Ratcliffe B, Wong M, Dossetor D, Hayes S. The association between social skills and mental health in school-aged children with autism spectrum disorder, with and without intellectual disability. *J Autism Dev Disord.* (2015) 45:2487–96. doi: 10.1007/s10803-015-2411-z
11. Ellingsen R, Bolton C, Laugeson E. Evidence-based social skills groups for individuals with autism spectrum disorder across the lifespan. In: Leaf JB, editor. *Handbook of Social Skills and Autism Spectrum Disorder: Assessment, Curricula, and Intervention*. Cham: Springer International Publishing (2017). p. 343–58.
12. Mendelson JL, Gates JA, Lerner MD. Friendship in school-age boys with autism spectrum disorders: a meta-analytic summary and developmental, process-based model. *Psychol Bull.* (2016) 142:601–22. doi: 10.1037/bul0000041
13. Baron-Cohen S. *Mindblindness: An Essay on Autism and Theory of Mind*. Cambridge, MA: MIT Press (1997).
14. Senju A. Atypical development of spontaneous social cognition in autism spectrum disorders. *Brain Dev.* (2013) 35:96–101. doi: 10.1016/j.braindev.2012.08.002
15. Moody CT, Laugeson EA. Social skills training in autism spectrum disorder across the lifespan. *Psychiatr Clin N Am.* (2020) 43:687–99. doi: 10.1016/j.psc.2020.08.006
16. Wright MF, Wachs S. Does peer rejection moderate the associations among cyberbullying victimization, depression, and anxiety among adolescents with Autism Spectrum Disorder? *Children.* (2019) 6:41. doi: 10.3390/children6030041
17. Scott M, Milbourn B, Falkmer M, Black M, Bölte S, Halladay A, et al. Factors impacting employment for people with autism spectrum disorder: a scoping review. *Autism.* (2019) 23:869–901. doi: 10.1177/1362361318787789
18. Anderson C, Butt C, Sarsony C. Young adults on the autism spectrum and early employment-related experiences: aspirations and obstacles. *J Autism Dev Disord.* (2021) 51:88–105. doi: 10.1007/s10803-020-04513-4
19. Solomon C. Autism and employment: implications for employers and adults with ASD. *J Autism Dev Disord.* (2020) 50:4209–17. doi: 10.1007/s10803-020-04537-w
20. Howlin P. Social disadvantage and exclusion: adults with autism lag far behind in employment prospects. *J Am Acad Child Adolesc Psychiatry.* (2013) 52:897–9. doi: 10.1016/j.jaac.2013.06.010
21. Cassidy SA, Robertson A, Townsend E, O'Connor RC, Rodgers J. Advancing our understanding of self-harm, suicidal thoughts and behaviours in autism. *J Autism Dev Disord.* (2020) 50:3445–9. doi: 10.1007/s10803-020-04643-9
22. Cappadocia MC, Weiss JA. Review of social skills training groups for youth with Asperger Syndrome and High Functioning Autism. *Res Autism Spectrum Disord.* (2011) 5:70–8. doi: 10.1016/j.rasd.2010.04.001
23. Frankel F, Myatt R, Feinberg D. Parent-assisted friendship training for children with autism spectrum disorders: effects of psychotropic medication. *Child Psychiatry Hum Dev.* (2007) 37:337–46. doi: 10.1007/s10578-007-0053-x
24. Mandelberg J, Frankel F, Cunningham T, Gorospe C, Laugeson EA. Long-term outcomes of parent-assisted social skills intervention for high-functioning children with autism spectrum disorders. *Autism.* (2014) 18:255–63. doi: 10.1177/1362361312472403
25. Reichow B, Steiner AM, Volkmar F. Social skills groups for people aged 6 to 21 with autism spectrum disorders (ASD). *Cochrane Database Syst Rev.* (2012) 7:CD008511. doi: 10.1002/14651858.CD008511.pub2
26. Tse J, Strulovitch J, Tagalakis V, Meng L, Fombonne E. Social skills training for adolescents with Asperger Syndrome and high-functioning autism. *J Autism Dev Disord.* (2007) 37:1960–8. doi: 10.1007/s10803-006-0343-3
27. Stichter JP, Herzog MJ, Visovsky K, Schmidt C, Randolph J, Schultz T, et al. Social competence intervention for youth with Asperger Syndrome and high-functioning autism: an initial investigation. *J Autism Dev Disord.* (2010) 40:1067–79. doi: 10.1007/s10803-010-0959-1
28. Webb BJ, Miller SP, Pierce TB, Strawser S, Jones WP. Effects of social skill instruction for high-functioning adolescents with Autism Spectrum Disorders. *Focus Autism Other Dev Disabil.* (2004) 19:53–62. doi: 10.1177/10883576040190010701
29. Gates JA, Kang E, Lerner MD. Efficacy of group social skills interventions for youth with autism spectrum disorder: a systematic review and meta-analysis. *Clin Psychol Rev.* (2017) 52:164–81. doi: 10.1016/j.cpr.2017.01.006
30. Wong C, Odom SL, Hume KA, Cox AW, Fettig A, Kucharczyk S, et al. Evidence-based practices for children, youth, and young adults with Autism

Spectrum Disorder: a comprehensive review. *J Autism Dev Disord.* (2015) 45:1951–66. doi: 10.1007/s10803-014-2351-z
31. Keifer CM, Mikami AY, Morris JP, Libsack EJ, Lerner MD. Prediction of social behavior in autism spectrum disorders: explicit versus implicit social cognition. *Autism.* (2020) 24:1758–72. doi: 10.1177/1362361320922058
32. Wolstencroft J, Robinson L, Srinivasan R, Kerry E, Mandy W, Skuse D. A systematic review of group social skills interventions, and meta-analysis of outcomes, for children with high functioning ASD. *J Autism Dev Disord.* (2018) 48:2293–307. doi: 10.1007/s10803-018-3485-1
33. McMahon CM, Lerner MD, Britton N. Group-based social skills interventions for adolescents with higher-functioning autism spectrum disorder: a review and looking to the future. *Adolesc Health Med Ther.* (2013) 2013:23–8. doi: 10.2147/AHMT.S25402
34. Gresham FM, Elliott SN. *Social skills rating system (SSRS)*. American Guidance Service (1990).
35. Lerner MD, Calhoun CD, Mikami AY, De Los Reyes A. Understanding parent-child social informant discrepancy in youth with high functioning autism spectrum disorders. *J Autism Dev Disord.* (2012) 42:2680–92. doi: 10.1007/s10803-012-1525-9
36. Lerner MD, Mikami AY. A preliminary randomized controlled trial of two social skills interventions for youth with high-functioning Autism Spectrum Disorders. *Focus Autism Other Dev Disabil.* (2012) 27:147–57. doi: 10.1177/1088357612450613
37. Bottema-Beutel K, Park H, Kim SY. Commentary on social skills training curricula for individuals with ASD: social interaction, authenticity, and stigma. *J Autism Dev Disord.* (2018) 48:953–64. doi: 10.1007/s10803-017-3400-1
38. Lerner MD, White SW. Moderators and mediators of treatments for youth with autism spectrum disorders. *Moderators Mediators Youth Treatment Outcomes.* (2015) 146. doi: 10.1093/med:psych/9780199360345.003.0007
39. Hall LJ, Leinert S, Jacquez J. A review of social skills manuals for adolescents with Autism Spectrum Disorder. *Curr Dev Disord Rep.* (2018) 5:77–88. doi: 10.1007/s40474-018-0134-5
40. McGinnis E, Sprafkin RP, Gershaw N, Klein PC. *Skillstreaming the Adolescent: A Guide for Teaching Prosocial Skills*. Champaign, IL: Research Press (2012).
41. Laugeson EA, Frankel F. *Social Skills for Teenagers With Developmental and Autism Spectrum Disorders: The PEERS Treatment Manual.* New York, NY: Routledge (2011).
42. Hotton M, Coles S. The effectiveness of social skills training groups for individuals with Autism Spectrum Disorder. *Rev J Autism Dev Disord.* (2016) 3:68–81. doi: 10.1007/s40489-015-0066-5
43. White SW, Koenig K, Scahill L. Group social skills instruction for adolescents with high-functioning Autism Spectrum Disorders. *Focus Autism Other Dev Disabil.* (2010) 25:209–19. doi: 10.1177/1088357610380595
44. Mirzaei SS, Pakdaman S, Alizadeh E, Pouretemad H. A systematic review of program circumstances in training social skills to adolescents with high-functioning autism. *Int J Dev Disabil.* (2020) 1–10. doi: 10.1080/20473869.2020.1748802
45. Zheng S, Kim H, Salzman E, Ankenman K, Bent S. Improving social knowledge and skills among adolescents with autism: systematic review and meta-analysis of UCLA PEERS® for adolescents. *J Autism Dev Disord.* (2021) 1–16. doi: 10.1007/s10803-021-04885-1
46. Laugeson EA, Park MN. Using a CBT approach to teach social skills to adolescents with autism spectrum disorder and other social challenges: the PEERS® method. *J Ration Emotive Cogn Behav Therapy.* (2014) 32:84–97. doi: 10.1007/s10942-014-0181-8
47. Gresham FM, Watson TS, Skinner CH. Functional behavioral assessment: principles, procedures, and future directions. *School Psychol Rev.* (2001) 30:156–72. doi: 10.1080/02796015.2001.12086106
48. Prata J, Lawson W, Coelho R. Parent training for parents of children on the autism spectrum: a review. *Health.* (2018) 5:3–8. doi: 10.21035/ijcnmh.2018.5.3
49. Corona LL, Janicki C, Milgramm A, Christodulu KV. Brief Report: reductions in parenting stress in the context of PEERS-A social skills intervention for adolescents with Autism Spectrum Disorder. *J Autism Dev Dis.* (2019) 49:5073–7. doi: 10.1007/s10803-019-04201-y
50. Rabin SJ, Laugeson EA, Mor-Snir I, Golan O. An Israeli RCT of PEERS®: intervention effectiveness and the predictive value of parental sensitivity. *J Clin Child Adolesc Psychol.* (2020) 1–17. doi: 10.1080/15374416.2020.1796681
51. Shum KK-M, Cho WK, Lam LMO, Laugeson EA, Wong WS, Law LSK. Learning how to make friends for chinese adolescents with autism spectrum disorder: a randomized controlled trial of the Hong Kong Chinese Version of the PEERS® intervention. *J Autism Dev Disord.* (2019) 49:527–41. doi: 10.1007/s10803-018-3728-1
52. Hong JK, Oh M, Bong G, Kim J-H, Bahn G, Cho I-H, et al. Age as a moderator of social skills intervention response among korean adolescents with Autism Spectrum Disorder. *J Autism Dev Disord.* (2019) 49:1626–37. doi: 10.1007/s10803-018-3859-4
53. Yamada T, Miura Y, Oi M, Akatsuka N, Tanaka K, Tsukidate N, et al. Examining the treatment efficacy of PEERS in Japan: improving social skills among adolescents with autism spectrum disorder. *J Autism Dev Disord.* (2020) 50:976–97. doi: 10.1007/s10803-019-04325-1
54. van Pelt BJ, Idris S, Jagersma G, Duvekot J, Maras A, van der Ende J, et al. The ACCEPT-study: design of an RCT with an active treatment control condition to study the effectiveness of the Dutch version of PEERS® for adolescents with autism spectrum disorder. *BMC Psychiatry.* (2020) 20:274. doi: 10.1186/s12888-020-02650-9
55. Laugeson EA, Gantman A, Kapp SK, Orenski K, Ellingsen R. A randomized controlled trial to improve social skills in young adults with Autism Spectrum Disorder: the UCLA PEERS® program. *J Autism Dev Disord.* (2015) 45:3978–89. doi: 10.1007/s10803-015-2504-8
56. Callenmark B, Kjellin L, Rönnqvist L, Bölte S. Explicit versus implicit social cognition testing in autism spectrum disorder. *Autism.* (2014) 18:684–93. doi: 10.1177/1362361313492393
57. Hull L, Petrides KV, Allison C, Smith P, Baron-Cohen S, Lai M-C, et al. "Putting on My Best Normal": social camouflaging in adults with autism spectrum conditions. *J Autism Dev Disord.* (2017) 47:2519–34. doi: 10.1007/s10803-017-3166-5
58. Fombonne E. Camouflage and autism. *J Child Psychol Psychiatry Allied Discipl.* (2020) 61:735–8. doi: 10.1111/jcpp.13296
59. Care DoHS. '*Right To Be Heard': The Government's Response to the Consultation on Learning Disability and Autism Training for Health and Care Staff* (2019).

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Circumscribed Interest Modulates Attention to Eyes in Boys With and Without Autism Spectrum Disorder

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Children with autism spectrum disorder (ASD) exhibit abnormal visual attention, such as diminished attention to eyes and enhanced attention to high-autism-interest objects. We tested whether high-autism-interest objects would modulate the attention to eyes in boys with ASD and typically developing (TD) boys. Twenty-two ASD and 22 TD children were presented simultaneously with human eyes and high/low-autism-interest objects (HAI/LAI) while their eye movements were recorded. We found that visual preference for eyes was influenced by competing objects in children with and without ASD. Specifically, both children with and without ASD showed reduced overall and first looking preference when eyes were paired with HAI objects relative to LAI objects. Children with ASD also showed reduced sustained viewing preference to the eyes after first looking at the eyes and late looking preference to the eyes after first looking at the objects in the HAI condition than the LAI condition, but these effects were absent in the TD group. Our study not only helps us understand some factors that impact attention to eyes, but also has implications for interventions aiming at improving eye contact in children with ASD.

Keywords: autism spectrum disorder, eye-avoidance, circumscribed interests, visual attention, eye movement

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by two main core symptoms—social communication deficits and restricted interests and repetitive behaviors (1). Most previous work has focused on one of these two symptoms, while only a few studies have focused on the relation between these two core symptoms (2). Of these studies, some found an intrinsic link between social communication deficits and repetitive behaviors (3–6), while others claimed independence of the two symptoms (7–9). Considering that there are distinctive subtypes of social communication deficits and repetitive behaviors in ASD, the question that whether the two core symptoms are related is not clear (10). The current study aims to explore this relationship in children with ASD using eye movements, viewed from the visual attention point.

The two core symptoms of ASD may be reflected in the visual looking time. For instance, along with socio-communicational deficits, many eye-tracking studies have explored whether people with ASD look less at eyes than typically developing (TD) people. Although findings from these studies are mixed (11–13), a recent meta-analysis of eye-tracking studies found a significant reduction in

attention to eyes in individuals with ASD than TD people (14). On the other hand, people with ASD are found to be interested in certain types of objects, referenced to circumscribed interests (CI), or high-autism-interest (HAI) stimuli (e.g., vehicles, computers, and repetitive movements) (14–17). These stimuli have been found to attract visual attention (15, 16, 18), activate neural reward circuitry (19), and induce pleasure responses (20) in people with ASD. Based on these findings, HAI objects are proposed to negatively affect the social development of people with ASD by occupying their visual attention and depriving them of sufficient social interaction experiences (16, 21). However, the relationship between visual attention to eyes, which plays an essential role in social interaction, and visual attention to HAI objects has received almost no empirical attention. From both theoretical and practical perspectives, there are significant implications of knowing whether attention to eyes in people with ASD would be improved if some factors are manipulated, such as presenting HAI or low-autism-interest (LAI) objects. Therefore, the current study aimed to investigate how HAI objects would modulate the attention to eyes in children with ASD.

In order to examine this modulation effect, we used the preferential looking paradigm by pairing human eyes with two types of competing stimuli, that is HAI or LAI objects, to explore visual preferences for eye region in children with and without ASD. Some studies have already used a similar paradigm to study the modulation effect of competing non-social objects on social stimuli like faces [e.g., (15, 16)]. However, this has been achieved via a less fine distinction between the early and late attentional components. As a result, it remains unclear whether the modulation effect is due to the consistent impacts over time or from local effects confined to particular times.

Our study expected that including HAI objects would increase the general interest level to this type of object and reduce the total looking time to eyes in children with ASD. This overall eye-preference index could reflect some combinations of initial orienting to and subsequent maintenance with stimuli, as well as looking time after initial orienting. In order to separate these components, we calculated prioritization index, sustained index, and late eye-preference index (see Data Analysis section for details) to test whether the influence of HAI on the attention to eyes was mainly driven by different mechanisms of attention. Rather than focusing simply on which object receives the greater amount of viewing time, the prioritization index indicates which object receives attentional priority in the scene. In daily life, the social meaning of eyes should be perceived very rapidly. Therefore, prioritizing for processing eyes is helpful for a successful social interaction. Additionally, the sustained index examines a sustained viewing time in the initial detection of an object. This index can reflect a general interest in an object. If people are interested in an object, they examine it longer after looking at it. Finally, the late eye-preference index examines total eye-looking time after first looking at or initial orienting to objects, but not total eye-looking across time. It may reflect a late attentional component, which is less likely to be influenced by low-level stimulus properties than an early component like prioritization index (see detailed discussions in the Discussion section). Therefore, this late eye-preference index is better than the overall eye-preference index to reflect top-down attention to the eyes.

TABLE 1 | Characteristics of the participants.

	ASD ($N = 22$)		TD ($N = 22$)		t
	M	*SD*	*M*	*SD*	
Age (years)	7.01	1.32	7.51	0.65	−1.59
Full Scale IQ†	100.95	17.29	96.41	10.50	1.05
ADOS Total Severity	8.86	1.39	–	–	–
SA Severity‡	8.73	1.42	–	–	–
RRB Severity§	8.27	0.94	–	–	–
ADI-R			–	–	–
Social Interaction	22.09	5.18	–	–	–
Communication	17.73	4.43	–	–	–
RRB	9.09	2.02	–	–	–
D Scale¶	3.45	1.22			

†IQ was measured using the Chinese abbreviated version of Wechsler Intelligence Scale for Preschool and Primary Children-Forth Edition (26), or Chinese abbreviated version of Wechsler Intelligence Scale for Children-Forth Edition (27); ‡SA Severity = ADOS Social Affect Severity; §RRB Severity = ADOS Restricted, Repetitive Behavior Severity; SA and RRB Severity were calculated according to Gotham et al. (28); ¶D Scale is abnormality of development evident at/before 36 months.

METHOD

Participants

After excluding children with ASD who had a low IQ (IQ<70, measured by Wechsler Intelligence Scale), 22 high-functioning boys with ASD and 22 age and IQ-matched TD boys from China were included in the current study. Sample size was determined by availability and was greater than or equal to that of other studies using a similar paradigm [e.g., (15, 16, 22)]. Furthermore, when we opted for a moderate effect size ($\eta_p^2 = 0.06$), 0.8 power, an alpha of 0.05, and 0.5 as correlation among repeated measures to perform power analysis by using G*Power software (23), a total sample of at least 34 individuals is required by a repeated measures analysis of variance (ANOVA) with Group (ASD and TD) as the between-subjects factor, and Condition (HAI and LAI) as the within-subjects factor.

We recruited boys only in our study to control for gender differences in interest in objects (22). The children with ASD were all previously diagnosed by professional pediatricians in licensed hospitals according to the criteria of ASD in DSM-V (1), and were further confirmed by using the Autism Diagnostic Observation Schedule [ADOS; (24)] and the Autism Diagnostic Interview-Revised [ADI-R; (25)]. The TD children were recruited from a typical primary school, and the teachers and parents reported no concern about any potential developmental or psychiatric disorder. All participants had normal or corrected to normal vision with no color-blindness. **Table 1** shows the participants' characteristics.

This research was conducted according to the ethical standards laid down in the 1964 Declaration of Helsinki and was

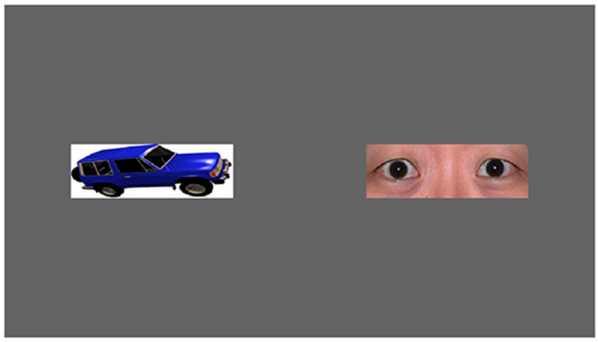

FIGURE 1 | Sample stimuli in the HAI condition.

approved by the Ethical Committee of the sponsoring university. We obtained all of the children's oral consent and their parents' written consent before the onset of the experiment.

Materials

The stimuli consisted of 24 images depicting the eye region cropped from different faces displaying fear expressions, which were extracted from the NimStim Face Stimulus Set (29), a free and widely used database [e.g., (30, 31)]. Fearful eyes were used as stimuli, given previous evidence that eye avoidance in ASD was most likely to occur when scanning threatening facial expressions (18). HAI object images included 12 different cars, and LAI object images included 12 different vegetables (15, 16). There were a total of 24 trials presented on a 21″ monitor. In each trial, one eye image was randomly paired with one HAI or one LAI image, resulting in 12 paired eyes and HAI object images (HAI condition), and 12 paired eyes and LAI object images (LAI condition) (**Figure 1**). The allocation (left/right) of stimuli within a trial was counterbalanced. Each image subtended a visual angle of 12×4° to the children.

Procedure

Children sat ∼60 cm away from a monitor. Eye movements were recorded by a Tobii Pro X3-120 eye tracker (Tobiitech Technology, Stockholm, Sweden; sampling rate: 120 Hz) during the whole experiment. Before the formal experiment, children were asked to pass a five-point calibration procedure. The calibration process was repeated when necessary until both eyes achieved good mapping on all five test positions (smaller than 1° visual angle).

In each trial, an attention-getter (a cartoon character subtending a visual angle of 4×4°) was first presented in the center of the screen, which disappeared when children's gaze was detected within the cued region. Then, one of the 24 paired images was presented for 3,000 ms, and children were asked to view it freely. The stimuli were presented in a randomized order with the constraint that the same condition and same eye position could not occur more than three in a row.

Data Analysis

Data Preprocessing

Trials with more than 30% missing gaze data (i.e., low-quality data defined as validity codes > 1 from Tobii raw data) were considered unreliable and excluded from the analysis [e.g., (32)] to ensure the quality of data, which was stricter than some previous studies (33, 34). Missing gaze data that had a gap shorter than 75 ms in the other trials were filled in using linear interpolation based on the last valid sample before the missing gap and the first valid sample after the gap. Average gaze positions of the left and right eyes were used to calculate fixations based on I-VT fixation filter (35) with the following parameters settings: (1) the velocity threshold was set at 30°/s; (2) Fixations close spatially and temporally (<0.5°, <75 ms) were merged to prevent longer fixations from being separated into shorter fixations because of data loss or noise; (3) Fixations shorter than 60 ms were discarded. Areas of interest (AOIs) were defined around the eyes and objects. In our analysis plan, trials would be further discarded if no fixations were detected in the two AOIs. However, no trials were discarded according to this criterion. The valid trial number was similar for the ASD ($M = 22.50$, $SD = 2.44$) and TD ($M = 23.55$, $SD = 1.47$) groups, $p > 0.05$.

Main Eye Movement Indices

Preliminary analysis revealed that the ASD group ($M = 1.52$ s, $SD = 0.48$ s) looked less at the two AOIs than the TD group ($M = 2.07$ s, $SD = 0.52$ s), $t_{(42)} = -3.62$, $p = 0.001$, Cohen's $d = 1.09$. Thus, in our primary analysis, in order to quantify the overall visual preference to the eye image relative to the object image, we converted total fixation data into proportion data. Using proportion data was also consistent with previous studies using the preferential looking paradigm (15–17). We calculated the *overall eye-preference index*, defined as the proportional total looking time on the eye AOI against the total looking time on both the eye and object AOIs. A well-above-chance level (50%) *eye-preference index* represents an overall looking preference for the eyes over the objects. We further calculated a *prioritization index*—frequencies of the first look at the eyes against the total valid trials as an initial orienting component of attention. A well-above-chance level of *prioritization index* represents a first preference for the eyes over the objects. Besides, we calculated the *sustained index*. First, we calculated the sum of the duration of all fixations of the first entry to the eye or object AOI, until a child shifted attention away from the AOI (sustained duration). The *sustained index* is defined as sustained duration on the eye AOI against the sum of sustained duration on the eye and object AOIs. This index represents maintaining of engagement with eyes after initial orientation relative to the object. Finally, *the late eye-preference index* was very similar to the *overall eye-preference index*. It was calculated as the proportional total looking time on the eye AOI against the total looking time on both the eye and object AOIs after first looking at an object AOI, but not the whole trial duration. The calculation of these eye movement indices can be referred to Holmqvis et al. (36).

RESULTS

Overall Eye-Preference Index

A 2 (Group: ASD and TD) × 2 (Condition: HAI and LAI) repeated measures ANOVA was conducted. Only the main effect of Condition was significant, $F_{(1,42)} = 13.05$, $p = 0.001$, $\eta_p^2 = 0.24$. Both groups showed decreased attention to eyes when HAI objects were present compared to when LAI objects were present (**Figure 2A**). The main effect of Group and the Group × Condition interaction effect were all not significant, $F_{(1,42)} = 0.54$, $p = 0.466$, $\eta_p^2 = 0.013$, and $F_{(1,42)} = 0.02$, $p = 0.876$, $\eta_p^2 < 0.001$, respectively.

We also compared the *eye-preference index* to the chance level by using a one-sample *t*-test with Bonferroni correction (alpha level = 0.0125 for four times comparison). Children with ASD showed a decreased looking preference for the eyes over the HAI objects, $t_{(21)} = -3.03$, $p = 0.006$, Cohen's $d = 0.65$, but not LAI objects, $t_{(21)} = -1.13$, $p = 0.272$, Cohen's $d = 0.24$. TD children showed no significant results, $t_{(21)} = -1.45$, $p = 0.162$, Cohen's $d = 0.31$, and $t_{(21)} = -0.12$, $p = 0.907$, Cohen's $d = 0.03$, for HAI and LAI objects, respectively.

Prioritization Index

Like the *eye-preference index*, only the main effect of Condition was significant, $F_{(1,42)} = 8.65$, $p = 0.005$, $\eta_p^2 = 0.171$. Both groups showed a reduction in the first preference for the eyes when HAI objects were present compared to when LAI objects were present (**Figure 2B**). The main effect of Group and the Group × Condition interaction effects were all not significant, $F_{(1,42)} = 0.07$, $p = 0.787$, $\eta_p^2 = 0.002$, and $F_{(1,42)} = 0.74$, $p = 0.395$, $\eta_p^2 = 0.017$, respectively.

We then compared the *prioritization index* to the chance level, and found that both groups showed a decreased first looking preference for the eyes over the HAI objects, $t_{(21)} = -3.80$, $p = 0.001$, Cohen's $d = 0.81$, and $t_{(21)} = -3.70$, $p = 0.001$, Cohen's $d = 0.79$, for the ASD and TD groups respectively, but not LAI objects, $t_{(21)} = -2.36$, $p = 0.028$, Cohen's $d = 0.50$, and $t_{(21)} = -1.42$, $p = 0.171$, Cohen's $d = 0.30$, for the ASD and TD groups, respectively.

Sustained Index

A 2 (Group: ASD and TD) × 2 (Condition: HAI and LAI) repeated measures ANOVA was conducted. Note that one TD child's first looks were all directed to the object in the HAI condition, thus the sustained index in the HAI condition was not available for this child. The main effect of Group was not significant, $F_{(1,41)} = 0.17$, $p = 0.680$, $\eta_p^2 = 0.004$. The main effect of Condition was significant, $F_{(1,41)} = 7.90$, $p = 0.008$, $\eta_p^2 = 0.162$. Importantly, the Group×Condition interaction was also significant, $F_{(1,41)} = 7.22$, $p = 0.010$, $\eta_p^2 = 0.150$. Simple effect analysis revealed that children with ASD had lower *sustained index* in the HAI condition than that in the LAI condition, $F_{(1,41)} = 15.48$, $p < 0.001$, $\eta_p^2 = 0.274$, but TD children had a similar *sustained index* in the HAI and LAI conditions, $F_{(1,41)} = 0.01$, $p = 0.931$, $\eta_p^2 < 0.001$ (**Figure 2C**).

Late Eye-Preference Index

A 2 (Group: ASD and TD) × 2 (Condition: HAI and LAI) repeated measures ANOVA was conducted. Note that one ASD child and one TD child did not look at the eye and object AOIs after initial orientation to the object in the LAI or HAI condition. Thus, the late eye-preference index was not available for these two children. The main effect of Group was not significant, $F_{(1,40)} = 0.01$, $p = 0.930$, $\eta_p^2 < 0.001$. The main effect of Condition was marginally significant, $F_{(1,40)} = 3.81$, $p = 0.058$, $\eta_p^2 = 0.087$. Importantly, the Group × Condition interaction effect was significant, $F_{(1,40)} = 4.55$, $p = 0.039$, $\eta_p^2 = 0.102$. Simple effect analysis revealed that children with ASD had lower *late eye-preference index* in the HAI condition than that in the LAI condition, $F_{(1,40)} = 8.35$, $p = 0.006$, $\eta_p^2 = 0.173$, while TD children had a similar *late eye-preference index* in the HAI and LAI conditions, $F_{(1,40)} = 0.02$, $p = 0.898$, $\eta_p^2 < 0.001$ (**Figure 2D**).

Correlations Between Autism Symptoms and Eye Movement Indices

We correlated the ADOS total severity of children with ASD with the main eye-movement indices. No significant correlations were found, all $ps > 0.05$.

DISCUSSION

The primary aim of the present study was to test whether attention to eyes in children with ASD depended on the type of competing non-social stimuli (HAI vs. LAI objects) that were also present. Using the preferential looking paradigm, we revealed that attention to eyes was influenced by competing objects in both children with ASD and TD children, such that a decreased visual preference for the eyes when they were paired with HAI objects compared to LAI objects was observed. However, the modulation effects were different for the two groups in the early and late attention.

First, we found a reduced overall preference for the eyes when eyes were paired with HAI objects relative to LAI objects in both children with ASD and TD children. Second, with regard to the early and late attentional components, it was observed that all groups showed an initial higher probability of attending to the eyes when LAI objects were presented than High objects. After first initiating to the eyes, children with ASD showed higher sustained viewing preference to the eyes when LAI objects were presented, whereas this effect was absent in the TD group. After first looking at the objects, children with ASD were also more likely to show a higher probability of attending to the eyes when LAI objects were presented. In contrast, this trend was not significant for TD children.

These findings suggested that attention to eyes was somewhat contextually dependent in children with ASD, so that presence of HAI relative to LAI objects would reduce the relative salience of eyes to a greater degree. There are two types of salience that will attract social attention (37). One is social salience, which will drive the top-down volitional attention. The other one is physical salience (e.g., color, contrast, and motion), which will reflexively trigger the attention in a bottom-up

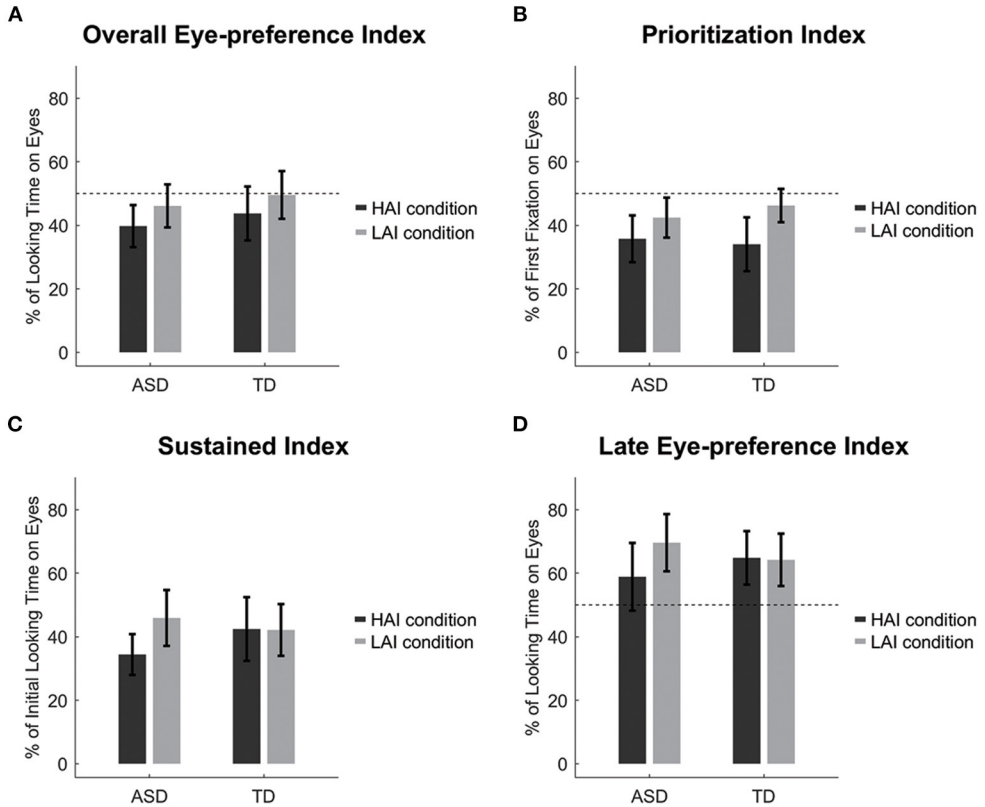

FIGURE 2 | Eye movement results. (**A**) Overall eye-preference index; (**B**) Prioritization Index; (**C**) Sustained index; (**D**) Late eye-preference index. Dashed lines represent the chance level and error bars represent standard error.

way. In general, we may expect physical salience to primarily influence initial orienting to eyes, whereas top-down control will dominate the late attention phase [e.g., (38)]. In the current study, low-level stimulus properties (e.g., contrast, color, luminance, shape, and size) were not controlled across different objects (i.e., HAI and LAI objects), like many previous studies (15, 16, 22). Thus, it is difficult to conclude whether the object content alone or content and low-level physical properties best explains the modulation effect of CI on initial attention to eyes. However, late attention, especially the late eye-preference index, is more likely to reflect children's motivation or interest in viewing the eyes because the physical salience of objects may lose its control in guiding attention in the late phase after viewing the objects. Furthermore, if the physical salience of objects plays a role in biasing the attention in the late phase, we would expect the non-social objects to modulate the late eye-preference index in TD children like the results of the prioritization index. Together, our study implies that HAI objects can occupy visual attention in both early and late attention phases, therefore depriving visual experiences with eyes in children with ASD. Future studies with a sophisticated design could further test the contribution of bottom-up and top-down attention to eyes. Greater care should also be taken to control the low-level stimulus properties in the future.

Our data from the TD group indicated that the modulation effects of CI on attention to the eyes were not specific to children with ASD—TD children also showed some similar effects. Previous studies presenting a single face or a face embedded in a social context have found that children with ASD always showed less eye-looking time than TD children (39, 40). In contrast to these studies, we only included eye regions to control other facial features' impact on eye-preference. Besides, we only used one type of emotion (fear) in eyes, which removed social salience conveyed by human expression. These manipulations might significantly reduce the social significance of the eyes, resulting in a reduced motivation to process the eyes in TD children and thus the absence of group differences in the eye preference. Another possibility is that we only included one competing object to pair with the eyes, whereas in previous studies, multiple competitive objects [e.g., mouth and nose within a face, or toys and body within a social scene; (39, 40)] were present, which may exacerbate the eye avoidance in children with ASD. Finally, the chosen HAI objects (i.e., cars) might also be highly attractive to TD boys, which

reduced the group difference. Future studies exploring how the attention to eyes in girls might be modulated by CI are recommended.

The modulation of HAI objects on gaze behavior is still informative for future clinical research and the development of interventions focusing on improving eye contact in ASDs. A number of interventions have tried to enhance the attention of individuals with ASD for socially relevant elements in a scene (41–43). Our study, from another perspective, suggests that in an intervention situation, making the non-social objects less salient could be used to increase social preference as a complementary approach. The presence of LAI objects could increase ASD children's propensity to look at the eyes first, heighten their interest in maintaining engagement with eyes after first looking at them, and improve their late looking preference to the eyes after first looking at the objects. However, it should be noted that we only used fearful eyes as stimuli, which was a limitation of our study. In reality, we usually look at a child in a non-fearful way. These settings could limit the generalizability of the current findigns. Thus, the implications for intervention should be taken with care, and future studies should test the generality of our findings to other expressions.

Another limitation in our study is that HAI objects we chose for children with ASD might also be interesting to TD children. Usually, HAI objects in ASD tend to be less attractive to TD children and are often idiosyncratic. Future studies using idiosyncratic HAI objects can replicate and extend our results.

In conclusion, we found that visual preference for eyes is influenced by competing objects in children with ASD—visual preference for eyes was reduced when HAI objects were present compared to when LAI objects were present. Our study not only helps us understand some factors that impact attention to eyes but also has implications for interventions aiming at improving eye contact in children with ASD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Association for Ethics and Human and Animal Protection in School of Psychological and Cognitive Sciences, Peking University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

QW: conceptualization, methodology, software, writing- original draft preparation, formal analysis, and visualization. SPH: formal analysis, resources, investigation, and software. CS: investigation and writing–review and editing. TL: investigation. CML: investigation and conceptualization. YW: investigation and conceptualization. LY: conceptualization, writing–review and editing, supervision, and funding acquisition. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington: American Psychiatric Press (2013). doi: 10.1176/appi.books.9780890425596
2. Mandy WP, Skuse DH. Research review: what is the association between the social-communication element of autism and repetitive interests, behaviours and activities? *J Child Psychol Psychiatry*. (2010) 49:795–808. doi: 10.1111/j.1469-7610.2008.01911.x
3. Lam KSL, Bodfish JW, Piven J. Evidence for three subtypes of repetitive behavior in autism that differ in familiality and association with other symptoms: evidence for three subtypes of repetitive behavior in autism. *J Child Psychol Psychiatry*. (2008) 49:1193–200. doi: 10.1111/j.1469-7610.2008.01944.x
4. Lee S, Odom SL, Loftin R. Social engagement with peers and stereotypic behavior of children with autism. *J Posit Behav Interv.* (2007) 9:67–79. doi: 10.1177/10983007070090020401
5. Loftin RL, Odom SL, Lantz JF. Social interaction and repetitive motor behaviors. *J Autism Dev Disord.* (2008) 38:1124–35. doi: 10.1007/s10803-007-0499-5
6. Richler J, Huerta M, Bishop SL, Lord C. Developmental trajectories of restricted and repetitive behaviors and interests in children with autism spectrum disorders. *Dev Psychopathol.* (2010) 22:55–69. doi: 10.1017/S0954579409990265
7. Happé F, Ronald A. The 'fractionable autism triad': a review of evidence from behavioural, genetic, cognitive and neural research. *Neuropsychol Rev.* (2008) 18:287–304. doi: 10.1007/s11065-008-9076-8
8. Happé F, Ronald A, Plomin R. Time to give up on a single explanation for autism. *Nat Neurosci.* (2006) 9:1218–20. doi: 10.1038/nn1770
9. Lord C, Jones RM. Annual Research Review: re-thinking the classification of autism spectrum disorders. *J Child Psychol Psychiatry.* (2012) 53:490–509. doi: 10.1111/j.1469-7610.2012.02547.x
10. Leekam SR, Prior MR, Uljarevic M. Restricted and repetitive behaviors in autism spectrum disorders: a review of research in the last decade. *Psychol Bull.* (2011) 137:562–93. doi: 10.1037/a0023341
11. Black MH, Chen N, Iyer KK, Lipp OV, Bölte S, Falkmer M, et al. Mechanisms of facial emotion recognition in autism spectrum disorders: Insights from eye tracking and electroencephalography. *Neurosci Biobehav Rev.* (2017) 80:488–515. doi: 10.1016/j.neubiorev.2017.06.016
12. Speer LL, Cook AE, McMahon WM, Clark E. Face processing in children with autism: effects of stimulus contents and type. *Autism.* (2007) 11:265–77. doi: 10.1177/1362361307076925
13. Tang J, Falkmer M, Horlin C, Tan T, Vaz S, Falkmer T. Face recognition and visual search strategies in autism spectrum disorders: amending

and extending a recent review by Weigelt et al. *PLoS ONE.* (2015) 10:e0134439. doi: 10.1371/journal.pone.0134439
14. Frazier TW, Strauss M, Klingemier EW, Zetzer EE, Hardan AY, Eng C, et al. A meta-analysis of gaze differences to social and nonsocial information between individuals with and without autism. *J Am Acad Child Adolesc Psychiatry.* (2017) 56:546–55. doi: 10.1016/j.jaac.2017.05.005
15. Sasson NJ, Elison JT, Turner-Brown LM, Dichter GS, Bodfish JW. Brief Report: Circumscribed attention in young children with autism. *J Autism Dev Disord.* (2011) 41:242–7. doi: 10.1007/s10803-010-1038-3
16. Sasson NJ, Touchstone EW. Visual attention to competing social and object images by preschool children with autism spectrum disorder. *J Autism Dev Disord.* (2014) 44:584–92. doi: 10.1007/s10803-013-1910-z
17. Wang Q, Hu Y, Shi D, Zhang Y, Zou X, Li S, et al. Children with autism spectrum disorder prefer looking at repetitive movements in a preferential looking paradigm. *J Autism Dev Disord.* (2018) 48:2821–31. doi: 10.1007/s10803-018-3546-5
18. Wang Q, Lu L, Zhang Q, Fang F, Zou X, Yi L. Eye avoidance in young children with autism spectrum disorder is modulated by emotional facial expressions. *J Abnorm Psychol.* (2018) 127:722–32. doi: 10.1037/abn0000372
19. Dichter GS, Richey JA, Rittenberg AM, Sabatino A, Bodfish JW. Reward circuitry function in autism during face anticipation and outcomes. *J Autism Dev Disord.* (2012) 42:147–60. doi: 10.1007/s10803-011-1221-1
20. Sasson NJ, Dichter GS, Bodfish JW. Affective responses by adults with autism are reduced to social images but elevated to images related to circumscribed interests. *PLoS ONE.* (2012) 7:e42457. doi: 10.1371/journal.pone.0042457
21. Elison JT, Sasson NJ, Turner-Brown LM, Dichter GS, Bodfish JW. Age trends in visual exploration of social and nonsocial information in children with autism. *Res Autism Spectr Disord.* (2012) 6:842–51. doi: 10.1016/j.rasd.2011.11.005
22. Harrop C, Jones D, Zheng S, Nowell SW, Boyd BA, Sasson N. Sex differences in social attention in autism spectrum disorder. *Autism Res.* (2018) 11:1264–75. doi: 10.1002/aur.1997
23. Faul F, Erdfelder E, Lang A-G, Buchner A. G* Power 3: a flexible statistical power analysis program for the social, behavioral, biomedical sciences. *Behav Res Methods.* (2007) 39:175–91. doi: 10.3758/BF03193146
24. Lord C, Risi S, Cook EH, Leventhal BL, DiLavore PC. The Autism Diagnostic Observation Schedule—Generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord.* (2000) 30:205–23. doi: 10.1023/A:1005592401947
25. Lord C, Rutter M, Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord.* (1994) 24:659–85. doi: 10.1007/BF02172145
26. Wechsler D. *Wechsler Intelligence Scale for Preschool and Primary Children–Fourth CN Edition, 4th Edn.* King-May Company (2014)b.
27. Wechsler D. *Wechsler Intelligence Scale for Children–Fourth CN Edition, 4th Edn*. King-May Company (2014)a.
28. Gotham K, Pickles A, Lord C. Standardizing ADOS scores for a measure of severity in autism spectrum disorders. *J Autism Dev Disord.* (2009) 39:693–705. doi: 10.1007/s10803-008-0674-3
29. Tottenham N, Borscheid A, Ellertsen K, Marcus DJ, Nelson CA. Categorization of facial expressions in children and adults: establishing a larger stimulus set. *Poster Presented at the Annual Meeting of the Cognitive Neuroscience Society*. San Francisco, CA (2002).
30. Barnard-Brak L, Abby L, Richman DM, Chesnut S. Facial emotion recognition among typically developing young children: a psychometric validation of a subset of NimStim stimuli. *Psychiatry Res.* (2017) 249:109–14. doi: 10.1016/j.psychres.2016.12.049
31. Houston JR, Pollock JW, Lien M-C, Allen PA. Emotional arousal deficit or emotional regulation bias? An electrophysiological study of age-related differences in emotion perception. *Exp Aging Res.* (2018) 44:187–205. doi: 10.1080/0361073X.2018.1449585
32. Wang Q, Hoi SP, Wang Y, Song C, Li T, Lam CM, et al. Out of mind, out of sight? Investigating abnormal face scanning in autism spectrum disorder using gaze-contingent paradigm. *Dev Sci.* (2019) 23:e12856. doi: 10.1111/desc.12856
33. Kleberg JL, Högström J, Nord M, Bölte S, Serlachius E, Falck-Ytter T. Autistic traits and symptoms of social anxiety are differentially related to attention to others' eyes in social anxiety disorder. *J Autism Dev Disord.* (2016) 47:3814–21. doi: 10.1007/s10803-016-2978-z
34. Nyström P, Bölte S, Falck-Ytter T, Team E. Responding to other people's direct gaze: alterations in gaze behavior in infants at risk for autism occur on very short timescales. *J Autism Dev Disord.* (2017) 47:3498–509. doi: 10.1007/s10803-017-3253-7
35. Olsen A. *The Tobii I-VT Fixation Filter. Algorithm Description.* Stockholm: Tobii Technology (2012).
36. Holmqvist K, Nyström M, Andersson R, Dewhurst R, Jarodzka H, Van de Weijer J. *Eye Tracking: A Comprehensive Guide to Methods and Measures*. Oxford: OUP Oxford (2011).
37. Laidlaw KE, Risko EF, Kingstone A. A new look at social attention: Orienting to the eyes is not (entirely) under volitional control. *J Exp Psychol Hum Percept Perform.* (2012) 38:1132–43. doi: 10.1037/a0027075
38. Langton SRH, Law AS, Burton AM, Schweinberger SR. Attention capture by faces. *Cognition.* (2008) 107:330–42. doi: 10.1016/j.cognition.2007.07.012
39. Jones W, Klin A. Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. *Nature.* (2013) 504:427–31. doi: 10.1038/nature12715
40. Yi L, Fan Y, Quinn PC, Feng C, Huang D, Li J, et al. Abnormality in face scanning by children with autism spectrum disorder is limited to the eye region: Evidence from multi-method analyses of eye tracking data. *J Vis.* (2013) 13:227–32. doi: 10.1167/13.10.5
41. Alvares GA, Chen NT, Notebaert L, Granich J, Mitchell C, Whitehouse AJ. Brief social attention bias modification for children with autism spectrum disorder. *Autism Res.* (2019) 12:527–35. doi: 10.1002/aur.2067
42. Amaral C, Mouga S, Simões M, Pereira HC, Bernardino I, Quental H, et al. A feasibility clinical trial to improve social attention in autistic spectrum disorder (ASD) using a brain computer interface. *Front Neurosci.* (2018) 12:e477. doi: 10.3389/fnins.2018.00477
43. Turner-Brown LM, Perry TD, Dichter GS, Bodfish JW, Penn DL. Brief Report: feasibility of social cognition and interaction training for adults with high functioning autism. *J Autism Dev Disord.* (2008) 9:1777–84. doi: 10.1007/s10803-008-0545-y

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BRIEF RESEARCH REPORT
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Impaired Recognition of Static and Dynamic Facial Emotions in Children With Autism Spectrum Disorder Using Stimuli of Varying Intensities, Different Genders, and Age Ranges Faces

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A multitude of research on facial emotion recognition (FER) in Autism Spectrum Disorders (ASD) have been published since several years. However, these studies have mainly used static high intensity stimuli, including adult and/or children facial emotions. This current study investigated FER in children with ASD using an innovative task, composed of a combination of static (114 pictures) and dynamic (36 videos) subtests, including children, adolescent, and adult male and female faces, with high, medium, and low intensity of basic facial emotions, and neutral expression. The ASD group consisted of 45 Tunisian verbal children, and the control group consisted of 117 tunisian typically developing children. Both groups were aged 7–12 years. After adjusting for sex, age, mental age, and school grade, the ASD group scored lower than controls on all tests except for the recognition of happiness and fear in the static subtest, and the recognition of happiness, fear, and sadness in the dynamic subtest ($p \geq 0.05$). In the ASD group, the total score of both the static and the dynamic subtest were positively correlated with the school grade ($p < 0.001$), but not with age, or mental age. Children with ASD performed better in recognizing facial emotions in children than in adults and adolescents on videos and photos ($p < 0.001$). Impairments in FER would have negative impact on the child's social development. Thus, the creation of new intervention instruments aiming to improve emotion recognition strategies at an early stage to individuals with ASD seems fundamental.

Keywords: autism, social cognition, facial emotions, emotion recognition, children

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INTRODUCTION

Facial expressions of emotion convey non-verbal cues for interferences with others. They allow us to understand motivations and intentions of others. Consequently, they are considered as one of the foundations of social interaction (1).

Over the decades since the 1970s, psychological studies have established that there were six universal basic emotions: sadness, disgust, anger, surprise, happiness, and fear (2–4). Izard (5) suggested that, at the age of six, typically developing individuals are able to recognize several facial emotional expressions, while other studies mentioned that this ability is only totally developed before adolescence (6–8). However, the aptitude to accurately identify emotions is not distributed uniformly across children and may negatively impact social interactions.

Autism spectrum disorders (ASD) are "neurodevelopmental disorders characterized by early-onset qualitative impairments in social interaction, verbal and non-verbal communication, associated with restricted and repetitive interests and behaviors" (9). As social cognition is particularly implicated in ASD, a large number of research have examined facial emotion recognition (FER) in this population over the last decades (10, 11). Recent research in ASD have shown that the ability to recognize facial emotion in children with ASD is not always associated with their intelligence (12, 13), contrarily to NT individuals in whom performance IQ could predict emotion recognition performance in children (14).

Several studies have focused on the assessment of basic emotions as they are primitive and universal reactions to outside stimuli and do not depend on cognitive processing or cultural environment. Even though there is some debate concerning the capacity of subjects with ASD to identify the basic facial emotions, there is more evidence to suggest that impairments of FER are constantly present in ASD (15–22). Recent literature reviews have shown important FER impairments in individuals with ASD (13, 23). Yet, several other studies did not replicate the same findings. This discrepancy was explained by different hypotheses. Indeed, some researchers suggested that FER in individuals with ASD is emotion-type-specific only manifesting for negative emotions such as fear (24, 25) and sadness (26). Other studies showed that these discrepant results may be explained by the use of tasks that lacked sensitivity to detect group differences. Lerner et al. (27) suggested that greater impairments in facial emotion recognition are present when adult facial expressions are presented to children with ASD, as opposed to child facial expressions. This hypothesis was supported by the study of Hauschild, indicating that adolescents, independently of ASD diagnostic status or severity of troubles had greater FER performance for child compared to adult faces. His findings suggested that "face processing abilities of adolescents with ASD may be influenced by experience with specific categories of stimuli, similar to their typically developing peers" (28). Therefore, we hypothesized that children with ASD would show greater performance in recognizing facial emotions of individuals having the same age range and that the assessment of facial emotion recognition could vary according to the age range of the model presented to the child.

The very mixed results on emotion recognition difficulties in ASD were also explained by "the use of very simplistic stimuli, i.e., "100% expression" or "full blown," which may produce ceiling effects" (29–31). In fact, it was recently suggested that "individuals with ASD perceive exaggerated emotional facial expressions as being more representative of real-life emotions and more realistic" (32). Therefore, they may show more emotion recognition difficulties for low intensity facial expressions as subtle facial expressions afford less emotional cues to the observer (33). In the study of Wong et al. (34), "low intensity emotions" had also been associated with more important impairments in FER, particularly with negative emotions. Subtle or "low intensity" facial expressions are frequently observed in daily life. Even if children with ASD often show good performance in FER in laboratory setting, they are likely to have difficulties in the recognition of subtle facial expressions in real life. Indeed, it is possible that the lack of impairment of FER in individuals with ASD in some studies is explained by the abnormal processing of facial emotions, using high intensity of stimuli. In accordance with some authors, we suggested that difficult tasks with different intensity of facial emotions are needed to highlight emotion recognition difficulties in ASD (24, 35, 36).

We also suggested that the assessment of FER in individuals with ASD using videos or dynamic stimuli would show better performance. Our hypothesis was based on several research. In the study of Harwood et al. (37), authors have found that the use of "moving faces" to assess FER among individuals with intellectual disability may facilitate facial affect recognition, in comparison to static stimuli. Concerning typically developing individuals, "dynamic displays" were better recognized than "static displays" and judged as being more realistic and intense" (38). In the study of Ambadar et al. (39), dynamic stimuli had facilitated the recognition of subtle facial expressions. In the neuroimaging research, differential patterns of brain activation in response to dynamic in comparison with static facial emotions have been identified (40). As naturally facial emotions are intrinsically dynamic, authors suggested that dynamic stimuli may have a better ecological validity than static stimuli, as they may activate richer neuronal, automatic, and behavioral consequences than static stimuli (40, 41).

It is also important to note that, to date, only a few studies investigating emotion recognition in people with ASD have included an assessment of neutral facial expressions (25, 36, 42). Neutral facial expressions are frequent and important in everyday life and could represent a source of confusion for individuals with ASD.

Additionally, only a few studies on misinterpretation of emotions have used a combination of static and dynamic test, including images and videos, and, to the best of our knowledge, none has used tests including a combination of children, adolescent and adult facial expressions with different levels of intensity of facial emotions.

Therefore, and in order to better understand FER impairments in ASD that could conduct us to the creation of intervention tools, we chose to use an innovating task that takes into account all of the aforementioned limitations of previous studies. The current study is unique in that we

used a recently developed and validated test, composed of a combination of static (pictures) and dynamic (videos) subtests, including children, adolescent, and adult faces, with high, medium, and low intensity of basic facial emotions, and neutral facial expression.

We hypothesized that:

(1) ASD group would show deficits in FER compared to control, expected mainly for negative emotions
(2) Performance in FER would vary according to the intensity of facial expression, with greatest deficits at lower intensities
(3) Deficits in the FER would be predominant in one type of support (video or pictures) with some suggestion that ASD group might show greatest performances with dynamic support, rather than with static images, with better performance in the identification of children's facial emotions.

MATERIALS AND METHODS

Participants

Data in our study were collected from children with ASD and neurotypical children (NT) and all included children were attending ordinary schools. Participants in the clinic sample were recruited from the Department of Child and Adolescent Psychiatry in Razi Hospital, Tunis, Tunisia. The sample consisted of 45 Tunisian verbal children, aged 7–12 years (mean age = 9.26, sex ratio = 6.5), diagnosed with autism spectrum disorder, according to the Diagnostic and Statistical Manuel of mental disorders- fifth edition (DSM-5) criteria, after a full assessment by a child psychiatrist. This diagnosis was confirmed by a trained rater who administered the Autism Diagnostic Interview-Revised (ADI-R) (43) (Mean scores were: social interaction = 13,60 ± 1.64; verbal communication = 15,09 ± 3,44; restricted and stereotyped behavior = 5.7 ± 1.25).

The control group (neurotypical or NT children) was recruited from several primary schools and consisted of 117 Tunisian typically developing children, aged 7–12 years (mean age 9.22, sex ratio = 0.88). They had no history of psychiatric disease, neurodevelopmental disorder, and no family history of autism spectrum disorder. Children were assessed with the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) (44) and those who had a present or a past psychiatric disorder were not included in the study.

All cases in both groups had a performance IQ >80. The fixed IQ cutoff was chosen so that to avoid the effects of deficits in receptive language and to select verbal children with ASD, who could be able to respond reliably to the test. Mental age was measured by The Tunisian version of the Differential scales of intellectual efficiency (EDEI)-A in its reduced form: the scale I "Vocabulary B" for verbal intelligence and the scale IV "categorical analysis" for non-verbal intelligence (45).

Exclusion criteria for both groups included: intellectual disability, a history of a traumatic brain injury, or seizure disorders, neurological or sensory deficits, substance use disorders that could affect children's cognitive functioning and children's performance during the test.

All the parents of selected children were invited to take part in the study, and provided written informed consent. The present study adhered to the tenets of the Declaration of Helsinki (2000).

Measures

The REF task is a Tunisian validated and computerized test. It consists on a downloadable application on Android, developed by child psychiatrists and psychologists working in the Department of Child and Adolescent Psychiatry in Razi Hospital (Tunis, Tunisia). It is a part of a Tunisian battery for the assessment of social cognition (non-verbal and verbal theory of mind, empathy, and FER).

The REF task is an innovating test, having good psychometric properties (in review in the journal Frontiers in Psychology, 15 jan 2021, Taamallah, A., Halayem, S., Rajhi, O., Ghazzai, M., Moussa, A., Touati, M., et al. Validation of the Tunisian test for facial emotion recognition: study in children from 7 to 12 years).

The test consists of a combination of a static and a dynamic subtest. The static subtest includes 114 photographs of actors mimicking six basic emotions (happiness, disgust, fear, surprise, sadness, and anger) and neutral expression with three levels of intensity of facial emotions for the six basic emotions: low, medium, and high.

The dynamic subtest includes 36 videos with actors mimicking six basic emotions.

There were three male and three female actors having three age ranges: children, adolescents, and adults. Each actor displayed the six basic emotions, as well as a neutral face. The task includes photos and videos with an equal number of faces for each gender, age range, emotions type, as well as an equal number of intensities for each facial emotion in the static subtest. The duration of each video varied between 3 and 5 s with facial expression moving from neutral facial expression to the basic emotion proposed.

The test items were coded according to Ekman's "Facial Action Coding System" (FACS) method, comparing each photograph to that of neutrality. Depending on the FACS system, facial muscle contractions are coded in units of action (AUs). The nomenclature includes 46 AUs identified by a number. For example, AU1 corresponds to the "inner brow raiser." For happiness, the units of action involved are AU6 (cheek raiser), AU12 (lip corner puller), and AU 25 (lips part). The intensity of the emotion depends on the number of AUs and the intensity of the contraction (46, 47). A professional photograph made the photos and the videos, and the recording sessions took place in a theater club.

The interface was made up of two parts: the upper part displayed the photo or video, and the lower part displayed seven choices corresponding to the seven emotions (six basic emotions and neutrality) written in Tunisian Arabic dialect (**Figure 1**).

Stimuli are presented in a random and pre-established order and the whole face was displayed each time. For videos, and after the clip is played, the static image of the final intensity remains on the screen until the forced choice is made.

The distance between the child and the screen was set as 40 cm. Children were provided with standardized instructions and supervised by a trained- researcher. Before initiating the assessment, all participants (NT children and children with ASD)

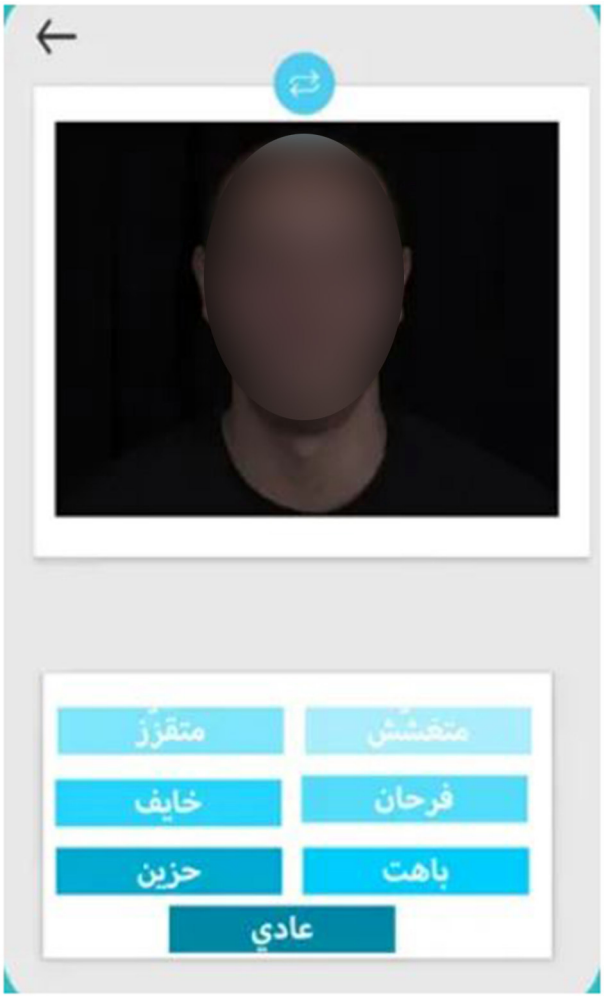

FIGURE 1 | Interface of the REF task.

were invited to read the seven choices of facial expressions (happiness, disgust, fear, surprise, sadness, and anger) to confirm that they could correctly recognize them. Then, children were asked to view each face and to identify and select the facial emotion that corresponds to each photo or video.

For all participants, we started by presenting the static part of the test, then the dynamic one.

During the task, each proposed facial expression with the proposals remains on the screen 15 s. After this time and when the children were not able to select his choice, the next stimuli were presented. Once a response is chosen for a given face, participants are not able to revise it, and the next proposal of facial emotion is presented.

The duration of the test varied between 20 and 40 min depending on the child's performance and his response time.

Data Analysis

Statistical analysis was performed using the Statistical Package for the Social Science (SPSS) version 26 for Windows. For descriptive statistics, we calculated the mean and the standard deviation for each of our continuous variables. For each of the continuous variables, normality was checked using Shapiro-Wilk's test. Indeed, according to the central limit theorem, a sampling distribution in samples larger than 30 tends to be normal, regardless of the shape of the data (48).

With large enough sample sizes (>30 or 40), the violation of the normality assumption should not cause major problems (4); this implies that we can use parametric procedures even when the data are not normally distributed.

To compare the sex distribution between groups, we used Pearson's Chi-square. To compare age, mental age, and school grade between the ASD group and the control group, we used Student's *t*-test for independent samples. To compare subscores within the same groups, we used the paired-samples *t*-test.

To examine the associations between the total scores for each of the static and dynamic subtests and age, mental age, and school grade, we used non-parametric Spearman's correlations.

To compare FER between ASD children and NT children, controlling for the effects of covariates (age, gender, mental age, and school grade) on emotion recognition scores, we chose to compare each of the subscale scores between groups using a separate univariate analysis of covariance (ANCOVA), and we adjusted the *p*-values to account for multiple comparisons. Since the number of subscores would make for too many dependent variables, it was more logical to run multiple separate univariate ANCOVA analyses than one single multivariate analysis of covariance (MANCOVA) analysis. Effect size was estimated using partial eta squares (η^2). We checked for variance homogeneity using the Levene's test and for linearity and homogeneity of regression slopes using scatterplots (plotting each of the FER subscores as separate dependent variables against the each of covariates, for each subgroup).

Holm-Bonferroni's correction was applied in case of multiple comparisons.

A significance level of $p = 0.05$ was applied for all statistical tests.

RESULTS

Table 1 summarizes the general characteristics of the ASD group ($n = 45$) in comparison with the NT group ($n = 117$). While the mean age was comparable between groups, the ASD groups had a higher proportion of males, a lower mental age, and tended to have fewer years of study.

In the ASD group, we found that the total score of the static subtest was positively correlated with school grade (rho = 0.404, $p = 0.009$), but not with age, or mental age. Similarly, the total score of the dynamic subtest was positively correlated with school grade (rho = 0.394, $p = 0.012$), but not with age or mental age. Both total scores for the static and dynamic subtests did not differ significantly between genders.

In the NT group, we found that the total score of the static subtest was positively correlated with age, mental age, and school grade (rho = 0.374, rho = 0.376, and rho = 0.394.; $p < 0.001$ for each correlation). Similarly, the total score of the dynamic subtest

TABLE 1 | General characteristics of the autism spectrum disorder group vs. the neurotypical group.

		ASD group $n = 45$	NT Group $n = 117$	p
Sex, *n* (%)	Male	39 (86.7%)	55 (47.0%)	<0.001
	Female	6 (13.3%)	62 (53.0%)	
Age, m ± SD		9.6 ± 1.5	9.2 ± 1.5	0.218
EDEI- Verbal mental age, m ± SD		8.7 ± 1.2	9.9 ± 0.9	<0.001
EDEI- Non verbal mental age, m ± SD		9.9 ± 2	10.9 ± 2.5	
EDEI- Mental age, m ± SD		9.3 ± 1.6	10.4 ± 1.7	
School grade, m ± SD		2.9 ± 1.4	3.5 ± 1.4	0.024

ASD, Autism spectrum disorder; NT, Neurotypical.
m, mean; SD, standard deviation; EDEI, The Differential Scales of Intellectual Efficiency.

was positively correlated with age, mental age, and school grade (rho = 0.414, rho = 0.318, and rho = 0.434.; $p < 0.001$ for each correlation). Both total scores for the static and dynamic subtests did not differ significantly between genders.

After adjusting for sex, age, mental age, and years of study, the ASD group scored lower than controls on all tests except for the identification of fear and happiness in the static subtest, and the identification of happiness, fear, and sadness in the dynamic subtest (**Table 2**).

Out of the different six basic emotions, both groups (ASD and NT) scored best in identifying happiness on photos as well as in videos ($p < 0.001$ when compared with any of the other emotions).

In the ASD group, there was no significant differences in FER scores based on the actor's gender for photos, but scores were higher in the video tests when the actor was female (10.33 ± 3.89 vs. 8.65 ± 3.57, $p < 0.001$).

It was also easier for individuals with ASD to accurately identify facial emotions in children than in adolescents on photos and videos (17.17 ± 7.07 vs. 15.48 ± 6.79, $p = 0.004$; and 7.16 ± 2.69 vs. 5.70 ± 2.46, $p < 0.001$, respectively). However, identifying facial emotions were easier in children than in adults in videos (7.16 ± 2.69 vs. 6.12 ± 2.44, $p < 0.001$), but not on photos.

ASD children had more difficulties recognizing low-intensity than medium-intensity emotions (14.19 ± 6.80 vs. 15.60 ± 6.51, $p < 0.001$) and exhibited more problems identifying medium-intensity than high-intensity emotions (15.60 ± 6.51 vs. 17.50 ± 7.08, $p =< 0.001$).

DISCUSSION

Difficulty in FER is one of the most frequently identified social-cognitive impairments in individuals with autism spectrum disorder (23). However, it is still unclear if all facial emotions are equally impaired or whether recognition of some emotions could be impaired to a lesser extent or spared (13). In the present study, significant impairments in the FER performances were observed. After adjusting for sex, age, mental age, and years of study, children with ASD have shown impairment in the identification of anger, disgust, surprise, sadness, and neutral expressions. However, the recognition of fear and happiness didn't vary between the two groups. In addition, happiness was the easiest facial emotion to recognize for ASD and NT children.

In neurological terms, several studies have suggested that the processing of fear and negative emotions was linked to the amygdala functioning (49–54). Therefore, atypical function of the amygdala in autism spectrum conditions could lead to poor identification of negative emotions (55–57), which is partly compatible with our findings. Additionally, "dysfunction of the amygdala in autism could be the cause of a lack of orienting to the eyes in a face" (58, 59). This hypothesis has been mentioned in several studies that have found that individuals with ASD focus more on the lower part (i.e., the mouth), than the upper part (e.g., the eyes) of the face in identifying facial emotions (26, 60–64). In fact, individuals with ASD may find it less complicated to identify happiness, as focusing of the lower part of the face could be sufficient to recognize this emotion (65, 66).

Concerning the recognition of surprise, Baron-Cohen et al. (67) have suggested that specific impairment in recognition of surprise could be explained by impairment in the theory of mind in individuals with autism. In fact, the only basic emotion that needs judgment of another person's mental state is surprise. Consequently, if there is impairment in mental state judgments in autism, recognition of surprise would be altered (67). Thereby, further research studying the link between FER (specially surprise) and theory of mind is needed.

Recent studies have shown that other social and emotional dysfunctions in ASD, such as such as alexithymia (68), poorer social skills (69), living skills (70), social motivation for peer interaction (71–73), communication (74), and social functioning (75) may negatively impact FER. In our study, we didn't study these impairments due to the lack of contextualized and adapted tools.

From another point of view, impairment in FER for children with ASD could also be explained by the limited time for answer since they were not given ample time to respond. Several research reported that people with autism might be slower in recognizing facial emotion and can accurately recognize basic emotions, with no difference in performance between autistic and neurotypical people when they are given enough time to select their choice [e.g., (29, 76–78)].

TABLE 2 | One-way analysis of covariance comparing performances in facial emotion recognition in children with autism spectrum disorder vs. neurotypical children, controlling for sex, age, mental age, and years of study.

		Static subtest			Dynamic subtest		
		F^a	p^a	η^2	F^a	p^a	η^2
Total score		57.207	0.000	0.300	29.984	0.000	0.195
Score per emotion type	Anger	20.805	0.000	0.099	22.711	0.000	0.156
	Disgust	23.083	0.000	0.174	28.198	0.000	0.162
	Happiness	1.212	0.448	0.021	1.495	0.448	0.006
	Fear	3.525	0.189	0.018	4.140	0.176	0.033
	Surprise	47.614	0.000	0.286	10.659	0.009	0.053
	Sadness	17.108	0.000	0.125	5.666	0.095	0.050
	Neutral	10.341	0.012	0.086	51.204	0.000	0.271
Score per gender of the actors	Male	41.858	0.000	0.246	38.132	0.000	0.217
	Female	61.113	0.000	0.300	12.084	0.008	0.081
Pictures per age range of the actors	Children	34.978	0.000	0.307	11.109	0.000	0.132
	Adolescents	62.240	0.000	0.213	18.637	0.008	0.069
	Adults	40.810	0.000	0.239	38.959	0.000	0.207
Pictures per emotion's intensity	Low	53.118	0.000	0.280			
	Medium	46.313	0.000	0.257			
	High	45.153	0.000	0.255			

[a]*Adjusted for sex, age, mental age, and years of study.*
p-values were adjusted for multiple comparison using Holm-Bonferroni's method.

Furthermore, these impairments may be due to the fact that individuals with ASD need more environmental or verbal contents, to identify accurately the facial emotion. Understanding emotions usually requires multi-sensory processing based on speech prosody and body and facial gestures (79–81).

Our study did not show a significant effect of age on FER performances in children with ASD and the accuracy of the FER was not positively associated with mental age. A recent meta-analysis, comparing FER in three age ranges (children, adolescents, and adults) has shown that "ASD was associated with deficits in FER across multiple expressions, and that these deficits were more pronounced in adults than in adolescents than in children and cannot be accounted for by intelligence" (12). The age range of our clinical sample (7–12 years) and the fact that we did not include adolescents and adults could explain our findings since younger subjects (children) with ASD seem to have better performances in FER than older subjects with ASD (adolescents and adults).

We also found that performances in FER (the total score of both static and dynamic subtest) were positively correlated with school grade in both groups. Our findings are in part consistent with those of Feinman and Entwisle. In their study, FER were assessed for children attending school and the study showed that FER increased significantly with each grade but leveled off between 8 and 11 years (82). These findings could be explained by the positive impact of the duration of social contact with peers that may improve emotion recognition and social skills for NT children and children with ASD.

In the present research, we used a combination of a static and a dynamic support. As the dynamic support could add ecological validity to the test compared with static support (40, 41), we hypothesized that children with ASD might show greater performance in dynamic subtest rather than static subtest. The ASD group performed worse than the NT sample in the static and dynamic subtest, with sadness being the only emotion that was better identified using the dynamic subtest, in comparison with the static subset. The dynamic subtest did not appear to improve FER considerably for children with ASD, in comparison with static stimuli. Thereby, our research did not support our hypothesis suggesting broad advantages associated with the use of dynamic stimuli. Our findings are consistent with those of Enticott et al. (83). Gepner et al. (84) suggested that children with ASD might show less impairments with slow dynamic displays of facial expressions. Studing FER in dynamic and realistic situations will be interesting for future research.

In both groups, we noticed a better FER of children's faces compared to those of adolescents and adults. Our findings are consistent of those of Lerner et al. (27), suggesting that more impairments in facial emotion recognition are found when adult facial expressions are presented to children with ASD, compared to child facial expressions. Thereby, the recognition of the same facial emotions, seen on age-peer faces could be better for both NT and ASD groups. Scherf et al. (85) suggested that "the own-age bias in face recognition, representing superior recognition abilities for faces of a similar age to the viewer, may emerge as a result of social reorientation toward peers during late-childhood and early-adolescence". One recent study reported that healthy adolescents were more accurate in the recognition of the identity of individual faces having their age than the identity of adult faces. These findings suggested that FER performance could be moderated by the age range of facial stimuli (86). In contrast, Vetter et al. (87), suggested a lack of this moderating effect (for

adolescents) in FER and reported similar accuracy in FER of adult and adolescent facial expressions in healthy adolescents. Thus, it seems possible that specifically children with ASD could exhibit greater difficulties identifying the facial emotions of people having different age ranges than their own, compared to adolescents and adults with ASD, and that the age of facial stimuli may moderate facial emotion perception for children with ASD. Thereby, further studies including and comparing facial stimuli of different age groups are needed in order to better specify the impact of the age range of facial stimuli on FER accuracy in individuals with ASD.

Performances on FER in the ASD group did not vary according to the gender of the actors in the static subtest, with a better performance in identifying facial emotions of female actors in the dynamic subtest. Our results may suggest that gender could affect the accuracy of FER in individuals with ASD with better performance in identifying facial emotions of female faces.

To date, none of all published studies has used pictures and videos of individuals of three age groups and different genders and none of them has compared performances on FER according to age and gender faces.

In our study, we assessed REF using three levels of facial emotion's intensity in the static subtest. For all intensities of emotions, the ASD group has shown worse performances compared to the NT sample. We also noticed that both groups were more accurate in identifying "high intensity" or "fully expressed" facial emotions with increasing difficulties at lower intensities. Our findings are in part consistent with previous recent findings: Wingenbach et al. (33), used a dynamic test with three levels of intensity of facial emotion and found that the ASD group had impairments in FER at low intensity, with greatest performance in identifying facial emotions at higher intensity.

Song and Hakoda (25) used morphing sequences of facial expressions with different intensities varying from 10 to 90% to study diminished sensitivity for FER recognition in children with autism spectrum disorder (14 ASD and 17 NT). They reported that the ASD group had higher thresholds than NT individuals for the recognition of facial emotions. In fact, at high intensities of facial emotions (e.g., 100%), all of the children with autism spectrum disorder were able to recognize facial expressions with the same accuracy of controls. However, as the facial emotions decreased in intensity, the FER accuracy in the ASD group was altered at a higher rate than that of the NT group. Authors suggested that people with autism spectrum disorder do not have a general, but a selective impairment in the recognition of basic emotions, limited to subtle and low intensity facial emotions and that they might use a compensatory mechanism that could help them to decode only high intensity facial emotion information (25). The differences between our results and those of the previously cited studies may be explained by the difference in power. Our study included a larger population, and thus had a better power to detect differences.

Limitations

Despite the several strengths of the present study, several limitations need to be acknowledged. The limited number of female participants in the clinical sample did not allow us to perform significant statistical analyses of sex differences. In fact, a gender effect in the recognition of some facial emotion has been reported in neutrotypical individuals in a recent study (14). Furthermore, our ASD sample only consisted of children and our results might not be generalizable to adolescents and adults with ASD.

In addition, the large difference in sample size between the ASD group and the NT group is another limitation which may induce difficulties in constructing and interpreting the ANCOVA models. This difference in sample sizes can explained by the fact that the population of neurotypical children was used for the validation of the tool and that the recruitment of verbal children with ASD, verbal, attending school and having normal intelligence was more difficult than that of the control group. To ensure the assumptions of the ANCOVA tests are met despite the different sample sizes, we checked for variance homogeneity using the Levene's test and for linearity and homogeneity of regression slopes using scatterplots (plotting each of the FER subscores as separate dependent variables against the each of covariates, for each subgroup).

Finally, we did not match the two groups by gender or IQ. We included age, gender and mental age as covariates in the ANCOVA analyses to control for their potential effects on FER scores. The choice of not matching groups by IQ was also based on the results of two recent meta-analyses that have shown that IQ had no impact on FER performances in children with ASD (12, 13). We did not match the controls to the ASD cases by gender, since previous studies did not show that gender was independently associated with performance in FER tasks (83).

CONCLUSION

Our study supports the findings that children with ASD have difficulties in FER. The ASD group has shown impairment in the recognition of all facial emotions except happiness and fear, with less pronounced difficulties for higher intensities of facial emotions and in the recognition of children facial emotions, compared to adolescents and adults' facial emotions. To the best of our knowledge, our study is the first one that used a test composed of a combination of static and dynamic subtests, including children, adolescent, and adult faces of males and females with high, low, and medium intensities of basic facial emotions, and neutral facial expression. Impairment in FER associated to ASD would have important negative impact in children's development, education, and social integration. Thus, it seems necessary to create new intervention instruments aiming to improve emotion recognition strategies in children with ASD at an early stage of development.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Porfesseur Rym Ghachem, Razi Hospital, Manouba, Tunisia. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SJ: elaboration of the research protocol, assessment of the ASD group, statistical analysis, and redaction of the article. SH: elaboration of the research protocol and correction of the article. AT: elaboration of the facial emotion recognition test and its administration for the control group. SE: assessment of the ASD group. OR, MG, and MM: administration of the test for the control group. AN, ZA, and MH: elaboration of the test. SO: statistical analysis and correction of the article. RF: statistical analysis. AB: elaboration of the test and of the research protocol and correction of the article. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Darwin C. *The Expression of the Emotions in Man and Animals*. London: Murray (1872). doi: 10.1037/10001-000
2. Ekman P, Friesen WV. Constants across cultures in the face and emotion. *J Pers Soc Psychol.* (1971) 17:124–9. doi: 10.1037/h0030377
3. Panksepp J. *Affective Neuroscience: The Foundations of Human and Animal Emotions*. New York, NY: Oxford University Press (1998).
4. Ekman P. Universals cultural differences in facial expressions of emotion. In: Cole J, editor. *Nebraska Symposium on Motivation*. New York: Academic Press (1972).
5. Izard CE. *The Face of Emotion*. New York, NY: Appleton Century Crofts (1971).
6. Tremblay C, Kirouac G, Dore F. The recognition of adults' and children's facial expressions of emotions. *J. Psychol.* (2001) 121:341–50. doi: 10.1080/00223980.1987.9712674
7. Rodger H, Vizioli L, Ouyang X, Caldara R. Mapping the development of facial expression recognition. *Dev. Sci.* (2015) 18:926–39. doi: 10.1111/desc.12281
8. Mancini G, Agnoli S, Baldaro B, Bitti PE, Surcinelli P. Facial expressions of emotions: recognition accuracy and affective reactions during late childhood. *J Psychol.* (2013) 147:599–617. doi: 10.1080/00223980.2012.727891
9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Washington, DC: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596
10. Tracy J, Robins R, Schriber R, Solomon M. Is emotion recognition impaired in individuals with autism spectrum disorders? *J Autism Dev Disord.* (2011) 41:102–9 doi: 10.1007/s10803-010-1030-y
11. Philip RCM, Whalley HC, Stanfield AC, Sprengelmeyer R, Santos IM, Young AW, et al. Deficits in facial, body movement and vocal emotional processing in autism spectrum disorders. *Psychol Med.* (2010) 40:1919–29. doi: 10.1017/S0033291709992364
12. Lozier LM, Vanmeter JW, Marsh AA. Impairments in facial affect recognition associated with autism spectrum disorders: a meta-analysis. *Dev Psychopathol.* (2014) 26:933–45. doi: 10.1017/S0954579414000479
13. Uljarevic M, Hamilton A. Recognition of emotions in autism: a formal meta-analysis. *J Autism Dev Disord.* (2013) 43:1517–26. doi: 10.1007/s10803-012-1695-5
14. Lawrence K, Campbell R, Skuse D. Age, gender, and puberty influence the development of facial emotion recognition. *Front Psychol.* (2015) 6:761. doi: 10.3389/fpsyg.2015.00761
15. Hobson RP. The autistic child's appraisal of expressions of emotion. *J Child Psychol Psychiatr.* (1986) 27:321–42. doi: 10.1111/j.1469-7610.1986.tb01836.x
16. Tantum D, Monaghan L, Nicholson H, Stirling J. Autistic children's ability to interpret faces: a research note. *J Child Psychol Psychiatr.* (1989) 30:623–30. doi: 10.1111/j.1469-7610.1989.tb00274.x
17. Davies S, Bishop D, Manstead ASR, Tantam D. Face perception in children with autism and Asperger's syndrome. *J Child Psychol Psychiatr.* (1994) 35:1033–57. doi: 10.1111/j.1469-7610.1994.tb01808.x
18. Celani G, Battacchi MW, Arcidiacono L. The understanding of the emotional meaning of facial expressions in people with autism. *J Autism Dev Disord.* (1999) 29:57–66. doi: 10.1023/A:1025970600181
19. Bolte S, Poustka F. The recognition of facial affect in autistic and schizophrenic subjects and their first degree relatives. *Psychol Med.* (2003) 33:907–15. doi: 10.1017/S0033291703007438
20. Berggren S, Engström AC, Bölte S. Facial affect recognition in autism, ADHD and typical development. *Cogn Neuropsychiatry.* (2016) 21:213–27. doi: 10.1080/13546805.2016.1171205
21. Griffiths S, Jarrold C, Pentonvoak IS, Woods AT, Skinner AL, Munafò MR. Impaired recognition of basic emotions from facial expressions in young people with autism spectrum disorder: assessing the importance of expression intensity. *J Autism Dev disord.* (2019) 49:2768–78. doi: 10.1007/s10803-017-3091-7
22. Pan N, Wu GH, Zhang L, Zhao YF, Guan H, Xu CJ, et al. Association between intelligence development and facial expression recognition ability in children with autism spectrum disorder. *Chin J Contemp Pediatr.* (2017) 19:275–9. doi: 10.7499/j.issn.1008-8830.2017.03.005
23. Harms MB, Martin A, Wallace GL. Facial emotion recognition in autism spectrum disorders: a review of behavioral and neuroimaging studies. *Neuropsycho Rev.* (2010) 20:290–322. doi: 10.1007/s11065-010-9138-6
24. Humphreys K, Minshew N, Leonard GL, Behrmann M. A fine-grained analysis of facial expression processing in high-functioning adults with autism. *Neuropsychologia.* (2007) 45:685–95. doi: 10.1016/j.neuropsychologia.2006.08.003
25. Song Y, Hakoda Y. Selective impairment of basic emotion recognition in people with autism: discrimination thresholds for recognition of facial expressions of varying intensities. *J Autism Dev Disord.* (2018) 48:1886–94. doi: 10.1007/s10803-017-3428-2
26. Boraston Z, Blakemore SJ, Chilvers R, Skuse D. Impaired sadness recognition is linked to social interaction deficit in autism. *Neuropsychologia.* (2007) 45:1501–10. doi: 10.1016/j.neuropsychologia.2006.11.010
27. Lerner MD, McPartland JC, Morris JP. Multimodal emotion processing in autism spectrum disorders: an event-related potential study. *Dev Cogn Neurosci.* (2013) 3:11–21. doi: 10.1016/j.dcn.2012.08.005
28. Hauschild KM, Felsman P, Keifer CM, Lerner MD. Evidence of an own-age bias in facial emotion recognition for adolescents with and without autism spectrum disorder. *Front Psychiatry.* (2020) 11:428. doi: 10.3389/fpsyt.2020.00428
29. Ozonoff S, Pennington BF, Rogers SJ. Are there emotion perception deficits in young autistic children? *J Child Psychol Psychiatr.* (1990) 31:343–61. doi: 10.1111/j.1469-7610.1990.tb01574.x
30. Baron-Cohen S, Jolliffe T, Mortimore C, Robertson M. Another advanced test of theory of mind: evidence from very high functioning adults with autism or Asperger syndrome. *J Child Psychol Psychiat.* (1997) 38:813–22. doi: 10.1111/j.1469-7610.1997.tb01599.x
31. Ogai M, Matsumoto H, Suzuki K, Ozawa F, Fukuda R, Uchiyama I, et al. fMRI study of recognition of facial expressions in high-functioning autistic patients. *Neuroreport.* (2003) 14:559–63. doi: 10.1097/00001756-200303240-00006

32. Walsh JA, Vida MD, Rutherford MD. Strategies for perceiving facial expressions in adults with autism spectrum disorder. *J Autism Dev Disord.* (2013) 44:1018–26. doi: 10.1007/s10803-013-1953-1
33. Wingenbach TSH, Ashwin C, Brosnan M. Diminished sensitivity and specificity at recognising facial emotional expressions of varying intensity underlie emotion-specific recognition deficits in autism spectrum disorders. *Res Autism Spectr Disord.* (2017) 34:52–61. doi: 10.1016/j.rasd.2016.11.003
34. Wong N, Beidel DC, Sarver DE, Sims V. Facial emotion recognition in children with high functioning autism and children with social phobia. *Child Psychiatry Hum Dev.* (2012) 43:775–94. doi: 10.1007/s10578-012-0296-z
35. Clark TF, Winkielman P, McIntosh DN. Autism and the extraction of emotion from briefly presented facial expressions: stumbling at the first step of empathy. *Emotion.* (2008) 8:803–9. doi: 10.1037/a0014124
36. Law Smith MJ, Montagne B, Perrett DI, Gill M, Gallagher L. A detecting subtle facial emotion recognition deficits in high-functioning Autism using dynamic stimuli of varying intensities. *Neuropsychol.* (2010) 48:2777–81. doi: 10.1016/j.neuropsychologia.2010.03.008
37. Harwood NK, Hall LJ, Shinkfield AJ. Recognition of facial emotional expressions from moving and static displays by individuals with mental retardation. *Am J Ment Retard.* (1999) 104:270–8. doi: 10.1352/0895-8017
38. Weyers P, Muhlberger A, Hefele C, Pauli P. Electromyographic responses to static and dynamic avatar emotional facial expressions. *Psychophysiology.* (2006) 43:450–3. doi: 10.1111/j.1469-8986.2006.00451.x
39. Ambadar Z, Schooler JW, Cohn JF. Deciphering the enigmatic face: the importance of facial dynamics in interpreting subtle facial expressions. *Psychol Sci.* (2005) 16:403–10. doi: 10.1111/j.0956-7976.2005.01548.x
40. Kilts CD, Egan G, Gideon DA, Ely TD, Hoffman JM. Dissociable neural pathways are involved in the recognition of emotion in static and dynamic facial expressions. *Neuroimage.* (2003) 18:156–68. doi: 10.1006/nimg.2002.1323
41. Johnston PJ, Enticott PG, Mayes AK, Hoy KE, Herring SE, Fitzgerald PB. Symptom correlates of static and dynamic facial affect processing in schizophrenia: evidence of a double dissociation? *Schizophr Bull.* (2010) 36:680–7. doi: 10.1093/schbul/sbn136
42. Eack SM, Mazefsky CA, Minshew NJ. Misinterpretation of facial expressions of emotion in verbal adults with autism spectrum disorder. *Autism.* (2015) 19:308–15. doi: 10.1177/1362361314520755
43. Rutter M, Le Couteur A, Lord C. *Autism Diagnostic Interview-Revised (ADIR).* Los Angeles: Western Psychological Services (2003).
44. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavas J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry.* (1998) 59:22–33. doi: 10.1037/t18597-000
45. Ben Rjeb R. *Les Echelles Différentielles d'Efficiences Intellectuelles, forme arabe (EDEI-A).* Tunis:Cogerh Sélection (2003).
46. Bartlett MS, Viola PA, Sejnowski TJ, Golomb BA, Larsen J, Hager JC, et al. Classifying facial action IEEE. *Trans Pattern Anal Mach Intell.* (1999) 21:974–89. doi: 10.1109/34.799905
47. Ekman P, Friesan W, Ellsworth P. *Emotion in the Human Face: Guidelines for Research and an Integration of Findings.* New York, NY: Pergamon Press (1972).
48. Ghasemi A, Zahediasl S. Normality tests for statistical analysis: a guide for non-statisticians. *Int J Endocrinol Metab.* (2012) 10:486–9. doi: 10.5812/ijem.3505
49. Adolphs R, Tranel D, Hamann S, Young AW, Calder AJ, Phelps EA, et al. Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia.* (1999) 37:1111–7. doi: 10.1016/S0028-3932(99)00039-1
50. Adolphs R. Fear, faces, and the human amygdala. *Curr Opin Neurobiol.* (2008) 18:166–72. doi: 10.1016/j.conb.2008.06.006
51. Anderson AK, Spencer DD, Fulbright RK, Phelps EA. Contribution of the anteromedial temporal lobes to the evaluation of facial emotion. *J Neuropsychol.* (2000) 14:526–36. doi: 10.1037/0894-4105.14.4.526
52. Schultz RT. Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. *Int J Dev Neurosci.* (2005) 23:125–41. doi: 10.1016/j.ijdevneu.2004.12.012
53. Ashwin C, Baron-Cohen S, Wheelwright S, O'Riordan M, Bullmore ET. Differential activation of the amygdale and the 'social brain' during fearful face-processing in Asperger syndrome. *Neuropsychologia.* (2007) 45:2–14. doi: 10.1016/j.neuropsychologia.2006.04.014
54. Killgore W, Oki M, Yurgelun-Todd D. Sex-specific developmental changes in amygdala responses to affective faces. *Neuroreport.* (2001) 12:427–33. doi: 10.1097/00001756-200102120-00047
55. Ashwin C, Chapman E, Colle L, Baron-Cohen S. Impaired recognition of negative basic emotions in autism: a test of the amygdala theory. *Soc Neurosci.* (2006) 1:349–63. doi: 10.1080/17470910601040772
56. Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SCR. The amygdala theory of autism. *Neurosci Biobehav Rev.* (2000) 24:355–64. doi: 10.1016/S0149-7634(00)00011-7
57. Howard MA, Cowell PE, Boucher J, Broks P, Mayes A, Farrant A, et al. Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. *Neuroreport.* (2000) 11:2931–5. doi: 10.1097/00001756-200009110-00020
58. Neumann D, Spezio ML, Piven J, Adolphs R. Looking you in the mouth: abnormal gaze in autism resulting from impaired top-down modulation of visual attention. *Soc Cogn Affect Neurosci.* (2006) 1:194–202. doi: 10.1093/scan/nsl030
59. Spezio M, Adolphs R, Hurley R, Piven J. Abnormal use of facial information in high-functioning autism. *J Autism Dev Disord.* (2007) 37:929–39. doi: 10.1007/s10803-006-0232-9
60. Gross TF. The perception of four basic emotions in human and nonhuman faces by children with autism and other developmental disabilities. *J Abnorm Child Psychol.* (2004) 32:469–80. doi: 10.1023/B:JACP.0000037777.17698.01
61. Klin A, Jones W, Schultz R, Volkmar F, Cohen D. Visual fixation patterns during viewing of naturalistic social situations as predictors social competence in individuals with autism. *Arch Gen Psychiatry.* (2002) 59:809–16. doi: 10.1001/archpsyc.59.9.809
62. Dalton KM, Nacewicz BM, Johnstone T, Schaefer HS, Gernsbacher MA, Goldsmith HH, et al. Gaze fixation and the neural circuitry of face processing in autism. *Nature.* (2005) 8:519–26. doi: 10.1038/nn1421
63. Pelphrey KA, Sasson NJ, Reznick JS, Paul G, Goldman BD, Piven J. Visual scanning of faces in autism. *J Autism Dev Disord.* (2002) 32:249–61. doi: 10.1023/A:1016374617369
64. Joseph RM, Tanaka J. Holistic and part-based face recognition in children with autism. *J Child Psychol Psychiatr.* (2003) 44:529–42. doi: 10.1111/1469-7610.00142
65. Adolphs R, Gosselin F, Buchanan TW, Tranel D, Schyns P, Damasio AR. A mechanism for impaired fear recognition after amygdala damage. *Nature.* (2005) 433:68–72. doi: 10.1038/nature03086
66. Grelotti DJ, Gauthier I, Schultz RT. Social interest and the development of cortical face specialization: what autism teaches us about face processing. *Dev Psychobiol.* (2002) 40:213–25. doi: 10.1002/dev.10028
67. Baron-Cohen S, Spitz A, Cross P. Do children with autism recognise surprise? A research note. *Cogn Emot.* (1993) 7:507–16. doi: 10.1080/02699939308409202
68. Cook R, Brewer R, Shah P, Bird G. Alexithymia, not autism, predicts poor recognition of emotional facial expressions. *Psychol Sci.* (2013) 24:723–32. doi: 10.1177/0956797612463582
69. Williams BT, Gray. K. The relationship between emotion recognition ability and social skills in young children with autism. *Autism.* (2013) 17:762–8. doi: 10.1177/1362361312465355
70. García-Villamisar D, Rojahn J, Zaja RH, Jorda M. Facial emotion processing and social adaptation in adults with and without autism spectrum disorder. *Res Autism Spectr Disord.* (2010) 4:755–62. doi: 10.1016/j.rasd.2010.01.016
71. Dawson G, Webb SJ, McPartland J. Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. *Dev Neuropsychol.* (2005) 27:403–24. doi: 10.1207/s15326942dn2703_6
72. Kohls G, Chevallier C, Troiani V, Schultz RT. Social 'wanting' dysfunction in autism: neurobiological underpinnings and treatment implications. *J Neurodev Disord.* (2012) 4:10. doi: 10.1186/1866-1955-4-10

73. Chevallier C, Kohls G, Troiani V, Brodkin ES, Schultz RT. The social motivation theory of autism. *Trends Cogn Sci.* (2012) 16:231–9. doi: 10.1016/j.tics.2012.02.007
74. Wallace GL, Case LK, Harms MB, Silvers JA, Kenworthy L, Martin A. Diminished sensitivity to sad facial expressions in high functioning autism spectrum disorders is associated with symptomatology and adaptive functioning. *J Autism Dev Disord.* (2011) 41:1475–86. doi: 10.1007/s10803-010-1170-0
75. Garman HD, Spaulding CJ, Webb SJ, Mikami AY, Morris JP, Lerner MD. Wanting it too much: an inverse relation between social motivation and facial emotion recognition in autism spectrum disorder. *Child Psychiatry Hum Dev.* (2016) 47:890–902. doi: 10.1007/s10578-015-0620-5
76. Piggot J, Kwon H, Mobbs D, Blasey C, Lotspeich L, Menon V, et al. Emotion attribution in high-functionning individuals with autistic spectrum disorder: a functional imaging study. *J Am Acad Child Adolesc Psychiatry.* (2004) 34:473–80. doi: 10.1097/00004583-200404000-00014
77. Ponnet KS, Roeyers H, Buysse A, de Clercq A, van der Heyden E. Advanced mind-reading in adults with Asperger syndrome. *Autism.* (2004) 8:249–66. doi: 10.1177/1362361304045214
78. Rump KM, Giovannelli JL, Minshew NJ, Strauss MS. The development of emotion recognition in individuals with autism. *Child Dev.* (2009) 80:1434–47. doi: 10.1111/j.1467-8624.2009.01343.x
79. Grossman JB, Klin A, Carter AS, Volkmar FR. Verbal bias in recognition of facial emotions in children with Asperger syndrome. *J Child Psychol Psychiatr.* (2002) 41:369–79. doi: 10.1111/1469-7610.00621
80. Klucharev V, Sams M. Interaction of gaze direction and facial expressions processing: ERP study. *Neuroreport.* (2004) 15:621–6. doi: 10.1097/00001756-200403220-00010
81. Lindner J, Rosén L. Decoding of emotion through facial expression, prosody and verbal content in children and adolesscents with Asperger's syndrome. *J Autism Dev Disord.* (2006) 36:769–77. doi: 10.1007/s10803-006-0105-2
82. Feinman S, Entwisle DR. Children's ability to recognize other children's faces. *Child Dev.* (1976) 47:506. doi: 10.2307/1128809
83. Enticott PG, Kennedy HA, Johnston PJ, Rinehart NJ, Tonge BJ, Taffe JR, et al. Emotion recognition of static and dynamic faces in autism spectrum disorder. *Cogn Emot.* (2014) 28:1110–8. doi: 10.1080/02699931.2013.867832
84. Gepner B, Deruelle C, Grynfeltt S. Motion and emotion: a novel approach to the study of face processing by young autistic children. *J Autism Dev Disord.* (2001) 31:37–45. doi: 10.1023/A:1005609629218
85. Scherf KS, Behrmann M, Dahl RE. Facing changes and changing faces in adolescence: a new model for investigating adolescent-specific interactions between pubertal, brain and behavioral development. *Dev Cogn Neurosci.* (2012) 2:199–219. doi: 10.1016/j.dcn.2011.07.016
86. Picci G, Scherf KS. From caregivers to peers: puberty shapes human face perception. *Psychol Sci.* (2016) 27:1461–73. doi: 10.1177/0956797616663142
87. Vetter NC, Drauschke M, Thieme J, Altgassen M. Adolescent basic facial emotion recognition is not influenced by puberty or own-age bias. *Front Psychol.* (2018) 9:956. doi: 10.3389/fpsyg.2018.00956

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When Alterations in Social Cognition Meet Subjective Complaints in Autism Spectrum Disorder: Evaluation With the "ClaCoS" Battery

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Background: Deficit in social communication is a core feature in Autism Spectrum Disorder but remains poorly assessed in classical clinical practice, especially in adult populations. This gap between needs and practice is partly due to a lack of standardized evaluation tools. The multicentric Research group in psychiatry GDR3557 (Institut de Psychiatrie) developed a new battery for social cognitive evaluation named "ClaCoS," which allows testing the main components of social cognition: Emotion Recognition, Theory of Mind, Attributional Style, and Social Perception and Knowledge. It further provides an assessment of subjective complaints in social cognition.

Methods: We compared the social cognition abilities of 45 adults with Autism Spectrum Disorder without intellectual disability and 45 neurotypically developed volunteers using the "ClaCoS" battery, in order to determine its relevance in the evaluation of social cognition impairments in autism. A correlational approach allowed us to test the links between subjective complaints and objectively measured impairments for the different components of social cognition.

Results: As expected, the Autism Spectrum Disorder group showed deficits in all four components of social cognition. Moreover, they reported greater subjective complaints than controls regarding their social abilities, correlated to the neuropsychological assessments.

Conclusion: The "ClaCoS" battery is an interesting tool allowing to assess social impairments in autism and to specify the altered components, for a better adjustment of tailored social cognition training programs. Our results further suggest that people

with Autism Spectrum Disorder have a good social cognitive insight, i.e., awareness into social cognitive functioning, and may thus benefit from social cognitive training tools.

Keywords: Autism Spectrum Disorder, adults, social cognition, assessment, subjective complaints

INTRODUCTION

Social Cognition in Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social functioning and restricted, repetitive patterns of behavior, interests, or activities (1).

Individuals with ASD experience daily challenges with social function, which frequently impact negatively their relationships and access to education or employment. Typically, children and adults with ASD encounter difficulties to understand other's emotional states or intentions. This may lead to inappropriate behaviors in social situations. Thus, despite good intellectual abilities, high functioning adults with ASD may ask inappropriate questions, act oddly and are therefore vulnerable to bullying and isolation. These difficulties have been linked to well-documented deficits in social cognition in ASD (2). Social cognition refers to the cognitive processes (i.e., emotional processing, interpretation, mentalizing…) which allow us to adapt our responses according to different social situations, in a flexible manner (3). The heterogeneity of ASD population explains that some people on the spectrum may lack very basic social skills [emotion perception, difficulty to make eye contact…; e.g. (4, 5)] while others are mainly impaired at higher cognitive levels [mentalizing, understanding jokes, or sarcasm…; e.g. (6, 7)].

Research on social cognition in ASD has essentially focused on emotional processing (i.e., identification of emotions from different cues, including facial expression) and theory of mind (i.e., ToM; ability to mentalize other's mental states which allow us to make inferences on their intentions, beliefs, and knowledge), showing alterations in both processes (8, 9). More precisely, considerable evidence suggested deficits in the discrimination and recognition of basic emotional facial expressions [(10–13); for reviews, see (14, 15)]. However, several studies failed to show poorer recognition of emotions in ASD, especially when considering adolescents or adults without intellectual disability, although daily life difficulties were still encountered e.g. (16–21). The type of stimuli used may explain this discrepancy: deficits in the recognition of emotional expressions are more consistently observed when facial emotional processing is made more difficult by the use of complex or subtle emotions (different intensities, dynamic faces…) compared to the presentation of more basic stimuli (static faces, basic emotional expressions, only high intensity…) [(10–13); for a review, see (14)]. In particular, studies manipulating the levels of emotional intensity reported lower emotional recognition abilities in children and adults with ASD without intellectual disability. These alterations appear more strongly when using mild affective expressions (22–27).

An influential theory considering social dysfunction in ASD puts forward an alteration of ToM [Mindblindness theory, (6)]. ToM deficits in ASD have been widely supported although results in the literature remain controversial [for a meta-analysis, see (28)]. Numerous studies show a delayed or incomplete development for ToM in children with ASD e.g. (8, 29). Moreover, better performance of children with ASD in ToM tasks has been associated with better social competence (30). The results are less consistent when considering high functioning adults with ASD (31, 32). ToM deficits in this population are best revealed by tasks which mirror the demands of real life social exchanges, such as "implicit" ToM tasks, tasks which consider response times or generally more ecological tasks (33, 34). This suggests that adults with ASD succeed in classical evaluations of ToM by using compensatory strategies to infer other people's mental state (35). This is in line with functional neuroimaging studies, which show that adults with ASD activate different brain regions when solving theory-of-mind tasks (36). However, these strategies may not be efficient enough in everyday life situations, which require to instantly understand other's intentions or feelings and to respond accordingly in a timely manner (37).

Moreover, social cognitive deficits in ASD could be a consequence of an atypical sensory processing. Indeed, a great number of studies using eye-tracking have shown different visual exploration in this population, with fewer gaze directed toward social comparatively to non-social elements [(38, 39); for meta-analyses, see (40, 41)]. Moreover, children and adults with ASD benefit less than neurotypical controls from supportive contextual cues in order to recognize emotional expressions (42, 43). These observations may be explained by a lack of interest for social information (44). It could also be linked to the bias toward local vs. global information (45, 46). This results in a difficulty to perceive visual elements as a whole, even more so when considering complex visual scenes. As a consequence, ASD individuals do not sufficiently process the salient visual features which are needed in order to understand typical social situations. Altogether, these results are consistent with deficits in social perception in ASD, although this term is not commonly used in this field of research.

The alterations in the perception and understanding of social situations may lead to misinterpretations and in some adults with ASD to attribution biases. Research in this domain is scarce. Nevertheless, the few studies conducted showed no self-blaming pattern but rather healthy and normal self-serving attributions (47–49). Blackshaw et al. (47) suggest that paranoid symptoms, clinically observed in some adolescents and adults with ASD, may be a consequence of their confusion in understanding subtle social interactions and social rules. This disability could be linked to a deficit in ToM and in social perception. It may also stem from past traumatic experiences such as bullying.

Social Cognition Evaluation in ASD

Most tools developed for neuropsychological evaluation of Emotional Processing present static photographs of highly expressive emotional expressions (e.g., Ekman Face Test) and often fail to show any impairment in ASD adults without intellectual disability (14). Indeed, it has been suggested that these adults have developed explicit cognitive, language-mediated or perceptual compensatory strategies. These strategies allow them to succeed in such classical neuropsychological evaluations of emotional perception (17, 35, 50). This further stresses the relevance of using more sensitive and ecological tools in order to assess emotional perception in this specific population.

Concerning Theory of Mind, the most classical tasks (i.e., false belief tasks; strange stories tasks…) do not sufficiently target subtle impairments encountered by adults with ASD without intellectual disability and especially in those with good verbal skills (7, 34, 51–53). These traditional tests either present static images or are based on verbal descriptions of social situations and may be solved by the use of a deductive rather than a spontaneous strategy (35, 37). Interestingly, some more ecological tasks have been developed in order to assess subtle ToM difficulties (33, 54). Among these, the MASC test has proven sensitive to reveal ToM alterations in adolescents and adults with ASD (55–60). It consists in the presentation of a short movie picturing a typical social situation (i.e., a Saturday night dinner with four young adults), thus providing a better ecological validity. Furthermore, it allows detecting hyper- or hypo-mentalizing tendencies, in addition to general ToM alterations.

To our knowledge there are very few standardized evaluation tools allowing the assessment of social perception deficits in ASD, and none of these have been standardized in French language. For instance, the Social Perception subtest from the Advanced Clinical Solution has been used to reveal such deficits in adolescents and adults with ASD (61), but is available only in English (62).

Similarly, only few standardized questionnaires have been developed in order to evaluate attribution biases (63). These questionnaires show some limitations, such as presenting few ambiguous situations with strong social cognitive biases. Moreover, they generally target paranoia and persecutory delusion rather than more general social cognitive biases. The latter might be observed in ASD but are rarely considered in clinical practice.

The "ClaCoS" Battery: A New Tool for Social Cognition Evaluation

Deficits in social cognition are observed in several psychiatric conditions other than ASD (schizophrenia, ADHD, bipolar disorder, anorexia…), and have been linked to functional outcome [e.g., (64–67); for reviews see (68, 69)]. In the field of schizophrenia, several programs which target specific social cognition deficits have shown significant improvements in real-world outcome. This raises an important issue concerning the assessment of social cognition in order to apply the most adapted treatment for each patient. To reach that goal, a group of experts have sought to specify the definition of social cognition in order to improve its assessment in clinical practice [the SCOPE project: Social Cognition Psychometric Evaluation; (70)]. They considered social cognition as a heterogeneous construct which includes several dimensions. Pinkham (70), in accordance with Green (71, 72), proposed four main core domains: [1] Emotion processing (i.e., identification of emotions from different cues, including facial expression); [2] Social perception (i.e., decoding and interpreting social cues by taking into account the social context) and social knowledge (i.e., knowledge of social rules, roles, and goals); [3] Theory of mind (i.e., ToM; ability to mentalize other's mental state which allow us to make inferences on their intentions, beliefs and knowledge); [4] Attributional style (positive or negative inference of events). Although these different dimensions are considered and assessed separately for both theoretical and practical reasons, they may not be independent from each other but rather partially overlapping (73).

Only few validated and standardized tools are available in French language for the clinical assessment of social cognition in adults (74). In this context, the multicentric Research group in psychiatry GDR3557- Institut de Psychiatrie (www.institutdepsychiatrie.org) developed a new battery for social cognition evaluation named "ClaCoS," which offers the advantage of exploring all four dimensions of social cognition identified by the SCOPE project. It further includes an evaluation of subjective complaints in these same four dimensions, which allows a comparison between subjective complaints in social functioning and objective evaluation. This social cognition battery has primarily a functional purpose, as it provides a singular profile of the patient's strengths and weaknesses in social cognition. This can further lead to an adjustment of tailored social cognition training programs. This battery can also be used in clinical practice, in line with a transnosographic view of social cognition deficits in different psychiatric conditions. Moreover, the "ClaCoS" battery includes ecological tools which could be of interest to assess subtle social cognition deficits encountered by adults with ASD without intellectual disability.

The aim of the present study was to examine the relevance of the "ClaCoS" battery for the assessment of social cognition in adults with ASD without intellectual disability compared to control typical developing subjects. Based on the existing literature, we expected the ASD group to be less efficient than the controls on the neuropsychological evaluation of all dimensions of social cognition, and in particular emotional perception, social perception and theory of mind. Concerning attributional style, this hypothesis could be more uncertain, as previous studies showed no difference between ASD and controls (75). Nevertheless, we predicted some differences in light of the paranoid symptoms which are clinically observed in some adults with ASD. Self-insight is typically considered to be altered in ASD (53). However, research on self-knowledge in ASD is sparse and yields mixed results, with some reports of preserved self-insight (76). By examining the links between subjective complaints and objectively measured impairments in the different components of social cognition, we wished to evaluate the self-consciousness of ASD adults with respect to their deficits in social functioning.

MATERIALS AND METHODS

The study was carried out in accordance with the Declaration of Helsinki and approved by the local Ethics Committee (CPP Lyon-Sud Est IV, no. 15/041; ANSM, no. 2015-A00580-49). Written informed consent to take part in the study was obtained from all participants. The control subjects were paid 30 euros for their participation.

Participants

All participants were enrolled in a multisite study assessing social cognition in adults with autism and schizophrenia with the "ClaCoS" Battery. This study was conducted in three sites in France: Child Psychiatry Department specialized in autism, University Hospital of Tours, in Tours; Hospital Le Vinatier in Lyon and Groupe Hospitalier Universitaire Paris, Psychiatry and Neuroscience in Paris.

Participants with ASD without intellectual disability (n = 45), aged from 18 to 48 years were locally recruited and tested in Tours (n = 20), and Paris (n = 25). They were diagnosed by expert clinicians according to DSM-5 criteria (1) and using the Autism Diagnostic Observation Schedule, Second Edition [ADOS-2; (77)] and/or the Autism Diagnostic Interview-Revised [ADI-R; (78)]. All but three participants with ASD were screened with the ADI interview. The ADOS-2 was administered to twenty-two participants, including the three participants for which the ADI scores could not be obtained. ASD participants were either not under medication or on a stable medication regimen for a minimum of 1 month.

Typical developing adults (n = 45), aged from 18 to 50 years were recruited from the local community in Tours (n = 8), Paris (n = 5) and Lyon (n = 32). They were screened for the absence of any neuropsychiatric disorder using the MINI [International Neuropsychiatric Interview (79)].

Exclusion criteria for both groups included: [1] the presence or history of neurological disorders affecting brain function, [2] the presence of severe visual or hearing impairments interfering with assessment, [3] the absence of French language proficiency or important reading difficulties and [4] an abuse of substance in the past month (tobacco excluded).

The control participants were selected from a larger dataset (n = 200) to match the ASD population in terms of gender, age and education. The demographic and clinical characteristics of both groups are shown in **Table 1**. Verbal and Performance Intelligence quotients (IQ) were assessed in the ASD group by the Wechsler Adult Intelligence Scale-Fourth Edition [WAIS-IV; (80)] (**Table 1**).

TABLE 1 | Participants characteristics.

	Patients with ASD		Controls (N = 45)	p
	N	Mean (SD)	Mean (SD)	
Age (years)	45	27.7 (7.9)	27.6 (7.8)	0.968
Gender (F:M)	45	10:35	9:36	0.796
Education (years)	45	13.0 (2.4)	13.3 (1.7)	0.693
ADOS-2 (social interactions +communication)	22	12.6 (4.6)	–	NA
ADI (social interactions)	42	18.8 (7.9)	–	NA
ADI (verbal communication)	42	13.1 (5.3)	–	NA
Verbal IQ	45	117 (18)	–	NA
Performance IQ	45	103 (18)	–	NA
Empathy quotient	40	24.7 (10.5)	39.1 (10.4)	<0.001
Rey tangled lines test				
Time (ms)	44	9.8 (3.9)	7.9 (2.5)	0.004
Number of errors	44	1.0 (1.8)	0.6 (1.1)	0.691
Cancellation task				
Time (ms)	44	101.9 (47.2)	78.5 (24.8)	0.005
Number of errors	44	0.5 (0.9)	0.2 (0.5)	0.224

Non-parametric Mann-Whitney or χ^2 tests were used to test group differences.

Social Cognitive Measures

All participants were tested in a silent room by an experienced neuropsychologist and placed, for computerized tests, at 23 inches from a 15-inch computer screen. They underwent a full assessment with the "ClaCoS" battery, developed by the multicentric Research group in psychiatry GDR3557 [for a more detailed presentation of each test, see (81)]. This new battery for social cognition evaluation included the following tests (**Figure 1**):

Self-Assessment of Social Cognition Impairments (ACSo)

The ACSo (82) is a self-administered questionnaire allowing to assess the subjective complaints of patients suffering from difficulties in the field of social cognition. Social cognition complaints are explored considering 4 dimensions: emotional perception, social perception and knowledge, theory of mind and attributional style. This allows the computation of 5 scores: a total score and 4 sub-scores corresponding to each domain.

Emotion Processing—Facial Emotion Recognition Test (TREF)

The TREF (83) assesses the ability to recognize five out of the six basic and universal emotions (happiness, anger, sadness, fear, and disgust). In addition, faces expressing contempt are presented, instead of surprise, as this more complex social emotion is of interest when considering psychiatric populations. Each emotion is presented with nine levels of intensity from 20 to 100%. The participants were asked to name the emotion expressed from the photos, using a forced choice among the six possible responses. This assessment provides an overall percentage of correct emotion recognition (global score) and for each emotion (score per emotion). Moreover, the level of intensity (global and per emotion) necessary for recognizing emotions with certainty was computed (recognition threshold). In this study, we specifically analyzed the global and per emotion percentage of correct recognition and recognition thresholds.

Social Perception and Knowledge—PerSo (GDR 3557)

The PerSo measures the perception of social situations, using pictures taken from the material "ColorCards—Social behavior."

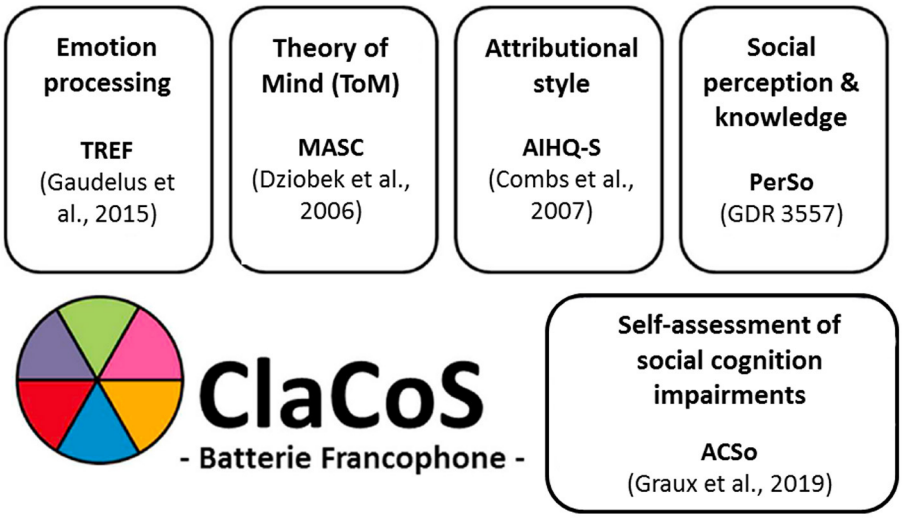

FIGURE 1 | Tests constituting the "ClaCoS" battery.

Participants completed 3 successive tasks. First, they were asked to list all the elements perceived in the picture, providing a global "fluency score." Then, they were instructed to explain the social situation freely, leading to a "non-indexed interpretation score." Indexed questions were then proposed if some of the expected elements were missing (main character; location; interactions), resulting in an "indexed interpretation score." A "total interpretation score" was then computed by adding the "non-indexed" and "indexed" interpretation scores. Finally, the participants were asked to extract a social rule that could be related to the card, producing a "social knowledge score."

Theory of Mind (ToM)—Mental States Attribution—Movie for the Assessment of Social Cognition (MASC)

The MASC test [(55); French Translation (58)] is a video-based task measuring ToM abilities. It is a 15-min movie featuring four people meeting on a Saturday evening. The movie is regularly interrupted by a screen displaying a question referring to the actors' mental states (emotions or feelings, thoughts and intentions). Four scores are rated: a total score (correct "ToM" responses) and 3 scores according to error types: a "less ToM" score ("undermentalization" answers), a "no ToM" score (literal answers, with no mentalization), and finally an "excessive ToM" score (over interpretative response).

Attributional Style—Ambiguous Intentions and Hostility Questionnaire-Short Version (AIHQ-S)

AIHQ-S measures attributional biases from ambiguous social situations [AIHQ-S, Adapted From Combs et al. (63); French Version by Angelard et al. in Preparation]. The participants were instructed to read each situation and to picture themselves in these situations. They were then asked to answer several questions to measure three scores: [1] a hostility bias (HB), reflecting how hostile they rated the other's actions toward themselves; [2] an attribution of responsibility score which is the average of three ratings from Likert scales: an intentionality score—IS (whether the person acted on purpose); an anger score—AS (how angry it would make them feel) and a blame score—BS (how much they would blame the other person); [3] an aggression bias (AB) corresponding to the level of aggression in their response.

In addition, empathy was assessed using the Empathy Quotient questionnaire [EQ, (84)]. The Rey Tangled Lines Test (85) and a cancellation task (86) were also included as control measures of visual discrimination and visuo-spatial attention abilities. Due to technical reasons, data from the EQ was not recorded for five ASD participants and from both the Rey tangled lines test and the cancellation task for one ASD participant. All control participants completed these three additional tasks.

Statistical Analysis

Statistical analyses were performed using STATISTICA v13.3 software (TIBICO®). For a better uniformity across the different analyses, non-parametric statistics were chosen, as there was a violation of the assumption of homogeneity of variance on some measures, according to the Levene's test. The Mann-Whitney non parametric *U* test was used for group comparisons. ANCOVAs were performed in order to control the effect of potential confounding variables. Relationships between subjective complaints and the neuropsychological measures were assessed with Spearman correlation analyses, considering the entire sample (ASD + controls). These were performed between each of the sub scores of the ACSo and the score obtained on the neuropsychological assessment of the corresponding dimension of social cognition (emotional perception, social perception and knowledge, theory of mind or attributional style), only when significant group comparisons were observed. Bonferonni correction for multiple analysis was applied.

RESULTS

Demographic and Clinical Characteristics

The ASD and control groups did not differ in terms of age, gender or education level (**Table 1**). As expected, ASD individuals showed lower empathy scores compared to matched controls. They were also slower on both visuo-spatial and attentional tests, while their accuracy was similar to the control group.

Comparative Results of Social Cognition Assessments in Adults With ASD and Controls

Self-Assessment of Social Cognition Impairments (ACSo)

The total score as well as all four sub-scores (emotional perception, social perception and knowledge, theory of mind and attributional style) were higher in adults with ASD compared to controls (all $p < 0.001$; **Table 2**).

Facial Emotion Recognition (TREF)

Adults with ASD required a higher threshold in order to correctly recognize emotional facial expressions from photographs (adjusted $p = 0.035$; **Table 2**). Moreover, a smaller recognition accuracy was observed with a trend in the ASD group compared to the controls (adjusted $p = 0.077$). This was found on the overall scores of correct recognition and recognition threshold but not when considering each emotion separately.

Social Perception and Knowledge (PerSo)

Adults with ASD were less efficient than control participants on the assessments of both the fluency and the interpretation of the social situation (**Table 2**). They listed fewer visual details from the perceptual scenes (fluency score; adjusted $p = 0.004$). Furthermore, the interpretation score was significantly lower in the ASD group compared to the controls when considering the indexed interpretation (adjusted $p = 0.015$) and with a trend for the total interpretation (adjusted $p = 0.060$).

Theory of Mind (MASC)

The total score (correct "ToM" answers) was higher in controls than in adults with ASD (adjusted $p < 0.001$; **Table 2**). More precisely, adults with ASD produced significantly more "no ToM" (adjusted $p = 0.028$) and "excessive ToM" (adjusted $p = 0.032$) answers compared to controls. No difference was found between adults with ASD and controls for the "less ToM" answer.

Attributional Style (AIHQ-S)

No difference was found between adults with ASD and controls for the hostility bias (**Table 2**). A significantly higher intentionality score (adjusted $p = 0.026$) was observed for adults with ASD compared to the controls, resulting in a trend for a greater attribution of responsibility score in the ASD group (adjusted $p = 0.062$). ASD and controls did not differ on the anger nor on the blame score. Moreover, the ASD participants showed a lower aggression bias than the controls (adjusted $p = 0.023$).

All differences previously reported between the ASD and controls remained significant after controlling for visuospatial discrimination and attentional abilities (all $F > 6.20$; $p < 0.05$).

Relationship Between Subjective Complaints and Social Cognition Assessments

Correlations were performed between the scores of each dimension of the ACSo and the results on the test designed to assess social cognitive impairments on the corresponding dimension of social cognition. This allowed us to examine the relationship between the participant's subjective complaints in specific domains of social cognition and the actual impairments measured through the neuropsychological assessment (**Figure 2**).

Facial Emotion Recognition (Relationship Between ACSo- Emotional Perception and TREF)

Subjective complaint concerning emotional perception (ACSo) was positively correlated with the emotion recognition threshold (TREF threshold; $r = 0.255$, $p = 0.015$). Thus, greater complaints concerning emotional perception were associated with overall higher thresholds needed in order to correctly recognize emotional facial expressions.

Social Perception and Knowledge (Relationship Between ACSo- Social Perception & PerSo)

Subjective complaint concerning social perception and knowledge (ACSo) was negatively correlated with the interpretation score (PerSo indexed interpretation score: $r = -0.279$, $p = 0.008$, adjusted $p = 0.015$). Subjective complaint concerning social perception and knowledge (ACSo) was not correlated with the fluency score (PerSo fluency, $r = -0.115$, $p = 0.280$).

Theory of Mind (Relationship Between ACSo- Theory of Mind and MASC)

Subjective complaint concerning theory of mind (ACSo) was negatively correlated with the total score (MASC; $r = -0.386$, $p < 0.001$, adjusted $p < 0.001$). Moreover, it was positively correlated with the "no ToM"($r = 0.253$, $p = 0.016$, adjusted $p = 0.048$) and with a trend to "excessive ToM" ($r = 0.243$, $p = 0.021$, adjusted $p = 0.063$) answers. The larger the complaint, the smaller the total score and the greater the "no ToM" and "excessive ToM" answers.

Attributional Style (Relationship Between ACSo- Attributional Style and AIHQ-S)

Subjective complaint concerning attributional style (ACSo) was positively correlated with the intentionality score ($r = 0.445$, $p < 0.001$, adjusted $p < 0.001$). Thus, larger complaints were associated with a higher attribution of the other's responsibility. No significant correlation was observed between subjective complaint concerning attributional style and the aggression bias ($r = -0.061$, $p = 0.568$).

TABLE 2 | Scores from the "ClaCoS" battery in adults with ASD and controls.

	ASD (*N* = 45) Mean (SD)	Controls (*N* = 45) Mean (SD)	*U*	*p*	Adjusted *p*
Self-assessment of social cognition impairments (ACSo)					
Total score	24.24 (8.0)	9.6 (5.1)	158.5	<0.001	<0.001
Emotional perception	3.5 (1.7)	1.3 (1.2)	293.0	<0.001	<0.001
Social perception and knowledge	6.4 (2.7)	2.5 (1.9)	262.0	<0.001	<0.001
Theory of mind	6.8 (2.4)	2.8 (1.7)	187.5	<0.001	<0.001
Attributional style	4.9 (2.8)	1.6 (1.4)	295.5	<0.001	<0.001
TREF-Facial emotion recognition					
% Of correct recognition	65.7 (10.2)	70.6 (6.4)	699.5	0.011	0.077
Happiness	87.2 (11.5)	91.1 (8.7)	925.0	0.468	3.276
Anger	61.1 (27.4)	68.1 (18.9)	909.5	0.406	2.842
Sadness	69.1 (19.6)	72.1 (19.2)	969.0	0.727	5.089
Fear	78.7 (15.7)	83.7 (13.5)	888.5	0.311	2.177
Disgust	57.7 (14.9)	62.2 (12.2)	933.5	0.522	3.654
Contempt	40.3 (21.9)	46.4 (17.9)	788.5	0.070	0.490
Recognition threshold	53.3 (9.9)	48.3 (6.6)	662.0	0.005	0.035
Happiness	32.3 (11.6)	29.4 (10.0)	886.5	0.291	2.037
Anger	58.6 (25.0)	50.2 (17.9)	800.5	0.086	0.602
Sadness	53.0 (18.9)	48.8 (16.8)	878.5	0.278	1.946
Fear	43.1 (16.0)	36.9 (14.6)	764.0	0.045	0.315
Disgust	58.1 (12.8)	55.0 (11.5)	858.5	0.206	1.442
Contempt	72.4 (17.8)	69.8 (13.6)	888.0	0.313	2.191
PerSo-Social perception and knowledge					
Fluency score	80.4 (36.9)	106.0 (31.7)	595.0	<0.001	0.004
Interpretation (total score)	19.2 (3.2)	20.9 (2.5)	703.0	0.012	0.060
Non-indexed interpretation	9.0 (2.0)	9.9 (1.7)	774.0	0.052	0.260
Indexed interpretation	10.2 (1.4)	11.0 (1.1)	660.5	0.003	0.015
Social knowledge score	4.8 (2.0)	5.6 (1.8)	770.5	0.048	0.240
MASC-theory of mind					
Total score	26.3 (5.4)	31.8 (3.6)	507.5	<0.001	<0.001
Error types					
Excessive ToM	7.2 (2.8)	5.1 (2.5)	688.0	0.008	0.032
Less ToM	7.7 (3.4)	6.1 (3.4)	808.5	0.098	0.392
No ToM	3.7 (2.1)	2.0 (1.7)	683.0	0.007	0.028
AIHQ-S-Attributional style					
Hostility bias	1.9 (0.7)	1.7 (0.6)	864.5	0.230	1.382
Attribution of responsibility score	2.8 (0.7)	2.4 (0.6)	694.0	0.010	0.062
Intentionality score-IS	3.1 (1.0)	2.6 (0.7)	659.5	0.004	0.026
Anger score- AS	2.3 (0.8)	2.1 (0.6)	811.5	0.104	0.626
Blame score- BS	2.8 (0.9)	2.5 (0.7)	771.0	0.051	0.307
Agression bias-AB	1.4 (0.4)	1.6 (0.4)	658.5	0.004	0.023

Results of Mann-Whitney non parametric tests used for groups comparisons (statistical values U, p and adjusted p-values after Bonferonni correction for multiple analysis). Significant effects are highlighted in gray.

DISCUSSION

The main goal of our study was to evaluate the relevance of the "ClaCoS" battery for the assessment of social cognition impairments in adults with ASD without intellectual disability. We further examined the links between subjective complaints and objectively measured impairments on the different components of social cognition. Overall, adults with ASD reported greater subjective complaints than controls in each of the four areas explored by the ACSo. They also showed deficits on all of the neuropsychological tests from the "ClaCoS" battery, which explored the same four main components of

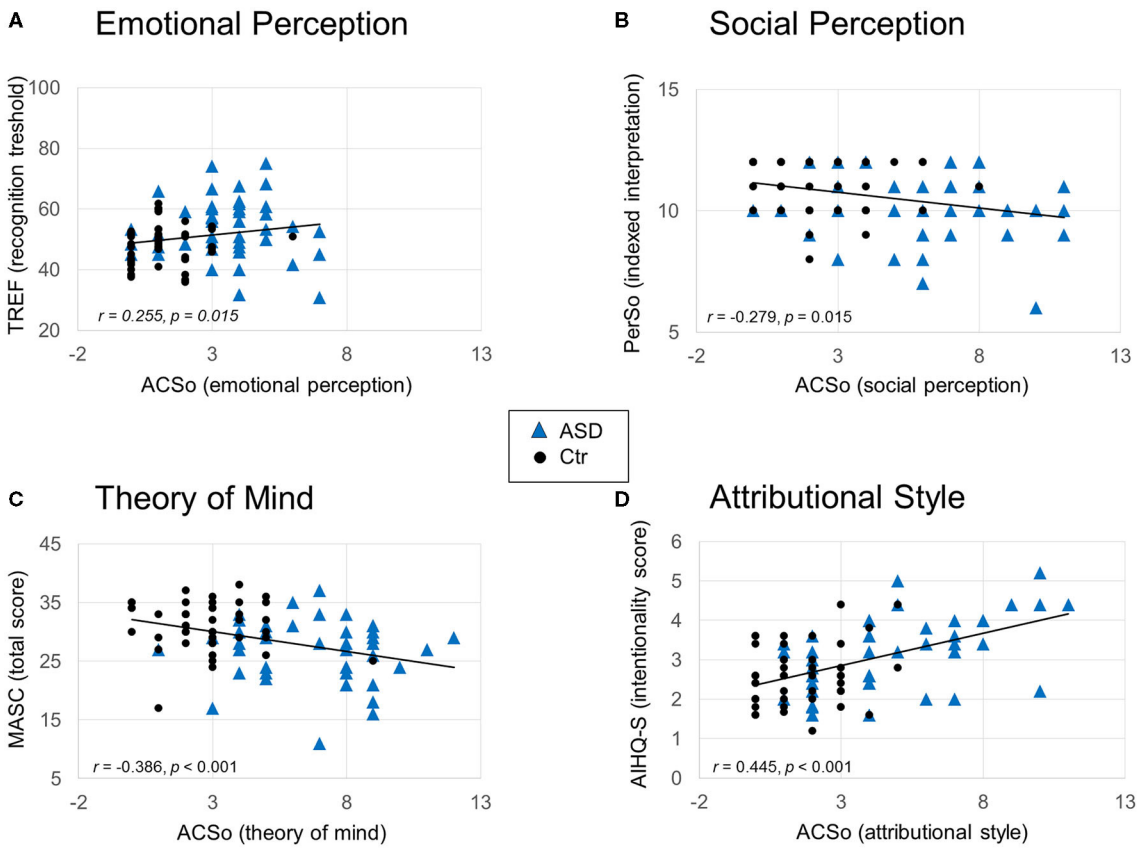

FIGURE 2 | Main correlations between subjective complaints and social cognition assessments for each of the four domains. Results of Spearman correlations are reported (statistical values r and adjusted p after Bonferonni correction for multiple analysis). **(A)** Emotional perception complaint plotted against the recognition threshold of the TREF. **(B)** Social perception and knowledge complaint plotted against the indexed interpretation score of the PerSo. **(C)** Theory of mind complaint plotted against the total score of the Masc. **(D)** Attributional style complaint plotted against the intentionality score of the AIHQ-S. The solid lines represent the linear regressions.

social cognition: emotional perception, social perception and knowledge, theory of mind and attributional style (70, 81). Moreover, each of the four sub-scores of the ACSo were correlated with the performance on the corresponding social cognitive assessment.

Differences Between ASD and Controls on Objective Evaluations

Adults with ASD were impaired in all four domains of social cognition assessed by the "ClaCoS" battery. Deficits in emotional perception and theory of mind are classically reported in ASD, while social perception and attributional style are less frequently explored. In particular, deficits in emotional perception and theory of mind constitute core features of ASD and are crucial clinical signs examined in the process of diagnosing ASD (1). However, classical social cognition tests often fail to show such deficits in adults with ASD without intellectual disability, due to a lack of sensitivity in this specific population [(7, 35, 51, 52); for a meta-analysis, see (15)]. Our results thus confirm that more challenging and ecological tests presenting either subtle expressions (i.e., the TREF) or ecologically valid and dynamic stimuli (i.e., the MASC) are particularly interesting tools in order to assess emotional perception and theory of mind impairments, respectively, in ASD adults without intellectual disability.

Using the TREF, in the ASD group compared to the controls, we observed a higher global recognition threshold and a trend for a lesser overall percentage of correct emotion recognition. Thus, the recognition threshold seems to be a more relevant measure in order to uncover impairments on emotional recognition in this population. Our result is consistent with an extensive amount of researches showing impairments on emotional processing in ASD [(9); for a meta-analysis, see (15)]. Moreover, this was observed as a global effect and was not related to a specific emotion. Taken together our results support the hypothesis of a broad impairment of emotion recognition in individuals with ASD [for a review, see (14)].

Adults with ASD showed lower scores at the PerSo compared to controls, suggesting impaired social perception. More precisely, they reported fewer visual elements from the social scenes (fluency score) and were less accurate in their interpretation of the depicted social situations. The difference

between groups on the number of visual elements reported does not seem to be exclusively linked to slower overall visuospatial or attentional abilities in ASD. Indeed, it remained significant when controlling for such effect of visual attention. It could rather reflect slower overall cognitive processing or more specifically slower verbal elaboration required in this task. It could also reflect a well-described lack of generation of new ideas (87–89). Concerning the interpretation scores, the indexed interpretation was significantly different between the two groups and this difference was observed with a trend for the total interpretation. This suggests that adults with ASD respond similarly as the typical developing controls when asked to freely describe the depicted social situation from pictures. However, they were less facilitated by the indexed question compared to controls, in line with a recent meta-analysis (40). Altogether, our study shows difficulties in the ASD group, in the identification of the main contextual visual elements which allow to understand social situations (i.e., location; main characters and interactions between these characters as well as emotions expressed). Although the term "social perception" is not common in the field of ASD research, eye-tracking studies reveal impaired attention toward social compared to non-social visual stimuli [(38, 39); for meta-analyses, see (40, 41)]. The lack of visual processing, and binding of the salient social and non-social contextual elements are likely to contribute to difficulties encountered by ASD individuals in understanding and thus adjusting to social situations. Nevertheless, the ASD individuals were able to identify social rules which suggests an absence of a general deficit in social knowledge *per se.* Indeed, ASD individuals may learn social rules, although in a somewhat rigid manner. However, they often encounter greater difficulties to conveniently apply these rules in everyday life (90). Hence, the PerSo constitutes an interesting tool to assess social perception and knowledge in ASD. To our knowledge, the PerSo is the only existing standardized tool that examines this component of social cognition, at least in French language.

As expected, we observed an impaired theory of mind (ToM), in line with previous studies showing that the MASC test is sensitive to reveal subtle ToM alterations in adults with ASD, without intellectual disability (55–60). Interestingly, our study shows two main types of errors in the ASD group compared to controls: greater "Excessive ToM" and "No ToM." Previous studies showed that ASD individuals made these types of errors more frequently than controls ("Excessive ToM," "Less-ToM," and "No ToM") (56–58). Moreover, these studies reported inconsistent findings, with either prominent over-mentalizing (excess) or under-mentalizing (less) errors, while concrete cognition (No) was systematically less frequent, in accordance with our study. The absence of difference between groups on the "Less ToM" errors in the present study and more generally the discrepancy across studies may depend upon sociodemographic specificities (e.g., education level, age, gender…). Our study supports the hypothesis of two different types of ToM impairments in ASD, with either an overmentalizing or an undermentalizing tendency (58). The concept of hyper- and hypo-mentalization has been introduced in schizophrenia research (91), some authors suggesting the existence of a continuum from hypo- to hyper- ToM, across different psychiatric illnesses (92). Further studies including patients with other psychiatric disorders such as schizophrenia are needed in order to test this hypothesis. This approach fits with a transnosographic view of common symptomatic profiles between patients with ASD and schizophrenia.

To date, there are very few studies focusing on attribution biases in ASD. This component of social cognition is rarely explored in clinical practice. The studies mainly focused on causal attribution (internal vs. external) and showed no differences on attributional style between ASD adolescents and adults compared to neurotypical individuals (47–49, 75). However, the present study specifically considers hostility and aggression biases as well as the different sub-dimensions leading to attribution of responsibility. Our results revealed higher attribution of responsibility (specific to the intentionality of other's actions) and lower aggression bias in the ASD group compared to controls, while no difference was observed on the hostility bias. Thus, adults with ASD without intellectual disability tend to consider other's actions as being more surely intentional in ambiguous social situations but mostly do not show paranoid ideas. They don't perceive other's actions in these ambiguous situations as particularly hostile toward themselves, do not experience more anger and do not blame others more than the controls do. They further tend to respond in a passive way, as illustrated by the lower aggression bias compared to controls. These results are consistent with the clinical observations of rigid thought and tendency to systemize in ASD individuals, which may explain the higher attribution of intentionality score (93). The AIHQ-S thus seems an interesting tool to help clinicians to separate ASD from other psychiatric disorders, particularly schizophrenia. Indeed, these two conditions can be difficult to distinguish in adult patients, with a risk of misdiagnosis (94). Paranoid ideations in ASD and in schizophrenia are a consequence of different mechanisms. Persecutory delusions are commonly seen in people with schizophrenia. However, paranoïd ideations observed in adults with ASD are generally linked to the negative social experiences (e.g., being teased, bullied, or rejected), or to the specific cognitive style of this population (rigid thought, focusing on details, alteration in ToM or in social perception) (47, 48). This can lead to interpretation biases, generally associated with behavioral reactions of avoidance and social isolation rather than with overtly aggressive behaviors (75). The "ClaCoS" should however be used with caution for purposes of differential diagnosis, in light of the frequent comorbid psychiatric conditions associated with ASD [e.g., ADHD, bipolar disorder, anxiety disorder…; for a review, see (95)]. Future studies including data of other population of patients are required in this perspective.

Links Between Subjective and Objective Evaluations

An interesting feature of the "ClaCoS" is the assessment of patients' subjective complaints in daily life in the field of

social cognition. To our knowledge, the ACSo is the first transnosographic scale examining this question. Our results suggest that adults with ASD without intellectual disability are able to express complaints from a self-report questionnaire. This short scale seems to constitute an interesting media which may help ASD adults to express the challenges they encounter in social situations, especially for those having difficulties in verbal expression or initiation. Interestingly, there was an association between subjective complaints and objective measures obtained from the neuropsychological assessment in all four domains of social cognition. These results tend to support the relevance of each neuropsychological test of the "ClaCoS" battery to assess the specific domain of social cognition which impacts the participant's everyday social functioning. They further suggest that ASD adults are aware of their social difficulties in different areas, in line with their good insight and metacognitive abilities (76, 96). In the validation study of the ACSo, Graux et al. (82) did not observe any correlation between objective and subjective assessments of social cognition components (emotional perception and theory of mind), suggesting an altered "social cognitive insight" in adults with psychiatric disorders. However, in a transnosographic perspective, statistical analyses were performed in patients with different diagnoses, including a majority of participants with schizophrenia and a limited number of participants with ASD.

Control Analyses and Limitations

It seems unlikely that our effects were mediated by socio-demographic factors, as the groups were matched according to age, gender, and educational level. Moreover, the ASD group had good intellectual and very efficient language abilities, as revealed by their IQ measures, suggesting that the deficits observed in the evaluation of social cognition are unlikely to be linked to poorer intellectual or verbal abilities. Note however that we could not fully control the impact of verbal and performance IQ, as these were not recorded in control participants. Although the ASD participants were slower on both visuo-spatial and attentional tests, they correctly processed the visual information. They were sufficiently engaged in the task but needed more processing time, consistently with previous observations (97, 98). Furthermore, all group differences remained significant when controlling for visual attention. Thus, the lower performances on social cognition tests in the ASD group cannot be exclusively explained by slower visuo-spatial attention and exploration abilities.

Our results should nevertheless be interpreted with several limitations. Although our population was larger than most studies considering the assessment of social cognition in ASD, it remains of a moderate sample size. Future studies including larger groups are needed in order to replicate these findings. In particular, the correlations reported here were of medium effect size (Cohen criterion) and thus have to be taken with caution. Moreover, the ASD participants had average or over-average Intellectual Quotients. Their verbal IQ was in average higher than the performance IQ. Future studies are required to evaluate whether these results can be generalized to ASD individuals with lower verbal or general intellectual abilities. More generally, the links between neurocognitive and social cognitive performance remains to be explored. The addition of other validated tools for social cognition evaluation could also be interesting as external validation of the tests constituting the "ClaCoS" battery. Furthermore, the use of clinical tools allowing the assessment of hyper- and hypo-mentalization in ASD could allow the identification of different clinical profiles, in line with the transnosographic view of psychiatric illnesses. Further studies including larger sample size and different clinical profiles are needed in order to confirm and extend the present results.

CONCLUSION

The "ClaCoS" is a functional evaluation battery of the four main dimensions of social cognition which may be altered in different psychiatric conditions, consistent with a transnosographic perspective. To our knowledge, "ClaCoS" is the only existing social cognitive battery including a subjective evaluation of the individual's impairment, as well as an assessment of attributional style. As a whole, the current study suggests that performance on the "ClaCoS" battery accurately reflects everyday life difficulties of adults with ASD. It seems to be a well-suited tool to help uncover alterations in specific domains of social cognition in this population. This allows the selection of the most appropriate therapeutic program according to each patient's functional profile: from the most basic perceptual processes to higher level metacognition abilities. Our study shows that ASD adults without intellectual disability have a good self-awareness of their impairments in different domains of social cognition which can lead to the specific challenges they encounter with social functioning in everyday life situation. Self-assessment helps to involve and motivate patients to participate in cognitive remediation therapy (99) and the effectiveness of these therapies relies in part on the patients' awareness of their disorders. Thus, our results are a good prognostic indicator for the engagement of ASD individuals in cognitive remediation programs. The "ClaCoS" battery further provides interesting new elements which may be contributive in a diagnostic procedure, alongside the classical tools and clinical evaluations, in a dimensional and lifelong evolving perspective of ASD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CPP Lyon Sud Est IV, No. 15/041; ANSM,

No. 2015-A00580-49. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SM-K, AT, LB, CD-A, EP, ZP, IC-M, BG, IA, JG, and EH-D made substantial contributions to conception and design. SM-K, AT, LB, CD-A, EP, ZP, IA, JG, and EH-D made substantial contributions to acquisition of data. SM-K, AT, SR, JG, and EH-D made substantial contributions to analysis and interpretation of data. SM-K, AT, LB, CD-A, EP, ZP, SR, IA, JG, EH-D, IC-M, BG, M-OK, NF, and FB-B participated in drafting the article. All authors contributed to, have approved the final manuscript and agree to be accountable for the content of the work.

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edn. Washington, DC: American Psychiatric Association (2013).
2. Frith U, Frith C. The social brain: allowing humans to boldly go where no other species has been. *Philos Trans R Soc B Biol Sci.* (2010) 365:165–76. doi: 10.1098/rstb.2009.0160
3. Adolphs R. The neurobiology of social cognition. *Curr Opin Neurobiol.* (2001) 11:231–9. doi: 10.1016/S0959-4388(00)00202-6
4. Hernandez N, Metzger A, Magné R, Bonnet-Brilhault F, Roux S, Barthelemy C, et al. Exploration of core features of a human face by healthy and autistic adults analyzed by visual scanning. *Neuropsychologia.* (2009) 47:1004–12. doi: 10.1016/j.neuropsychologia.2008.10.023
5. Pelphrey KA, Sasson NJ, Reznick JS, Paul G, Goldman BD, Piven J. Visual scanning of faces in autism. *J Autism Dev Disord.* (2002) 32:249–61. doi: 10.1023/A:1016374617369
6. Baron-Cohen S. *Mindblindness: An Essay on Autism and Theory of Mind*. Cambridge, MA: MIT Press (1995). doi: 10.7551/mitpress/4635.001.0001
7. Mathersul D, McDonald S, Rushby JA. Understanding advanced theory of mind and empathy in high-functioning adults with autism spectrum disorder. *J Clin Exp Neuropsychol.* (2013) 35:655–68. doi: 10.1080/13803395.2013.809700
8. Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a "theory of mind"? *Cognition.* (1985) 21:37–46. doi: 10.1016/0010-0277(85)90022-8
9. Hobson RP. The autistic child's appraisal of expressions of emotion: a further study. *J Child Psychol Psychiatry.* (1986) 27:671–80. doi: 10.1111/j.1469-7610.1986.tb00191.x
10. Clark TF, Winkielman P, McIntosh DN. Autism and the extraction of emotion from briefly presented facial expressions: stumbling at the first step of empathy. *Emotion.* (2008) 8:803–9. doi: 10.1037/a0014124
11. Humphreys K, Minshew N, Leonard GL, Behrmann M. A fine-grained analysis of facial expression processing in high-functioning adults with autism. *Neuropsychologia.* (2007) 45:685–95. doi: 10.1016/j.neuropsychologia.2006.08.003
12. Loth E, Garrido L, Ahmad J, Watson E, Duff A, Duchaine B. Facial expression recognition as a candidate marker for autism spectrum disorder: how frequent and severe are deficits? *Mol Autism.* (2018) 9:7. doi: 10.1186/s13229-018-0187-7
13. Rump KM, Giovannelli JL, Minshew NJ, Strauss MS. The development of emotion recognition in individuals with autism. *Child Dev.* (2009) 80:1434–47. doi: 10.1111/j.1467-8624.2009.01343.x
14. Harms MB, Martin A, Wallace GL. Facial emotion recognition in autism spectrum disorders: a review of behavioral and neuroimaging studies. *Neuropsychol Rev.* (2010) 20:290–322. doi: 10.1007/s11065-010-9138-6
15. Uljarevic M, Hamilton A. Recognition of emotions in autism: a formal meta-analysis. *J Autism Dev Disord.* (2013) 43:1517–26. doi: 10.1007/s10803-012-1695-5
16. Castelli F. Understanding emotions from standardized facial expressions in autism and normal development. *Autism Int J Res Pract.* (2005) 9:428–49. doi: 10.1177/1362361305056082
17. Grossman JB, Klin A, Carter AS, Volkmar FR. Verbal bias in recognition of facial emotions in children with Asperger syndrome. *J Child Psychol Psychiatry.* (2000) 41:369–79. doi: 10.1111/1469-7610.00621
18. Jones CRG, Pickles A, Falcaro M, Marsden AJS, Happé F, Scott SK, et al. A multimodal approach to emotion recognition ability in autism spectrum disorders. *J Child Psychol Psychiatry.* (2011) 52:275–85. doi: 10.1111/j.1469-7610.2010.02328.x
19. Loveland KA, Tunali–Kotoski B, Chen YR, Ortegon J, Pearson DA, Brelsford KA, et al. Emotion recognition in autism: verbal and nonverbal information. *Dev Psychopathol.* (1997) 9:579–93. doi: 10.1017/S0954579497001351
20. Ozonoff S, Pennington BF, Rogers SJ. Are there emotion perception deficits in young Autistic Children? *J Child Psychol Psychiatry.* (1990) 31:343–61. doi: 10.1111/j.1469-7610.1990.tb01574.x
21. Tracy JL, Robins RW, Schriber RA, Solomon M. Is emotion recognition impaired in individuals with Autism Spectrum disorders? *J Autism Dev Disord.* (2011) 41:102–9. doi: 10.1007/s10803-010-1030-y
22. Doi H, Fujisawa TX, Kanai C, Ohta H, Yokoi H, Iwanami A, et al. Recognition of facial expressions and prosodic cues with graded emotional intensities in adults with asperger syndrome. *J Autism Dev Disord.* (2013) 43:2099–113. doi: 10.1007/s10803-013-1760-8
23. Kennedy DP, Adolphs R. Perception of emotions from facial expressions in high-functioning adults with autism. *Neuropsychologia.* (2012) 50:3313–9. doi: 10.1016/j.neuropsychologia.2012.09.038
24. Law Smith MJ, Montagne B, Perrett DI, Gill M, Gallagher L. Detecting subtle facial emotion recognition deficits in high-functioning Autism using dynamic stimuli of varying intensities. *Neuropsychologia.* (2010) 48:2777–81. doi: 10.1016/j.neuropsychologia.2010.03.008
25. Song Y, Hakoda Y. Selective impairment of basic emotion recognition in people with Autism: discrimination thresholds for recognition of facial expressions of varying intensities. *J Autism Dev Disord.* (2018) 48:1886–94. doi: 10.1007/s10803-017-3428-2
26. Wingenbach TSH, Ashwin C, Brosnan M. Diminished sensitivity and specificity at recognising facial emotional expressions of varying intensity underlie emotion-specific recognition deficits in autism spectrum disorders. *Res Autism Spectr Disord.* (2017) 34:52–61. doi: 10.1016/j.rasd.2016.11.003
27. Wong N, Beidel DC, Sarver DE, Sims V. Facial emotion recognition in children with high functioning Autism and children with social phobia. *Child Psychiatry Hum Dev.* (2012) 43:775–94. doi: 10.1007/s10578-012-0296-z
28. Chung YS, Barch D, Strube M. A meta-analysis of mentalizing impairments in adults with schizophrenia and autism spectrum disorder. *Schizophr Bull.* (2014) 40:602–16. doi: 10.1093/schbul/sbt048

29. Tager-Flusberg H. Evaluating the theory-of-mind hypothesis of Autism. *Curr Dir Psychol Sci.* (2007) 16:311–5. doi: 10.1111/j.1467-8721.2007.00527.x
30. Peterson CC, Garnett M, Kelly A, Attwood T. Everyday social and conversation applications of theory-of-mind understanding by children with autism-spectrum disorders or typical development. *Eur Child Adolesc Psychiatry.* (2009) 18:105–15. doi: 10.1007/s00787-008-0711-y
31. Dahlgren SO, Trillingsgaard A. Theory of mind in non-retarded children with Autism and Asperger's Syndrome. a research note. *J Child Psychol Psychiatry.* (1996) 37:759–63. doi: 10.1111/j.1469-7610.1996.tb01469.x
32. Ozonoff S, Pennington BF, Rogers SJ. Executive function deficits in high-functioning Autistic Individuals : relationship to theory of mind. *J Child Psychol Psychiatry.* (1991) 32:1081–105. doi: 10.1111/j.1469-7610.1991.tb00351.x
33. Murray K, Johnston K, Cunnane H, Kerr C, Spain D, Gillan N, et al. A new test of advanced theory of mind: The "Strange Stories Film Task" captures social processing differences in adults with autism spectrum disorders. *Autism Res.* (2017) 10:1120–32. doi: 10.1002/aur.1744
34. Livingston LA, Carr B, Shah P. Recent advances and new directions in measuring theory of mind in Autistic adults. *J Autism Dev Disord.* (2019) 49:1738–44. doi: 10.1007/s10803-018-3823-3
35. Livingston LA, Happé F. Conceptualising compensation in neurodevelopmental disorders: reflections from autism spectrum disorder. *Neurosci Biobehav Rev.* (2017) 80:729–42. doi: 10.1016/j.neubiorev.2017.06.005
36. Frith U, Frith C. Development and neurophysiology of mentalizing. *Philos Trans R Soc B Biol Sci.* (2003) 258:459–73. doi: 10.1098/rstb.2002.1218
37. Senju A. Spontaneous theory of mind and its absence in autism spectrum disorders. *Neurosci Rev J Bringing Neurobiol Neurol Psychiatry.* (2012) 18:108–13. doi: 10.1177/1073858410397208
38. Klin A, Jones W, Schultz R, Volkmar F, Cohen D. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Arch Gen Psychiatry.* (2002) 59:809–16. doi: 10.1001/archpsyc.59.9.809
39. Riby D, Hancock PJB. Looking at movies and cartoons: eye-tracking evidence from Williams syndrome and autism. *J Intellect Disabil Res JIDR.* (2009) 53:169–81. doi: 10.1111/j.1365-2788.2008.01142.x
40. Chita-Tegmark M. Social attention in ASD: a review and meta-analysis of eye-tracking studies. *Res Dev Disabil.* (2016) 48:79–93. doi: 10.1016/j.ridd.2015.10.011
41. Frazier TW, Strauss M, Klingemier EW, Zetzer EE, Hardan AY, Eng C, et al. A meta-analysis of gaze differences to social and nonsocial information between individuals with and without Autism. *J Am Acad Child Adolesc Psychiatry.* (2017) 56:546–55. doi: 10.1016/j.jaac.2017.05.005
42. Da Fonseca D, Santos A, Bastard-Rosset D, Rondan C, Poinso F, Deruelle C. Can children with autistic spectrum disorders extract emotions out of contextual cues? *Res Autism Spectr Disord.* (2009) 3:50–6. doi: 10.1016/j.rasd.2008.04.001
43. Sasson NJ, Pinkham AE, Weittenhiller LP, Faso DJ, Simpson C. Context effects on facial affect recognition in schizophrenia and autism: Behavioral and eye-tracking evidence. *Schizophr Bull.* (2016) 42:675–83. doi: 10.1093/schbul/sbv176
44. Chevallier C, Kohls G, Troiani V, Brodkin ES, Schultz RT. The social motivation theory of Autism introduction: social motivation and social cognition, two competing. *Trends Cogn Sci.* (2012) 16:231–9. doi: 10.1016/j.tics.2012.02.007
45. Rondan C, Deruelle C. Global and configural visual processing in adults with autism and Asperger syndrome. *Res Dev Disabil.* (2007) 28:197–206. doi: 10.1016/j.ridd.2006.02.007
46. Happé F, Frith U. The neuropsychology of autism. *Brain J Neurol.* (1996) 119:1377–400. doi: 10.1093/brain/119.4.1377
47. Blackshaw AJ, Kinderman P, Hare DJ, Hatton C. Theory of mind, causal attribution and paranoia in Asperger syndrome. *Autism.* (2001) 5:147–63. doi: 10.1177/1362361301005002005
48. Craig JS, Hatton C, Craig FB, Bentall RP. Persecutory beliefs, attributions and theory of mind: comparison of patients with paranoid delusions, Asperger's syndrome and healthy controls. *Schizophr Res.* (2004) 69:29–33. doi: 10.1016/S0920-9964(03)00154-3
49. Kestemont J, Vandekerckhove M, Bulnes LC, Matthys F, Van Overwalle F. Causal attribution in individuals with subclinical and clinical autism spectrum disorder: an fMRI study. *Soc Neurosci.* (2016) 11:264–76. doi: 10.1080/17470919.2015.1074104
50. Spezio ML, Adolphs R, Hurley RSE, Piven J. Abnormal use of facial information in high-functioning autism. *J Autism Dev Disord.* (2007) 37:929–39. doi: 10.1007/s10803-006-0232-9
51. Bowler DM. "Theory of Mind" in Asperger's syndrome. *J Child Psychol Psychiatry.* (1992) 33:877–93. doi: 10.1111/j.1469-7610.1992.tb01962.x
52. White S, Hill E, Happé F, Frith U. Revisiting the strange stories: revealing mentalizing impairments in autism. *Child Dev.* (2009) 80:1097–117. doi: 10.1111/j.1467-8624.2009.01319.x
53. Frith U, Happé F. Theory of mind and self-consciousness: what is it like to be Autistic? *Mind Lang.* (1999) 14:82–9. doi: 10.1111/1468-0017.00100
54. Eddy CM. What do you have in mind? Measures to assess mental state reasoning in neuropsychiatric populations. *Front Psychiatry.* (2019) 10:425. doi: 10.3389/fpsyt.2019.00425
55. Dziobek I, Fleck S, Kalbe E, Rogers K, Hassenstab J, Brand M, et al. Introducing MASC: a movie for the assessment of social cognition. *J Autism Dev Disord.* (2006) 36:623–36. doi: 10.1007/s10803-006-0107-0
56. Isaksson J, Van't Westeinde A, Cauvet É, Kuja-Halkola R, Lundin K, Neufeld J, et al. Social cognition in autism and other neurodevelopmental disorders: a co-twin control study. *J Autism Dev Disord.* (2019) 49:2838–48. doi: 10.1007/s10803-019-04001-4
57. Lahera G, Boada L, Pousa E, Mirapeix I, Morón-Nozaleda G, Marinas L, et al. Movie for the assessment of social cognition (MASC): Spanish validation. *J Autism Dev Disord.* (2014) 44:1886–96. doi: 10.1007/s10803-014-2061-6
58. Martinez G, Alexandre C, Mam-Lam-Fook C, Bendjemaa N, Gaillard R, Garel P, et al. Phenotypic continuum between autism and schizophrenia: evidence from the Movie for the Assessment of Social Cognition (MASC). *Schizophr Res.* (2017) 185:161–6. doi: 10.1016/j.schres.2017.01.012
59. Müller N, Baumeister S, Dziobek I, Banaschewski T, Poustka L. Validation of the movie for the assessment of social cognition in adolescents with ASD: fixation duration and pupil dilation as predictors of performance. *J Autism Dev Disord.* (2016) 46:2831–44. doi: 10.1007/s10803-016-2828-z
60. Schaller U, Rauh R. What difference does it make? Implicit, explicit and complex social cognition in autism spectrum disorders. *J Autism Dev Disord.* (2017) 47:961–79. doi: 10.1007/s10803-016-3008-x
61. Holdnack J, Goldstein G, Drozdick L. Social perception and WAIS-IV performance in adolescents and adults diagnosed with asperger's syndrome and Autism. *Assessment.* (2011) 18:192–200. doi: 10.1177/1073191110394771
62. Pearson. *Advanced Clinical Soultions for WAIS-IV and WMS-IV*. San Antonio, TX: Pearson (2009).
63. Combs DR, Penn DL, Wicher M, Waldheter E. The Ambiguous Intentions Hostility Questionnaire (AIHQ): a new measure for evaluating hostile social-cognitive biases in paranoia. *Cognit Neuropsychiatry.* (2007) 12:128–43. doi: 10.1080/13546800600787854
64. Green MF. Impact of cognitive and social cognitive impairment on functional outcomes in patients with schizophrenia. *J Clin Psychiatry.* (2016) 77:8–11. doi: 10.4088/JCP.14074su1c.02
65. Treasure J, Schmidt U. The cognitive-interpersonal maintenance model of anorexia nervosa revisited: a summary of the evidence for cognitive, socio-emotional and interpersonal predisposing and perpetuating factors. *J Eat Disord.* (2013) 1:13. doi: 10.1186/2050-2974-1-13
66. Uekermann J, Kraemer M, Abdel-Hamid M, Schimmelmann BG, Hebebrand J, Daum I, et al. Social cognition in attention-deficit hyperactivity disorder (ADHD). *Neurosci Biobehav Rev.* (2010) 34:734–43. doi: 10.1016/j.neubiorev.2009.10.009
67. Vlad M, Raucher-Chéné D, Henry A, Kaladjian A. Functional outcome and social cognition in bipolar disorder: is there a connection? *Eur Psychiatry J Assoc Eur Psychiatry.* (2018) 52:116–25. doi: 10.1016/j.eurpsy.2018.05.002
68. Hoertnagl CM, Hofer A. Social cognition in serious mental illness. *Curr Opin Psychiatry.* (2014) 27:197–202. doi: 10.1097/YCO.0000000000000055
69. Porcelli S, Van Der Wee N, van der Werff S, Aghajani M, Glennon JC, van Heukelum S, et al. Social brain, social dysfunction and social withdrawal. *Neurosci Biobehav Rev.* (2019) 97:10–33. doi: 10.1016/j.neubiorev.2018.09.012
70. Pinkham AE. Social cognition in schizophrenia. *J Clin Psychiatry.* (2014) 75:14–9. doi: 10.4088/JCP.13065su1.04

71. Green MF, Olivier B, Crawley JN, Penn DL, Silverstein S. Social Cognition in Schizophrenia: recommendations from the measurement and treatment research to improve cognition in Schizophrenia new approaches conference. *Schizophr Bull.* (2005) 31:882–7. doi: 10.1093/schbul/sbi049
72. Green MF, Leitman DI. Social Cognition in Schizophrenia. *Schizophr Bull.* (2008) 34:670–2. doi: 10.1093/schbul/sbn045
73. Merceron K, Cady F, Vilà E, Prouteau A. Évaluation de la cognition sociale dans la schizophrénie : intérêts et limites. In: *Neuropsychologie clinique de la schizophrénie*. Paris: Dunod (2011). p. 161–99. doi: 10.3917/dunod.prout.2011.01.0161
74. Merceron K, Prouteau A. Évaluation de la cognition sociale en langue française chez l'adulte: outils disponibles et recommandations de bonne pratique clinique. *LÉvolution Psychiatr.* (2013) 78:53–70. doi: 10.1016/j.evopsy.2013.01.002
75. Spain D, Sin J, Freeman D. Conceptualising paranoia in ASD: a systematic review and development of a theoretical framework. *Res Autism Spectr Disord.* (2016) 25:97–111. doi: 10.1016/j.rasd.2016.02.002
76. Schriber RA, Robins RW, Solomon M. Personality and self-insight in individuals with autism spectrum disorder. *J Pers Soc Psychol.* (2014) 106:112–30. doi: 10.1037/a0034950
77. Lord C, Rutter M, DiLavore P, Risi S, Gotham K, Bishop SL. *ADOS-2: échelle d'observation pour le diagnostic de l'autisme – Seconde édition*. (B. Rogé et al. Trad. 2015) Hogrefe (2012).
78. Rutter M, Lecouteur A, Lord C. *ADI-R: Entretien semi-structuré pour le diagnostic de l'autisme*. B. Rogé et al. Trad.2011. Hogrefe (2003).
79. Sheehan DV, Lecrubier Y, et al. *Mini-International Neuropsychiatric Interview French version 6.0.0.* (Y. Lecrubier Trad.) Sheehan DV (2009).
80. Wechsler D. *Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV)*. San Antonio, TX: NCS Pearson (2008).
81. Peyroux E, Prost Z, Danset-Alexandre C, Brenugat-Herne L, Carteau-Martin I, Gaudelus B, et al. From "under" to "over" social cognition in schizophrenia: is there distinct profiles of impairments according to negative and positive symptoms? *Schizophr Res Cogn.* (2019) 15:21–9. doi: 10.1016/j.scog.2018.10.001
82. Graux J, Thillay A, Morlec V, Sarron PY, Roux S, Gaudelus B, et al. A transnosographic self-assessment of social cognitive impairments (ACSO): first data. *Front Psychiatry.* (2019) 10:847. doi: 10.3389/fpsyt.2019.00847
83. Gaudelus B, Virgile J, Peyroux E, Leleu A, Baudouin JY, Franck N. Mesure du déficit de reconnaissance des émotions faciales dans la schizophrénie. Étude préliminaire du test de reconnaissance des émotions faciales (TREF). *Encephale.* (2015) 41:251–9. doi: 10.1016/j.encep.2014.08.013
84. Baron-Cohen S, Wheelwright S. The empathy quotient: an investigation of adults with asperger syndrome or high functioning autism, and normal sex differences. *J Autism Dev Disord.* (2004) 34:163–75. doi: 10.1023/B:JADD.0000022607.19833.00
85. Rey A. *L'examen clinique en psychologie.* Paris: Presses universitaires de France (1964).
86. Mesulam MM. *Principles of behavioral neurology*. Philadelphie, Etats-Unis d'Amérique: F. A. Davis (1985).
87. Carmo JC, Duarte E, Pinho S, Marques JF, Filipe CN. Verbal fluency as a function of time in autism spectrum disorder: an impairment of initiation processes? *J Clin Exp Neuropsychol.* (2015) 37:710–21. doi: 10.1080/13803395.2015.1062082
88. Spek A, Schatorjé T, Scholte E, van Berckelaer-Onnes I. Verbal fluency in adults with high functioning autism or Asperger syndrome. *Neuropsychologia.* (2009) 47:652–6. doi: 10.1016/j.neuropsychologia.2008.11.015
89. Turner MA. Generating novel ideas: fluency performance in high-functioning and learning disabled individuals with Autism. *J Child Psychol Psychiatry.* (1999) 40:189–201. doi: 10.1111/1469-7610.00432
90. Kasari C, Patterson S. Interventions addressing social impairment in autism. *Curr Psychiatry Rep.* (2012) 14:713–25. doi: 10.1007/s11920-012-0317-4
91. Frith CD. Schizophrenia and theory of mind. *Psychol Med.* (2004) 34:385–9. doi: 10.1017/S0033291703001326
92. Abu-Akel A. Impaired theory of mind in schizophrenia. *Pragmat Cogn.* (1999) 7:247–82. doi: 10.1075/pc.7.2.02abu
93. Baron-Cohen S, Lombardo MV. Autism and talent: the cognitive and neural basis of systemizing. *Dialogues Clin Neurosci.* (2017) 19:345–53. doi: 10.31887/DCNS.2017.19.4/sbaroncohen
94. Takara K, Kondo T, Kuba T. How and why is autism spectrum disorder misdiagnosed in adult patients? From diagnostic problem to management for adjustment. *Ment Health Fam Med.* (2015) 11:73–88. doi: 10.25149/1756-8358.1102011
95. Hossain MM, Khan N, Sultana A, Ma P, McKyer ELJ, Ahmed HU, et al. Prevalence of comorbid psychiatric disorders among people with autism spectrum disorder: an umbrella review of systematic reviews and meta-analyses. *Psychiatry Res.* (2020) 287:112922. doi: 10.1016/j.psychres.2020.112922
96. Huang AX, Hughes TL, Sutton LR, Lawrence M, Chen X, Ji Z, et al. Understanding the self in individuals with autism spectrum disorders (ASD): a review of literature. *Front Psychol.* (2017) 8:1422. doi: 10.3389/fpsyg.2017.01422
97. Lazar M, Miles LM, Babb JS, Donaldson JB. Axonal deficits in young adults with High Functioning Autism and their impact on processing speed. *NeuroImage Clin.* (2014) 4:417–25. doi: 10.1016/j.nicl.2014.01.014
98. Oliveras-Rentas RE, Kenworthy L, Roberson RB, Martin A, Wallace GL. WISC-IV profile in high-functioning autism spectrum disorders: impaired processing speed is associated with increased autism communication symptoms and decreased adaptive communication abilities. *J Autism Dev Disord.* (2012) 42:655–64. doi: 10.1007/s10803-011-1289-7
99. Vianin P. *La Remédiation Cognitive Dans la Schizophrénie*. Mardaga (2013).

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