NEUROBIOLOGY AND COGNITION ACROSS THE AUTISM-PSYCHOSIS SPECTRUM

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NEUROBIOLOGY AND COGNITION ACROSS THE AUTISM-PSYCHOSIS SPECTRUM

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EDITORIAL
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Editorial: Neurobiology and Cognition Across the Autism-Psychosis Spectrum

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Editorial on the Research Topic

Neurobiology and Cognition Across the Autism-Psychosis Spectrum

Although Autism Spectrum Conditions (ASC) and Schizophrenia Spectrum Conditions (SSC) are recognized as distinct diagnostic categories with independent features, they share a history of clinical entanglement stemming from overlapping symptomatology, particularly in the area of social behavior (1). Examination of cognition and the neurobiology of ASC and SSC, both in the conditions themselves and within their subclinical manifestations, offers potential for illuminating the shared and unique mechanisms underlying their social characteristics. In recent years, both direct comparisons of ASC and SSC and continuous explorations of the autism-psychosis spectrum have begun to show promise for producing more precise segmentation and greater clinical utility than traditional comparisons to non-clinical controls. Such studies ultimately may help to inform etiological understanding, improve screening and diagnosis, and provide more targeted support.

The goal of this Frontiers Research Topic is to showcase innovative new work examining cognitive and neurobiological features of the autism-psychosis spectrum. Consistent with the primary focus of research activity in this area, included articles can be organized under two primary subsections: Cognition and Neurobiology.

Collectively, the articles on cognition suggest that both ASC and SSC are often (but not always) characterized by neuro- and social cognitive differences compared to non-affected controls that relate in both direct and indirect ways to the broader functional and social disabilities associated with the conditions. For instance, Sijtsma et al. demonstrate that adolescents with more autistic-like experiences are less likely to be nominated as friends by their peers despite no relation found between autistic-like experiences and social cognitive performance or self-reported rates of friendships. This suggests that traditional social cognitive measures may not always capture the social differences associated with subclinical autistic characteristics affecting peer relationships. Relatedly, Larson et al. found that autistic people who have experienced psychosis had higher rates of schizotypy and emotional difficulties than both neurotypical controls and autistic people with no psychosis history despite little to no difference between the groups on measures of perspective taking. Their findings also highlight a previously under-recognized clinical characteristic associated with schizotypal traits: high affective lability, which refers to elevated shifting between different emotional states. Likewise, the work by van der Linden et al. also suggests that the full impact of psychotic experiences (PE) among autistic individuals are not well-understood. Their paper indicates that autistic people do not differ from controls in lifetime PE but do report more frequent momentary PE and greater distress associated with their PE. They conclude that stress may serve as an important risk factor for PE among autistic individuals. Meanwhile, the papers by

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Maat et al. and Abu-Akel et al. demonstrate that the presence of cross-diagnostic symptoms along the autism-psychosis spectrum may produce novel cognitive effects in autistic people not seen in autism alone. In Maat et al., response time latency to social and non-social stimuli was increased among autistic adolescents who present with features of psychosis. Specifically, those with attenuated psychosis syndrome, a condition defined by subclinical positive symptoms associated with risk of subsequent psychosis, did not differ from controls on measures of pattern, face, or emotion recognition, but exhibited slower response times to stimuli. Similarly, Abu-Akel et al. found that autistic people with co-occurring schizotypal personality disorder (SPD) and higher positive psychotic symptoms exhibited more sustained (but not inhibitory) attention relative to individuals with autism or SPD alone. Such findings suggest that autistic and positive symptoms may diametrically influence sustained attention and, more broadly, highlight the need for better understanding the relationship between autism and SPD and the effects of dual diagnosis.

The paper by Deste et al. also reports combinatory effects, but unlike the Larson et al. and Maat et al. papers that examined autistic people with features of psychosis, their study focuses on autistic symptoms among patients with schizophrenia and their association with relationship outcomes. In line with a recent large-scale study in psychotic patients and their siblings (2), they find that higher autism symptoms constitute a significant predictor of poor social relationships in schizophrenia, even after controlling for other relevant demographic and clinical variables. Autism and schizophrenia, however, are not only characterized by social difficulties but also multisensory processing difficulties, and the paper by Noel et al. offers a direct comparison of visual-tactile spatial multisensory processing in the two conditions. They find that both groups do not differ from non-affected controls on a cross-modal congruency, but autistic adults exhibit a smaller and more restricted peri-personal space (i.e., the space immediately around the body) than both controls and adults with schizophrenia. Additionally, they find an association between smaller peri-personal space and social symptoms, suggesting a link between some aspects of multisensory processing and social-emotional functioning. Next, Kuo and Eack provide the first systematic review and meta-analytic comparison of non-social cognitive abilities in autism and schizophrenia. In contrast to studies of social cognition that do not show many performance differences between the groups (3–5), their comparison revealed superior performance in autism on working memory, visuospatial memory and learning, language, and comparable performance on processing speed, attention, and verbal comprehension. These distinguishable cognitive profiles extended from adolescence to middle adulthood and collectively indicate important neurocognitive differences that may serve as distinguishing mechanisms of their overlapping reductions in social cognitive performance.

As many of these studies highlight, clinical differentiation across the autism-psychosis spectrum can be difficult among those presenting with co-occurring mental health conditions and shared social characteristics. One paper in the collection (Demetriou et al.) examines the utility of using machine learning to differentiate autism, early psychosis, and social anxiety disorder based on a comprehensive battery of neurocognitive, social cognitive, and mood assessments. Social cognition, visuospatial memory, and mood (e.g., depression, anxiety, and stress) differentiated the clinical groups from a neurotypical control group and the social anxiety group from the autism and early psychosis groups. The autism and early psychosis groups were more difficult to differentiate, with only psychomotor speed and stress distinguishing them.

The cognitive differences characterizing the autism-psychosis spectrum are supported by an underlying neurobiology that five papers in this collection seek to better understand. First, Barlati et al. offer an incisive review of the shared and divergent neuroanatomical, neurofunctional, and molecular markers of social cognition in autism and schizophrenia. Consistent with the goals of this Frontiers Research Topic, their review is organized in accordance with a Research Domain Criteria perspective that seeks to identify behavioral and biological signatures of clinical symptoms spanning diagnostic conditions, and as such serves as a useful summary and guide for future research initiatives. Relatedly, Nair et al. provide a comprehensive narrative review of functional connectivity studies of social cognition in autistic adolescents and those with early-onset psychosis and contextualize these findings within a developmental framework. They conclude that disruptions in default mode network connectivity are associated with social difficulties in both groups but are less relevant to other features of each condition. Meanwhile, Samaey et al. provide a more focused review of the neural underpinnings of one social cognitive ability in particular, facial expression processing, and conclude that altered connectivity and activation in the fusiform gyrus and amygdala among autistic individuals and those with primary psychosis may be influenced by adverse childhood events. They argue that more integrative studies across clinical conditions, framed within a developmental context, are needed to fulfill the promise of identifying selective biomarkers.

Conclusions from these three reviews are supported by two empirical papers in the collection. Brady et al. examined associations between brain connectivity and social cognition in sample of people with psychosis and neurotypical controls and found evidence across both samples that implicated a cerebellar-parietal circuit strongly linked with social cognitive ability. They highlight this circuit as a potential trans-diagnostic biomarker of reduced social cognitive performance. Meanwhile, Foss-Feig et al. leveraged a longitudinal sample to examine the P300 ERP component as a potential indicator of conversion to psychosis among individuals at clinical high risk (CHR) with a history of autism. Unlike previous findings suggesting that P300 amplitude reductions predict psychosis in CHR populations without autism, they found enhanced neural responses during attentional orienting tasks in their small sample of individuals

with combined CHR and autism. Such a result is consistent with other papers in this Research Topic indicating that the combination of symptoms across the autism-psychosis spectrum may interact in unpredicted ways and not follow a simple main effect framework.

AUTHOR CONTRIBUTIONS

NS wrote the first draft of the manuscript. AP and TZ contributed intellectually to the manuscript and helped revise it. All authors have read and approved the submitted version.

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SYSTEMATIC REVIEW
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Meta-Analysis of Cognitive Performance in Neurodevelopmental Disorders during Adulthood: Comparisons between Autism Spectrum Disorder and Schizophrenia on the Wechsler Adult Intelligence Scales

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Autism Spectrum Disorder (ASD) and schizophrenia are neurodevelopmental disorders which show substantial cognitive heterogeneity in adulthood, yet it remains unclear whether cognitive profiles may overlap across these diagnoses. Thus, the aim of this review was to summarize comparisons between ASD and schizophrenia on nonsocial cognition in adulthood. To minimize between-study heterogeneity in a relatively small literature, subtest scaled scores from the Wechsler Adult Intelligence Scale were compared between ASD (N=190) and schizophrenia (N=260) in six studies comprising a total of 450 participants. Meta-analyses of 11 subtests indicated that participants with ASD demonstrated significantly better performance than schizophrenia for visuospatial perception and reasoning and problem solving (Hedge's g=0.636), as well as visual attention and organization (g=0.433-0.475). Participants with ASD also demonstrated better performance than those with schizophrenia for working memory (g=0.334) and language (g=0.275), and generally comparable performance on processing speed and verbal comprehension. These findings were largely stable across age, sex, intelligence quotient (IQ), intellectual disability, scale version, and age- and sex-matching. Overall, ASD and schizophrenia showed striking differences in visuospatial perception and reasoning and problem solving, small differences in working memory and language, and substantial overlap in processing speed and verbal comprehension. These cognitive profiles were generally stable from adolescence to middle adulthood. To our knowledge, this is the first review to summarize comparisons of nonsocial cognition in verbal adults with ASD or schizophrenia. These findings are consistent with and substantially extend prior meta-analyses of case-control studies for ASD and schizophrenia (8, 9), which also suggest that, in comparison to neurotypical controls, ASD demonstrates smaller cognitive impairments than schizophrenia across most cognitive domains, particularly working

memory, visuospatial learning/memory, and language. Our findings therefore highlight the importance of comparing cognition transdiagnostically to inform the etiologies of these neurodevelopmental disorders and to refine shared and unique targets for remediating cognition.

Keywords: intelligence, general cognition, nonsocial cognition, transdiagnostic, cross-diagnosis, development, Asperger syndrome, psychosis

INTRODUCTION

Autism spectrum disorder (ASD) and schizophrenia are both neurodevelopmental disorders which show substantial difficulties with both social and nonsocial information processing (1, 2). Although these two disorders have different peak ages of onset, with ASD emerging early in childhood (3) and schizophrenia emerging in late adolescence and early adulthood (4), their neurodevelopmental trajectories may be associated with similar cognitive impairments during adulthood (5–7). Recent meta-analyses of cognitive functioning in adulthood within these two disorders indicate that both conditions show deficits compared to typically developing adults in the same cognitive domains, including processing speed, attention and vigilance, working memory, visuospatial learning/memory, verbal learning/memory, language, and reasoning and problem-solving (8, 9). However, no review to date has investigated direct comparisons of nonsocial cognition in adulthood between these two disorders. Given that nonsocial cognition is an important predictor of functional outcomes in both disorders (10, 11), comparing nonsocial cognition between ASD and schizophrenia is critical for adapting common strategies for remediating cognition to improve functional outcomes across these neurodevelopmental disorders.

Although the domains of cognitive impairments appear to be overlapping in ASD and schizophrenia, little evidence to date bears directly upon whether the magnitudes of these impairments are comparable across disorders. Thus far, most studies comparing cognitive functioning across ASD and schizophrenia have investigated social cognitive abilities such as theory of mind and emotion processing (12). Meta-analyses of these studies suggest that ASD and schizophrenia demonstrate relatively similar performance across social cognitive domains (12). Although 19 studies were included in this meta-analysis, findings for each social cognitive domain were informed by three to eight studies which each contributed largely non-overlapping measures. Thus, meta-analytic comparisons are tempered by substantial method heterogeneity across the contributing studies.

Relatively fewer studies have examined the extent to which nonsocial cognitive abilities may overlap or differ from each other across ASD and schizophrenia (7, 13, 14). These studies have largely drawn upon standardized cognitive batteries, the most common of which are the Wechsler Adult Intelligence Scales [WAIS; (15, 16)]. To our knowledge, only one study has compared nonsocial cognition between ASD and schizophrenia using a cognitive battery that does not include the WAIS (7). Thus, although there is a smaller pool of studies that compare nonsocial cognitive performance across ASD and schizophrenia compared to the number of studies that compare social cognitive performance across these diagnoses, the common use of the WAIS to assess nonsocial cognitive performance reduces method heterogeneity compared to the use of different batteries across studies.

Beyond studies that directly compare nonsocial cognition between ASD and schizophrenia, the most relevant support for shared and distinct features in nonsocial cognition across ASD and schizophrenia come from recent comprehensive meta-analyses comparing cognitive performance within these disorders to neurotypical controls. Across domains, verbal adults with ASD demonstrate comparable performance to neurotypical controls for attention and vigilance and working memory but show cognitive impairments particularly for social cognition (Hedge's g=-0.80 to -1.09), followed by nonsocial cognitive processes including processing speed (g=-0.61), verbal learning and memory (g=-0.55), and reasoning and problem-solving (g=-0.51) (9). In comparison, adults with first-episode schizophrenia, who have had less exposure to psychotropic medication relative to adults who are later in their schizophrenia course, show substantial difficulties across all social and nonsocial cognitive domains relative to neurotypical controls, with impairments ranging from 0.6 to 1.4 standard deviations below that of neurotypical performance (8). Mirroring cognitive deficits that have been implicated in ASD, cognitive domains that are impacted in schizophrenia include processing speed, perception, attention/vigilance, working memory, episodic memory, verbal learning, visual learning, executive functioning, affective processing, and social cognition (17, 18).

Overall, verbal adults with ASD appear to show deficits in specific cognitive domains and comparable performance to controls in other cognitive domains, consistent with a multiple-deficit model (19, 20). In contrast, adults with schizophrenia demonstrate widespread cognitive deficits across most cognitive domains, consistent with a generalized cognitive deficit (21). Across cognitive domains meta-analyzed within each diagnosis (8, 9), deficits appear more pronounced in schizophrenia than in ASD, with differences in overall effect size estimates approximating 0.3 to 0.6 standard deviations between the two conditions. Notably, the effect size estimates overlap for cognitive domains including processing speed, attention/vigilance, reasoning and problem solving, and social cognition, but do not overlap for working memory, visuospatial learning/memory, and language. Taken together, relative to neurotypical controls, ASD demonstrates smaller cognitive

impairments than schizophrenia across most cognitive domains, with discrepancies being most evident for working memory, visuospatial learning/memory, and language.

The primary aim of this meta-analysis was to examine the extent to which ASD and schizophrenia show overlapping and unique impairments in nonsocial cognition on the most widely used cognitive battery for assessing domain functioning across these disorders, the WAIS (15, 16). We aimed to compare specific cognitive functioning across studies in a relatively small literature while simultaneously minimizing the heterogeneity in sensitivity and specificity across different cognitive measures that may inform a given cognitive domain. We therefore decided to adopt a conservative approach to consolidate effect size estimates from studies of nonsocial cognition across ASD and schizophrenia. Specifically, consolidating estimates for a given subtest from similar versions of a standardized battery reduces heterogeneity across studies and increases the precision of meta-analytical estimates relative to comparisons combining different cognitive measures. Supporting the utility of this approach, the theoretical, psychometric, and administrative consistencies across WAIS versions facilitate valid comparisons of differences in cognitive domain performance across ASD and schizophrenia. To our knowledge, this is the first study to systematically review nonsocial cognitive domain performance across ASD and schizophrenia.

METHODS

Search Strategies

Peer-reviewed journal articles were screened to meet all of the following inclusion criteria:

1. The full-text article was published in English.
2. Participants were diagnosed based on criteria listed in the Diagnostic and Statistical Manual of Mental Disorders (version III-R or IV) (22, 23) or International Classification of Diseases (version 9 or 10) (24, 25).
3. The ASD group included only verbal individuals with a primary diagnosis of autism, high-functioning autism, or Asperger syndrome.
4. The schizophrenia group included only individuals with a primary diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder.
5. Subtest performance was reported by group for multiple subtests from a standardized Wechsler Adult Intelligence Scale.

As depicted in **Figure 1**, 1654 peer-reviewed journal articles published before February 15, 2019 were electronically identified using a conjunction of the following free-text search terms, "schizophreni*", "autis* OR Asperger", and "Wechsler" in two comprehensive journal databases, PubMed (n=33 articles) and PsycINFO (n=1621 articles). Duplicate publications were removed using EndNote X8 bibliographic software yielding 1446 articles. A total of 24 journal articles were examined after abstract, and 19 articles were not included after full-text read because they did not include subtest scores. Six articles met all inclusion criteria and were included in this systematic review after full-text read.

Selection of Cognitive Domains

The WAIS versions identified in this meta-analysis have age-based norms from large, population-based normative samples with ages ranging from approximately 16 to 90 years (15, 16). We examined all WAIS subtests with at least four contributing studies. Thus, a total of 11 subtests were meta-analyzed. The WAIS is comprised of four different indexes, representing four cognitive domains (15, 16).

For Verbal Comprehension, which encompasses language as well as verbal reasoning, four subtests were included:

1. Similarities: this subtest prompts the participant to describe how two words or concepts are similar, to assess verbal reasoning;
2. Information: this subtest prompts the participant to describe their understanding of widely-known factoids, to assess general knowledge;
3. Vocabulary: this subtest prompts the participant to define the meanings of terms, to assess verbal knowledge, verbal expression, and concept formation;
4. Comprehension: this supplemental subtest prompts the participant to describe how they integrate and adapt to social information, to assess verbal reasoning and social inference.

For Perceptual Reasoning, which encompasses visuospatial abilities and reasoning and problem solving, two subtests were included:

1. Block Design: this timed subtest prompts the participant to recreate spatial patterns using blocks, to assess spatial reasoning;
2. Picture Completion: this timed supplemental subtest prompts the participant to identify missing parts in pictures, to assess attention, visual perception and organization.

For Working Memory, which encompasses attention and working memory, two subtests were included:

1. Digit Span: this subtest prompts the participant to verbally repeat strings of numbers forwards or backwards, to assess auditory working memory, attention, and concentration;
2. Arithmetic: this subtest prompts the participant to solve arithmetic problems presented as stories, to assess auditory working memory, concentration, and quantitative reasoning.

For Processing Speed, one subtest was included:

1. Digit Symbol Coding: this subtest prompts the participant to assess psychomotor speed, motor coordination, visual perception, attention, and concentration.

Finally, two additional subtests were included:

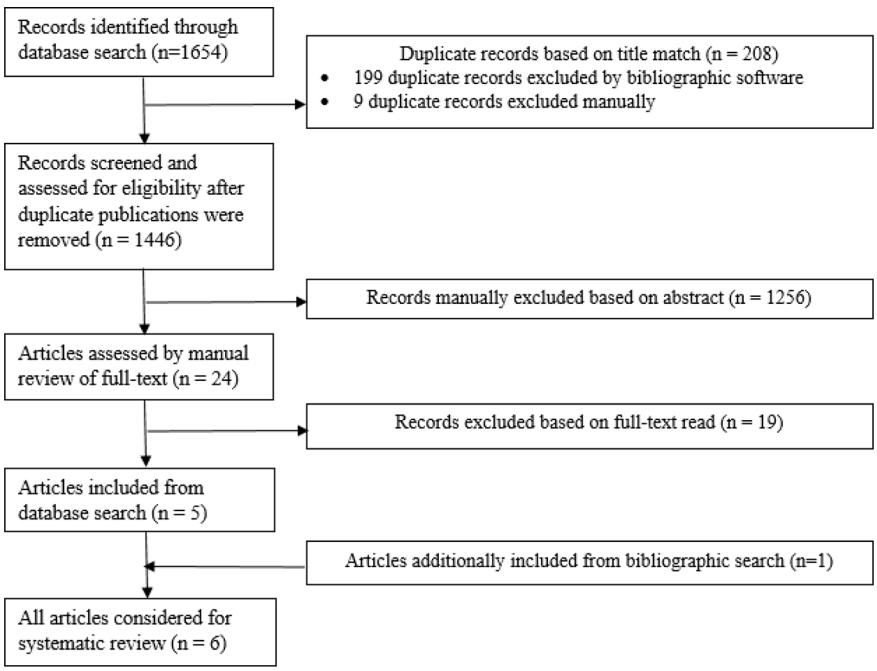

FIGURE 1 | Flowchart depicting systematic review process.

1. Object Assembly: this supplemental subtest prompts the participant to solve visual puzzles, to assess visual anticipation, visual perception, and motor reasoning;
2. Picture Arrangement: this timed supplemental subtest prompts the participant to order scrambled series of cards depicting social events, to assess nonverbal reasoning, sequencing and social inference.

Interestingly, in a confirmatory analysis study of all 14 WAIS-III subtests, the last two subtests, Picture Arrangement and Object Assembly, and Picture Completion, comprise a Social Cognition domain (26), suggesting that these subtests may be associated with social cognitive abilities.

Data Extraction

The scaled score mean and standard deviation for each subtest for each group was extracted from the included studies and entered on two occasions by the first author. Scaled scores are age-adjusted and standardized to a sample distribution with a mean of 10 and a standard deviation of 3 (range=1-19), with higher scores indicating better performance. Where data were only available for subgroups of a schizophrenia sample in one study (27), we pooled the subgroup estimates to derive an overall estimate for the schizophrenia sample.

Meta-Analysis

Random-effect meta-analyses of cognitive subtest performance were performed using the R package, metafor (28), weighting the studies by their inverse variance, which reflects the study sample size. We used Hedge's *g* as the bias-corrected effect size of mean group differences. To characterize subtest performance within groups, we used the R package, meta (29), to estimate the random-effect inverse-variance weighted mean and standard error of performance within groups. Random-effect models were estimated instead of fixed-effect models due to the requirement that the true effect size does not vary between studies and the substantial Type I bias in significance tests for mean effect sizes and moderators in fixed-effects models (30).

Heterogeneity

To quantify the heterogeneity in effect sizes across studies, we computed the I^2 (31), which is the percentage of variation across studies that is due to heterogeneity rather than chance. We further assessed potential publication bias attributable to small studies with Egger's regression test (ERT) (32), which investigates correlations between effect sizes and sample sizes. A significant ERT may indicate that the effect size estimate may be biased by a selection of small sample studies. For subtests with significant mean group differences, we also examined whether the effect size estimates may be biased by the file-drawer problem by calculating a fail-safe number, which is the number of studies with null results that would have to be added to the current set of studies to raise the significance level of the effect size to p=.05 (33). We also conducted sensitivity analyses eliminating the only contributing study that included adolescents in addition to adults (13). This study assessed participants as young as 14 years using the Wechsler Intelligence Scale for Children-Revised [WISC-R; (34)] and reported results combining the WISC-R scores with the WAIS-R scores (13).

Meta-Regression

For significant findings, we examined whether the effect sizes were moderated by key sample characteristics, including age (mean sample age), sex (mean sample proportion of males), intellectual disability (inclusion or exclusion of participants who had an estimated IQ<70; in addition, one study in Turkey included participants who had ≥12 years of education as a proxy for lack of intellectual disability, as eligibility for post-secondary education is based on standardized test performance assessing cognitive abilities (35), and scale version (WAIS, WAIS-III, or WAIS-R). Although the scaled scores for each participant were based on age-based norms, we also examined whether the effect sizes were moderated by mean group differences in age and sex. Education was reported in only three studies (14, 27, 35), and was therefore not examined as a possible moderator. As clinical and functioning characteristics of the groups were not reported consistently across studies, we were unable to examine the effects of these potential moderators. Given the number of meta-regression analyses conducted, we adopted a conservative cutoff for statistical significance at $p<0.01$.

RESULTS

Sample Characteristics

Descriptive characteristics of the included studies are presented in **Table 1**. The number of included WAIS measures for each study ranged from 4 to 14 (median=11), and a minimum of 375 participants contributed to each subtest meta-analysis. All studies were cross-sectional and included at least 13 participants in each diagnostic group, with mean group sizes of 43 participants in the ASD groups and 32 participants in the schizophrenia groups.

Age

Across studies, groups were matched for mean age ($t(4)=0.519$, $p=.631$). Participant groups had mean ages ranging from 16 to 41, allowing for comparisons of age-related differences in cognitive functioning from adolescence to middle adulthood, with the group mean ages approximating 28.2 years of age (*S.D.*=7.8 years).

TABLE 1 | Description of studies included in meta-analysis reporting cognitive domain performance in autism and schizophrenia, sorted by increasing mean sample age.

Characteristic	Group	Mean Across Studies	Bölte, Rudolf (13)	Goldstein, Minshew (27) ‡	Marinopoulou, Lugnegård (14)	Murphy (36)	Mançe Çalişir, Atbaşoğlu (35)	de Boer, Spek (37)
Test Version			WISC-R, WAIS-R	WAIS-R	WAIS-III	WAIS-R	WAIS ^	WAIS-III
Number of Included Measures		10	11	11	14	4	7	14
N	ASD	43	20	31	50	13	32	114
	SZ	32	20	80	33	13	17	27
Recruitment	ASD		N/A	N/A	Outpatient clinic and adult rehabilitation records	Forensic psychiatric hospital	N/A	Mental health institution
	SZ		University hospital inpatient and outpatient clinics	Veterans' hospital inpatient clinic	Outpatient clinic	Forensic psychiatric hospital	Newspaper advertisement	Mental health institution
Diagnosis	ASD		Autism	High-functioning autism excluding Asperger syndrome	Asperger syndrome	Asperger syndrome	Autism and Asperger syndrome	High-functioning autism and Asperger syndrome
	SZ		Schizophrenia	Schizophrenia	Schizophrenia, schizoaffective disorder, schizophreniform disorder	Schizophrenia	Schizophrenia	Schizophrenia
Age (years)	ASD	28.2 (7.8)	16.8 (2.1)	21.4 (9.8)	27.7 (3.9)	32.1 (6.5)	33.9 (9.4)	37.4 (10.6)
	SZ	28.4 (9.1)	16.6 (1.5)	–	29.1 (4.3)	30.2 (4.2)	24.6 (3.2)	41.5 (9.3)
Sex (% male)	ASD	68%	55%	–	50%	100%	53%	81%
	SZ	73%	55%	100%	55%	100%	47%	78%
Education	ASD		–	10.7 (2.9)	14% some college	–	16.1 (2.6)	–
	SZ		–	–	21% some college	–	13.4 (1.1)	–
Intellectual Disability			No exclusion +	Excluded IQ<70	Excluded IQ<70	No exclusion	Excluded education <12 years	Excluded IQ<80
Estimated IQ	ASD	98.0 (8.9)	82.5 (24.1)	99.6 (13.1)	102.4 (12.3)	100.1 (15.9)	–	105.3 (12.5)
	SZ	90.8 (9.1)	83.9 (22.3)	–	94.5 (13.4)	82.9 (8.3)	–	101.9 (12.3)

ASD, autism spectrum disorder; SZ, schizophrenia. N/A, not available. WAIS-III: Wechsler Adult Intelligence Scale-Third Edition (15); WAIS-R: Wechsler Adult Intelligence Scale-Revised (16); WISC-R: Wechsler Intelligence Scale for Children-Revised (34).

‡ Goldstein, Minshew (27) divided schizophrenia into four clusters: Moderately Impaired, High Functioning, Severely Impaired, and Severely Impaired Psychomotor.

+30% of ASD group has comorbid epilepsy.

^Scale version is Turkish translation of the first scale version (38) due to difficulties with norming for subsequent editions.

Sex

Across studies, groups were not evenly matched for sex ratios (χ^2 (10)=82.535, p<0.001), with a smaller proportion of males in the ASD groups compared to the SZ groups. In line with epidemiological estimates of sex ratios for ASD and schizophrenia during early through middle adulthood (4, 39), all the participant groups, except for a schizophrenia group in one study, included more males than females (mean group proportion ~70% male).

IQ

Across studies, IQ was within overlapping range between groups (t(3)=1.711, p=.186). All studies except for two (13, 36) excluded participants who had an IQ lower than 70 or had fewer than 12 years of education. Overall, all except one study reported an estimated full-scale IQ, with mean group IQs being approximately 98.0 for the ASD groups and 90.8 for the schizophrenia groups.

Diagnostic Comparisons of Language and Verbal Comprehension

Table 2 presents the results of the meta-analyses for each WAIS subtest, whereas **Figure 2** depicts the random-effects, inverse-variance weighted subtest means and standard errors calculated within each group.

Forestplots depicting WAIS subtest effect sizes are presented for Similarities (**Figure 3**), Information (**Figure 4**), Vocabulary (**Figure 5**), and Comprehension (**Figure 6**). On average, ASD and schizophrenia participants generally performed within the average range for measures of language and verbal comprehension, with both groups demonstrating the highest scores for Information (scaled score mean=11.84 for ASD and 10.81 for schizophrenia) and the lowest scores for Comprehension (scaled score mean=9.81 for ASD and 8.81 for schizophrenia). Across the four included subtests of Verbal Comprehension, only Vocabulary differed significantly between ASD and schizophrenia, with ASD demonstrating better performance than schizophrenia. The effect size was small (g=0.275, p=.027) with relatively little heterogeneity across studies that was unlikely to be attributable to chance (I^2=10.9%), suggesting that diagnostic differences in Vocabulary performance are fairly homogenous across studies. Doubling the sample size to include an additional four null-effect studies would be sufficient to render the overall effect nonsignificant (fail-safe number=4), leading us to interpret this result cautiously. The effect size for Vocabulary remained significant after eliminating the only contributing study that included adolescents (13).

Performance on the three other subtests comprising the Verbal Comprehension Index, Similarities, Information, and

TABLE 2 | Summary of meta-analyses comparing mean group differences in cognitive functioning between autism and schizophrenia.

Cognitive Domain	Number of Studies	Combined ASD *n*	Combined SZ *n*	ASD Scaled Score	SZ Scaled Score	Effect Size	Effect Size 95% C.I.	Effect Size *p*-value	I^2	ERT (*p*-value)	Fail-Safe *n*
VCI: Similarities	6	260	190	10.81 (0.47)	9.42 (0.97)	0.389	(-0.061, 0.839)	.090	77.0	1.027 (.305)	–
VCI: Information	5	247	177	11.84 (0.54)	10.81 (0.90)	0.287	(-0.034, 0.608)	.079	53.5	-0.797 (.425)	–
VCI: Vocabulary	4	215	160	9.98 (0.48)	9.06 (0.61)	0.275*	(0.031, 0.519)	.027	10.9	-0.736 (.462)	4
VCI: Comprehension	5	247	177	9.81 (0.82)	8.81 (0.74)	0.321	(-0.063, 0.704)	.101	66.9	-0.043 (.966)	–
PRI: Block Design	6	260	190	10.84 (0.33)	8.82 (0.75)	0.636**	(0.177, 1.095)	.007	77.4	0.488 (.626)	65
PRI: Picture Completion	4	215	160	9.30 (0.55)	8.26 (0.44)	0.433***	(0.203, 0.663)	<.001	0.0	-1.923 (.055)	13
WMI: Digit Span	6	260	190	9.74 (0.35)	8.96 (0.41)	0.213	(-0.051, 0.476)	.113	35.4	0.994 (.320)	–
WMI: Arithmetic	5	247	177	10.10 (0.56)	8.98 (0.63)	0.334*	(0.056, 0.612)	.019	38.4	-0.236 (.814)	12
PSI: Digit Symbol Coding	6	260	190	7.93 (0.71)	6.73 (0.45)	0.385	(-0.056, 0.826)	.087	76.1	0.851 (.395)	–
Object Assembly	4	215	160	10.25 (0.32)	8.64 (0.80)	0.475*	(0.083, 0.868)	.018	63.8	-0.593 (.553)	20
Picture Arrangement	4	215	160	9.45 (0.84)	7.72 (0.68)	0.672	(-0.054, 1.397)	.070	88.9	-1.318 (.187)	–

ASD, autism spectrum disorder; SZ, schizophrenia; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index. For scaled scores, means weighted by group inverse variance are presented with standard errors in parentheses. Scaled scores are age-adjusted to have a sample distribution centered at a mean of 10 and a standard deviation of 3 (range=1-19), with higher scores indicating better performance.

*C.I., confidence interval. *p<.05; **p<.01; ***p<.001.*

I^2 (31): percentage of variation across studies that is due to heterogeneity rather than chance.

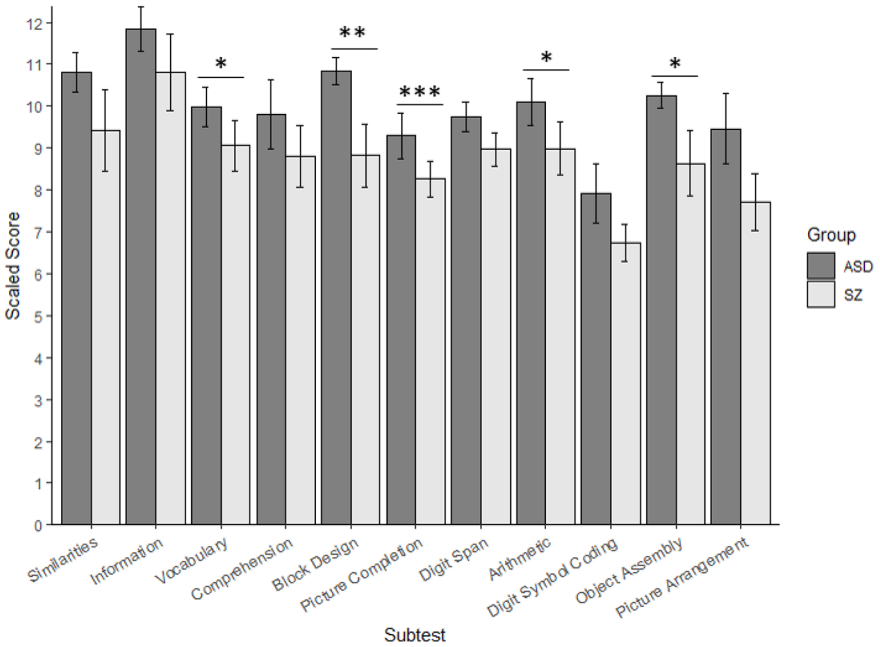

FIGURE 2 | Cognitive Performance on the Wechsler Adult Intelligence Scale in Autism and Schizophrenia. ASD, autism spectrum disorder; SZ, schizophrenia. Random-effects, inverse-variance weighted subtest means and standard errors calculated for each group are presented with the significance of the meta-analytic effect size (the bias-corrected group mean difference). Although standard errors may overlap between groups for a given subtest, the effect size may be significant given that the effect sizes are bias-corrected, and vice versa. *p<.05; **p<.01; ***p<.001.

Comprehension did not differ significantly between ASD and schizophrenia. These nonsignificant findings may be in part due to the substantial heterogeneity across studies observed for these subtest comparisons (I^2=53.5-77.0%). Across all subtests, the ERT was nonsignificant, suggesting that the results are unlikely to be attributable to small-sample bias. Meta-regressions indicated that all results were largely independent of age, sex, intellectual disability, and scale version.

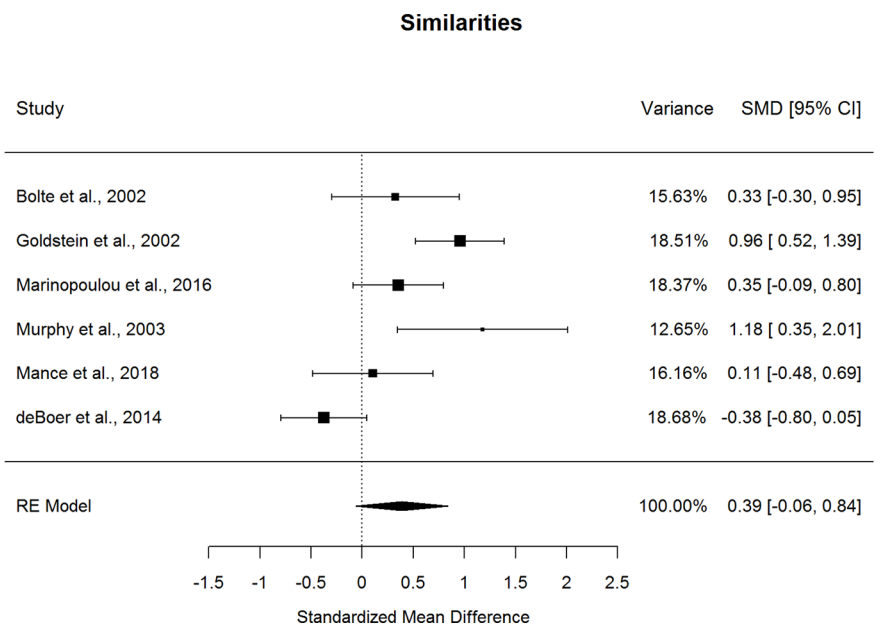

FIGURE 3 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in similarities scores.

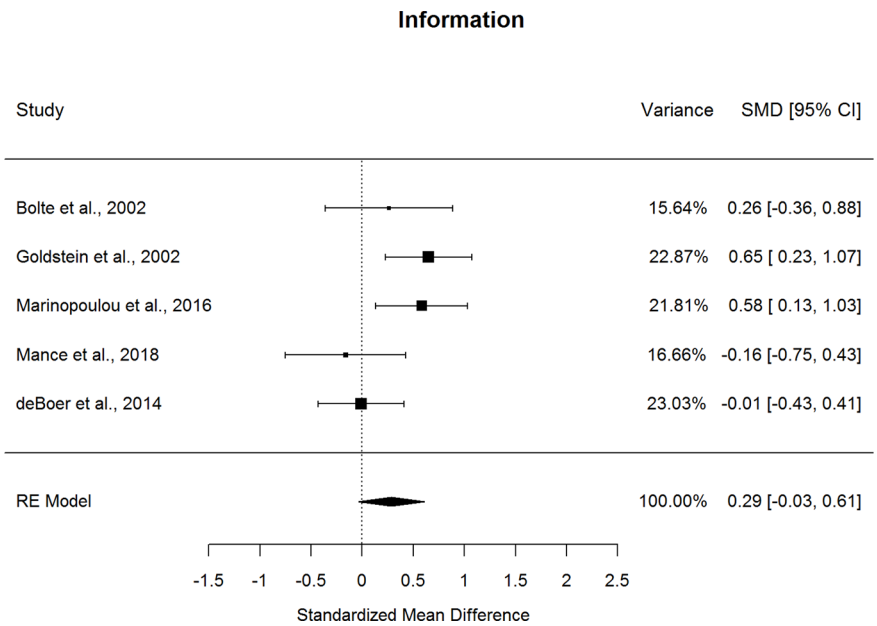

FIGURE 4 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in information scores.

Overall, ASD and schizophrenia show similar performance for assessments of verbal reasoning, general knowledge, and the ability to describe abstract social norms and expressions from early through middle adulthood, with small advantages in ASD compared to schizophrenia for verbal comprehension and expression.

Diagnostic Comparisons of Visuospatial Abilities and Reasoning and Problem-Solving

Forestplots depicting WAIS subtest effect sizes are presented for Block Design (**Figure 7**) and Picture Completion (**Figure 8**). ASD and schizophrenia participants also performed within the

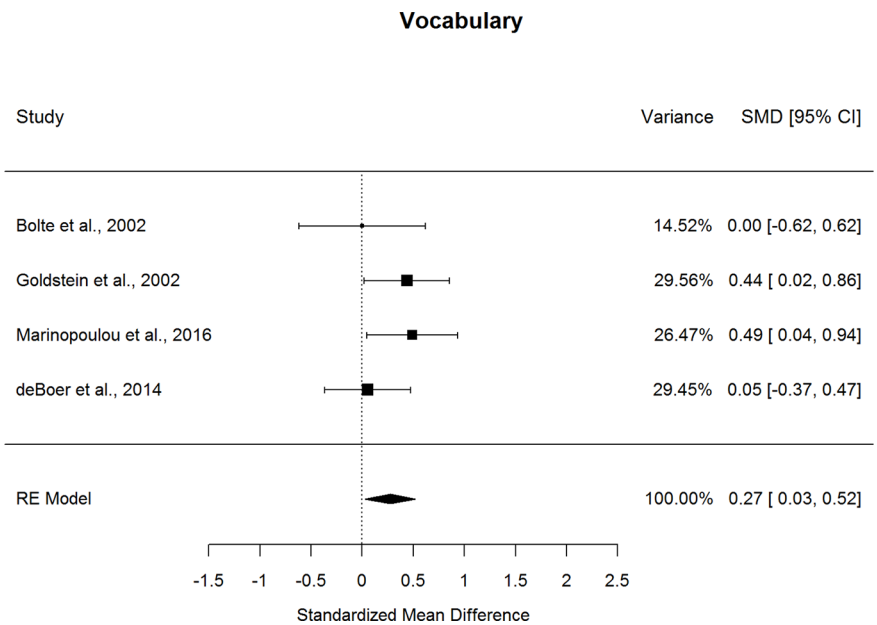

FIGURE 5 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in vocabulary scores.

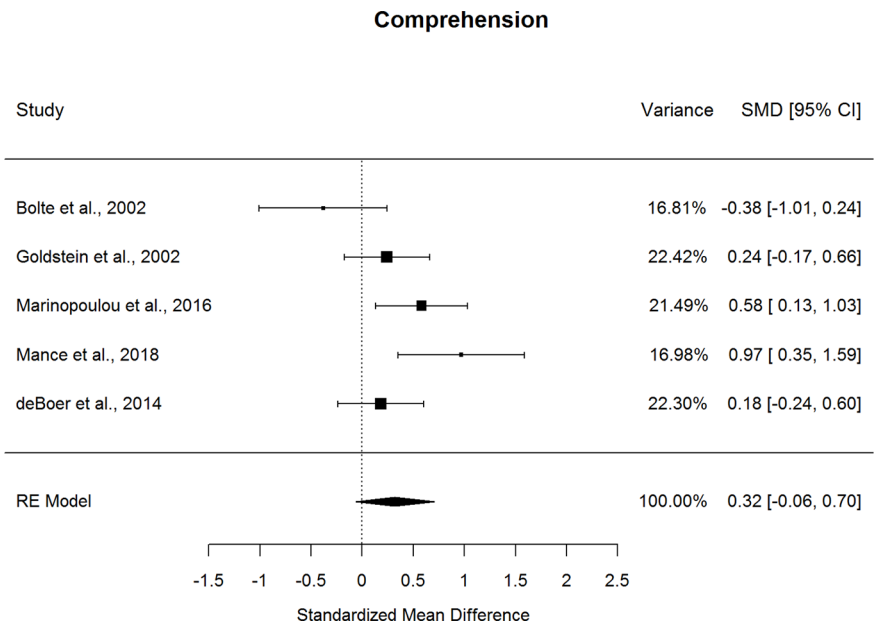

FIGURE 6 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in comprehension scores.

average range for measures of visuospatial abilities and reasoning and problem solving, with both groups demonstrating higher scores for Block Design (scaled score mean=10.84 for ASD and 8.82 for schizophrenia) and lower scores for Picture Completion (scaled score mean=9.30 for ASD and 8.26 for schizophrenia). ASD performed better than schizophrenia on both Perceptual Reasoning subtests. Although there was substantial heterogeneity across studies for Block Design (I^2=77.4%), a medium effect size was still observed (g=0.636, p=.007), with ASD demonstrating substantially better performance than schizophrenia. On the other hand, very little heterogeneity was observed across studies for Picture Completion (I^2=0.0%), for which a medium effect size was observed (g=0.433, p<0.001), suggesting that ASD consistently showed better performance than schizophrenia for

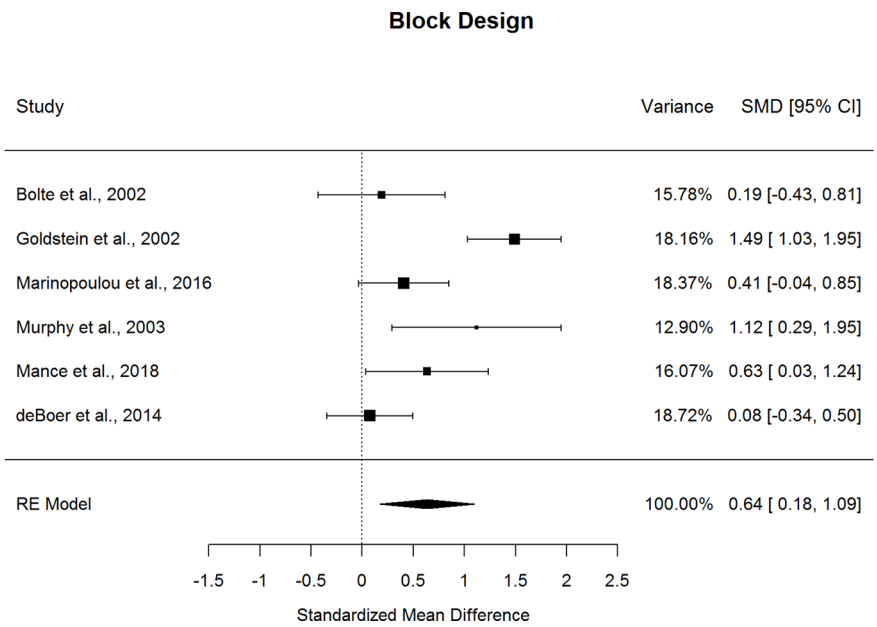

FIGURE 7 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in block design scores.

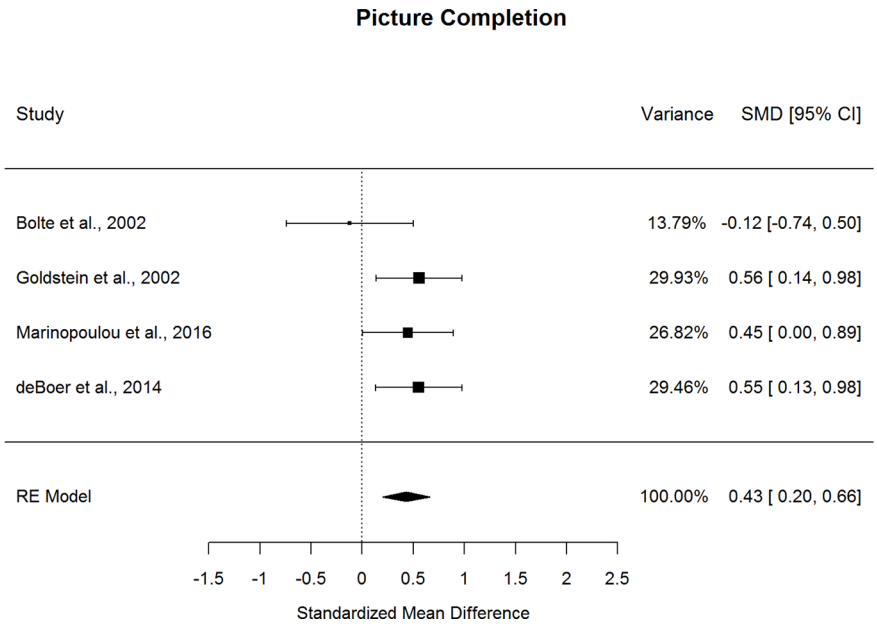

FIGURE 8 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in picture completion scores.

this subtest. Here again, the ERT was nonsignificant, suggesting that small samples were unlikely to bias these results. Furthermore, the fail-safe numbers were substantially larger than the number of included studies, requiring 65 null-effect studies to render the effect size for Block Design nonsignificant, and 13 null-effect studies to render the effect size for Picture Completion nonsignificant. The effect sizes for both Block Design and Picture Completion also remained significant after eliminating the only contributing study that included adolescents (13). Thus, these results are unlikely to change substantially by including many unpublished studies of null effect. These findings were stable across age, sex, intellectual disability, scale version, and matching for age or sex, as indicated by meta-regression results. Overall, these findings indicate that ASD demonstrates strengths in visuospatial processing and reasoning and problem solving compared to schizophrenia from early through middle adulthood.

Diagnostic Comparisons of Attention and Working Memory

Forestplots depicting WAIS subtest effect sizes are presented for Digit Span (**Figure 9**) and Arithmetic (**Figure 10**). On average, ASD and schizophrenia participants generally performed within the average range for measures of attention and working memory, with both groups demonstrating higher scores for Arithmetic (scaled score mean=10.10 for ASD and 8.98 for schizophrenia) and lower scores for Digit Span (scaled score mean=9.74 for ASD and 8.96 for schizophrenia). The findings were mixed for the two Working Memory subtests, despite similar levels of heterogeneity across studies for both subtests (I^2=35.4-38.4%). In particular, ASD and schizophrenia demonstrated similar performance on Digit Span. However, ASD demonstrated better performance than schizophrenia for Arithmetic, with a small effect size (g=0.334, p=.019). The ERT was nonsignificant for both subtests, suggesting a lack of small-sample bias. With a reasonably large fail-safe number of 12 compared to the number of contributing studies (k=5), the finding for Arithmetic is unlikely to change even by doubling the sample size by including additional null-effect studies. Similarly, even after eliminating the only contributing study that included adolescents (13), ASD demonstrated better Arithmetic performance than schizophrenia. The results were not moderated by age, sex, IQ, intellectual disability, scale version, or matching for age or sex. Overall, these findings suggest that ASD and schizophrenia show some differences in working memory performance from early to middle adulthood.

Diagnostic Comparisons of Processing Speed

Forestplots depicting WAIS subtest effect sizes are presented for Digit Symbol Coding (**Figure 11**). ASD and schizophrenia participants performed within the borderline range for the included measure of processing speed (scaled score mean=7.93 for ASD and 6.73 for schizophrenia). ASD and schizophrenia did not demonstrate significant differences in Digit Symbol Coding performance. However, the magnitude of the differences varied by mean sample age but not by other moderators, such that ASD demonstrated greater advantages in Digit Symbol Coding performance over schizophrenia in middle adulthood compared to early adulthood (t(6)=-2.595, p=.009, I^2=24%, Adjusted R^2=90%). This suggests that differences between ASD and schizophrenia in processing speed may change with age, with strengths for ASD relative to schizophrenia increasing with age.

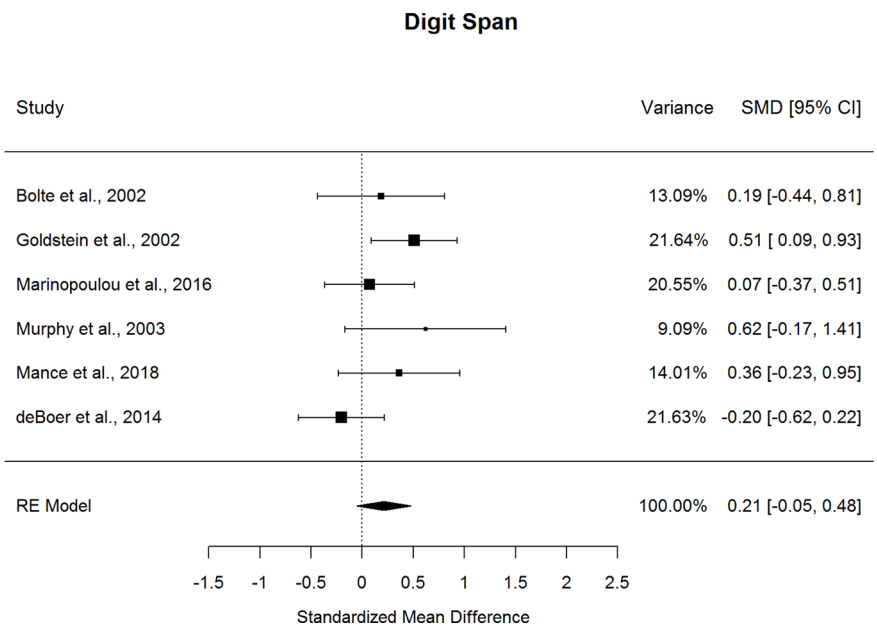

FIGURE 9 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in digit span scores.

Diagnostic Comparisons of Abilities Associated with Social Cognition

Forestplots depicting WAIS subtest effect sizes are presented for Object Assembly (**Figure 12**) and Picture Arrangement (**Figure 13**). On average, ASD and schizophrenia participants performed within the normal range for abilities associated with social cognition, with higher scores for Object Assembly (scaled score mean=10.25 for ASD and 8.64 for schizophrenia) than Picture Arrangement (scaled score mean=9.45 for ASD and 7.72 for schizophrenia). Of the two additional subtests, which have been found to tap into social cognition (26), ASD performed better than schizophrenia on Object Assembly (g=0.475, p=.018) but demonstrated similar performance to schizophrenia for Picture Arrangement. The fail-safe number of 20 for Object Assembly suggests that this finding is

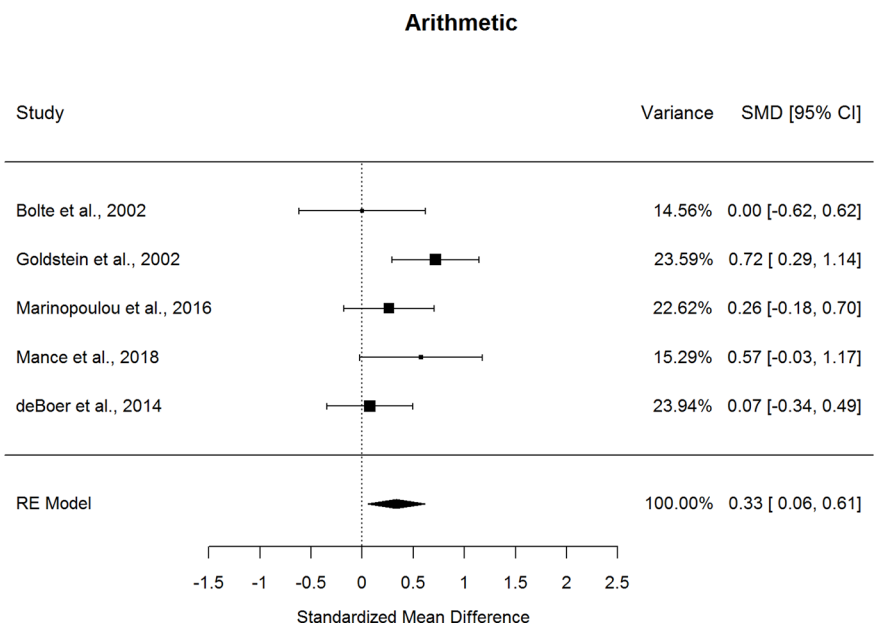

FIGURE 10 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in arithmetic scores.

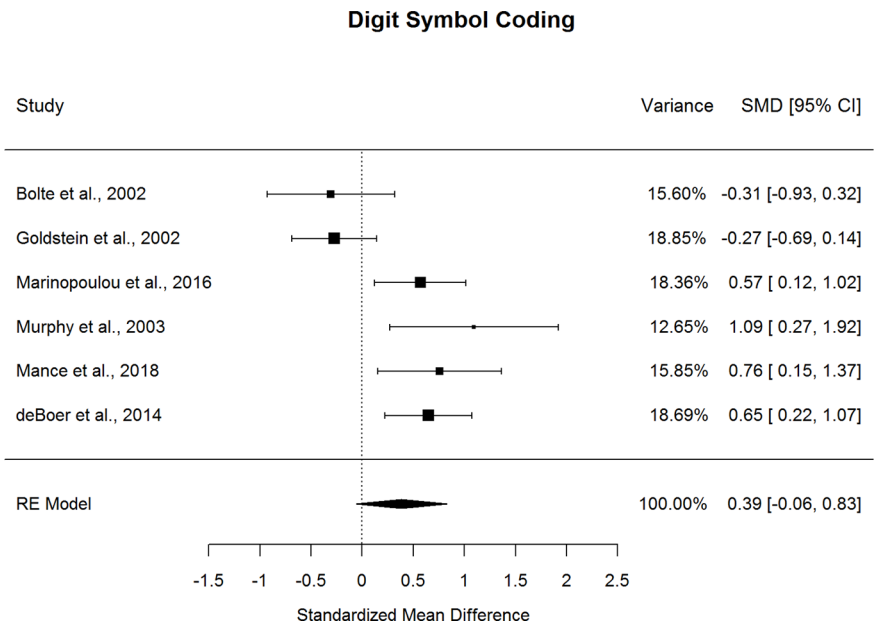

FIGURE 11 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in digit symbol coding scores.

unlikely to change unless at least 20 additional null-effect studies were included. Furthermore, ASD showed better performance than schizophrenia for Object Assembly even after removing the only contributing study that included adolescents (13). Both subtests showed considerable heterogeneity across studies (I^2=63.8-88.9%) and were unlikely to be biased by small-sample studies. Furthermore, the results were not moderated by age, sex, IQ, intellectual disability, scale version, or matching for age or sex.

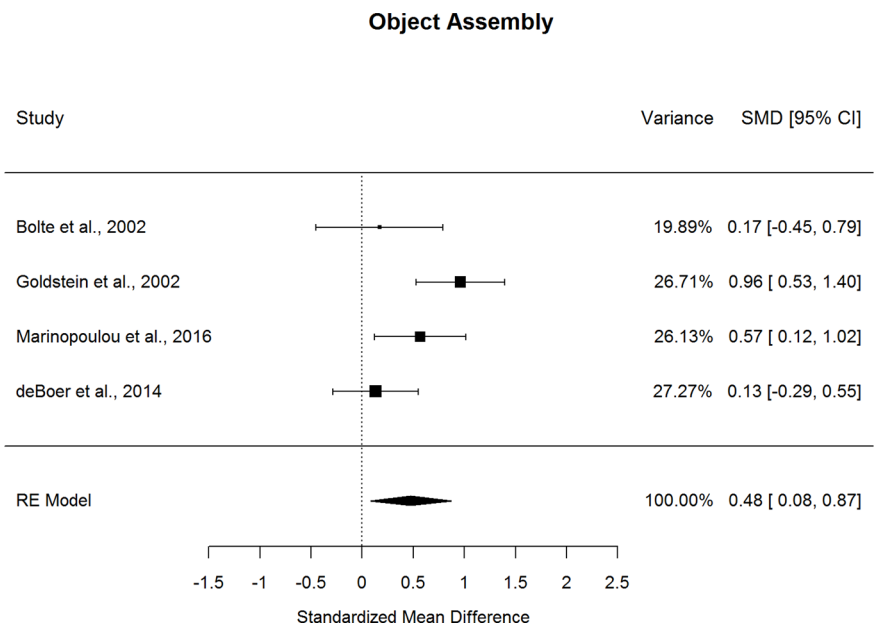

FIGURE 12 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in object assembly scores.

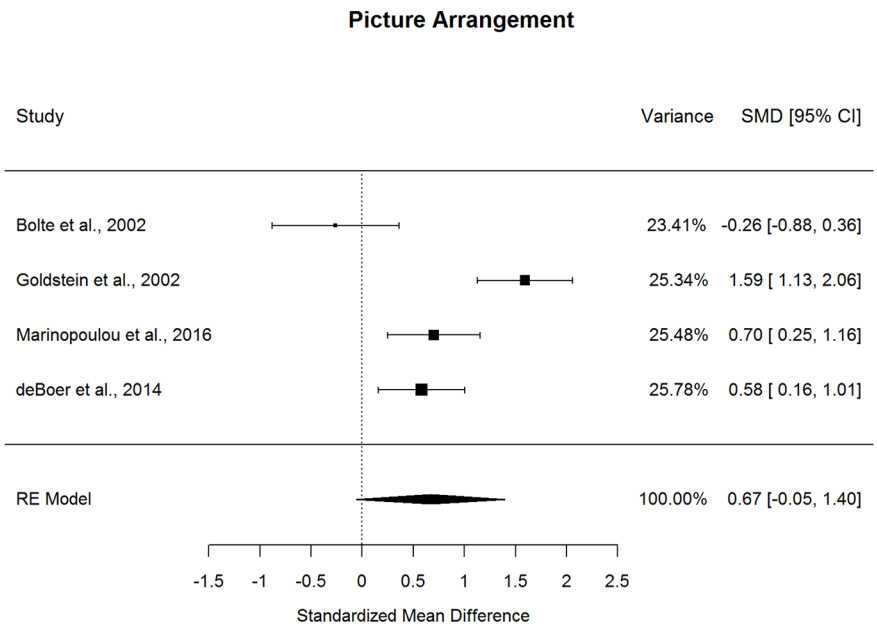

FIGURE 13 | Random effect (re) meta-analysis of standardized mean difference (smd) between autism and schizophrenia groups in picture arrangement scores.

DISCUSSION

To our knowledge, this is the first study to systematically review comparisons of nonsocial cognition between ASD and schizophrenia, consolidating all reports to date of WAIS subtest comparisons across 450 participants. Across domains, ASD and schizophrenia demonstrated generally comparable performance on processing speed and verbal comprehension. In contrast, ASD demonstrated better performance than schizophrenia for visuospatial processing and reasoning and problem-solving (g=0.636), followed by visual attention and organization (g=0.433-0.475), working memory (g=0.334) and language (g=0.275). Overall, although ASD and schizophrenia perform similarly across many subtests, where these neurodevelopmental disorders diverge in nonsocial cognitive functioning, ASD consistently bears advantages over schizophrenia. Even for the subtests which did not show statistically significant differences between ASD and schizophrenia, all effect sizes were in the same direction, with ASD tending to demonstrate better performance than schizophrenia.

This study substantially extends prior literature investigating nonsocial cognition within each neurodevelopmental disorder. In particular, our findings are consistent with effect size estimates across separate meta-analyses examining ASD or schizophrenia relative to neurotypical controls, which suggested working memory (Arithmetic), visuospatial processing, reasoning and problem solving (Block Design, Picture Completion, and Object Assembly), and language (Vocabulary) as cognitive domains in which ASD may demonstrate better performance than schizophrenia (8, 9). Of the five cognitive measures for which ASD showed better performance compared to schizophrenia, the most prominent differences were observed for three measures of visuospatial abilities: Block Design, Picture Completion, and Object Assembly. This suggests that, though the autism participants in all the contributing studies are verbal, they demonstrate comparable difficulties to schizophrenia in verbal abilities and show less severe difficulties with visuospatial abilities. To the extent that these social cognitive abilities rely upon visual perception and organization of nonsocial stimuli (26), ASD may demonstrate some advantages over schizophrenia in social cognition.

This pattern of cognitive performance differences was largely consistent across key demographic variables. The only meta-regression that reached statistical significance was the relationship between mean sample age and Digit Symbol Coding, a processing speed measure. Here, ASD showed better performance than schizophrenia with increasing age from late adolescence to middle adulthood, suggesting that the divergence in Digit Symbol Coding performance between ASD and schizophrenia becomes more pronounced with age. Notably, Digit Symbol Coding is the measure that most highly differentiates schizophrenia from controls of all neuropsychological measures (40). Autism demonstrates minimal age-related changes in WAIS measures of processing speed, including Digit Symbol Coding, from ages 6 through 39 (41). In contrast, schizophrenia demonstrates substantial declines in Digit Symbol Coding between late childhood (age 7-13) and middle adulthood (age 38) (42). Bearing in mind that the age ranges for these studies extend earlier into childhood, age-related changes in processing speed differences between ASD and schizophrenia may be attributable to stable

performance across age in autism and declining performance with age in schizophrenia.

Other than age-related changes in the difference between ASD and schizophrenia for Digit Symbol Coding, diagnostic comparisons for nonsocial cognition were not attributable to age, sex, intellectual disability, scale version, IQ, nor group differences in age and sex. Given the wide age range of the groups, with a mean age ranging from 16 to 41, and the diverse sex ratios, ranging from equal sex ratios to completely male, this suggests that similarities and differences in nonsocial cognitive performance are largely consistent from early through middle adulthood across sexes for these neurodevelopmental disorders. Notably, intellectual disability was not a significant moderator of the findings, supporting the generalizability of these diagnostic patterns of relative strengths and weaknesses in nonsocial cognition to individuals with substantial impairments in general cognitive ability. Furthermore, given that IQ did not differ significantly between groups within most studies and that IQ was not a significant moderator for any of the findings, the mean group differences in subtest performance likely reflect relative strengths and weaknesses in specific cognitive domains rather than differences in general cognitive ability.

Taken together, the magnitude of similarities and differences between ASD and schizophrenia in nonsocial cognition differs across domains, with differences being most obvious for visuospatial abilities and reasoning and problem-solving, and to a lesser extent, working memory and language. The current review extends prior literature comparing other cognitive domains between ASD and schizophrenia, notably, social cognition (12). In the current meta-analysis, we identified multiple nonsocial cognitive domains in which ASD and schizophrenia demonstrate significantly different performance levels. In contrast, ASD does not show significant differences from schizophrenia in social cognitive domains, as described in the most recent meta-analysis (12). It should be noted that three to eight studies contributed to each social cognitive domain analyzed in the prior meta-analysis (12), comparable to the sample sizes for the nonsocial cognitive measures analyzed in the current meta-analysis. However, a wide range of measures were consolidated for each social cognitive domain in the meta-analysis of social cognitive measures (12), whereas measures were analyzed separately across similar versions of a standardized cognitive battery in this meta-analysis of nonsocial cognitive measures, thereby reducing method heterogeneity and likely increasing our ability to detect group differences in nonsocial cognition. Indeed, here we found that ASD demonstrated better performance than schizophrenia for two visuospatial processing measures that comprise a social cognition factor (26). This further suggests that group differences in social cognitive performance may vary depending on whether the social cognitive measures used rely heavily on visuospatial processing abilities, which may have been a source of methodological heterogeneity in the prior meta-analysis of social cognition (12). Our findings therefore suggest the importance of examining not only social cognition, but also nonsocial cognition, to gain a fuller picture of cognitive functioning performance across ASD and schizophrenia.

Considerations

Overall, our findings emphasize the importance of examining nonsocial cognitive processes in addition to social cognitive processes across ASD and schizophrenia. Building upon this work, we may investigate whether these transdiagnostic similarities and differences in cognitive functioning may arise from shared biological processes and may be remediated by similar strategies (43). Despite the pathophysiological and treatment implications of our findings, certain limitations should be considered. In particular, measurement equivalence is constrained across WAIS versions, most notably due to the Flynn effect, whereby group mean IQ scores increase over time (44). Relevant to the scale versions that are most frequently used in the current study, the largest discrepancies in how a given group may perform across the WAIS-R (i.e. the second edition of the WAIS) and the WAIS-III are observed for timed subtests, including Object Assembly and Coding, whereas the smallest differences are observed for untimed subtests, including Digit Span and Information (45). The authors of the contributing studies generally did not report when data were collected in relation to the availability of the most recent scale version. However, given that the effect sizes that we meta-analyzed were based on the difference between ASD and schizophrenia groups *within* a WAIS subtest version rather than *across* WAIS subtest versions, to the extent that both groups are similarly impacted by measurement changes across scale versions, our results are unlikely to be systematically biased by measurement error to the Flynn effect and/or to other sources of measurement variance across WAIS versions (44, 46). This interpretation is further supported by our finding that scale version did not moderate mean group differences in cognitive performance. In addition, although each contributing study contributed multiple cognitive measures, the meta-analyses would benefit from more studies contributing to each measure. Because the WAIS does not include measures of visual or verbal memory, we were unable to examine cognitive functioning in these domains. Thus, this work may be further expanded upon by using transdiagnostically validated cognitive batteries that include measures of memory, such as the MATRICS Consensus Cognitive Battery (47).

We acknowledge additional considerations beyond measurement in interpreting our findings. Specifically, some studies included participants with high-functioning autism whereas other samples included participants with a range of autism severity. Likely due to the inclusion of verbal adults with ASD, the group mean IQ across the ASD groups in the meta-analyses is comparable to that of normative samples (i.e. with a mean score approximating 100 and standard deviation approximating 10). Our study inclusion criteria for the ASD group reflects the strong selection bias in autism research, where approximately 94% of participants with ASD do not have an intellectual disability for studies published in autism-specific journals in 2016, and only 2% of ASD participants in these studies are minimally or non-verbal (48). Along with this heterogeneity in severity, although ASD often co-occurs with other disorders, such as attention-deficit/hyperactivity disorder, the included studies did not account for these diagnoses. Finally, given the substantial differences

across the included studies in the clinical characterization of the groups, we were unable to examine clinical and functional moderators of group differences in nonsocial cognition. Our study therefore provides a rationale for recommending the use of consistently validated measures of cognitive ability, the inclusion of participants across the full range of verbal and intellectual abilities in ASD and schizophrenia, and the careful characterization of clinical features across ASD and schizophrenia.

Implications

In summary, ASD and schizophrenia demonstrate some overlapping and distinctive patterns of cognitive functioning, with similar performance on processing speed, attention, and verbal comprehension and ASD performing better than schizophrenia on working memory, language, and especially, visuospatial perception and reasoning. These findings are consistent with and substantially extend prior meta-analyses of case-control studies for ASD and schizophrenia (8, 9). Our findings thus highlight the importance of going beyond investigating social cognition in ASD and schizophrenia to characterize nonsocial cognition across these neurodevelopmental disorders. Ultimately, this review provides a launching point from which we can develop and adapt transdiagnostic strategies to bolster cognitive functioning across ASD and schizophrenia.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

SK contributed conception and design of the study, conducted the literature review, extracted the data, organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. SE provided substantive feedback on the analysis and interpretation of the results. All authors contributed to manuscript revision, read and approved the submitted version.

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Autistic Symptoms and Social Cognition Predict Real-World Outcomes in Patients With Schizophrenia

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Objective: Real-world functioning is a complex construct influenced by different factors. The impact of social cognition and autism spectrum disorder (ASD) symptoms on different aspects of the life of people with schizophrenia has been demonstrated independently, but it is unclear how these factors are related to functioning when considered concurrently. We hypothesized that ASD symptoms could play a major role in predicting real-world functioning in schizophrenia.

Methods: Existent databases from two studies (SCOPE Phase 3 and SCOPE Phase 5), in which a total of 361 patients (mean age 41.7 years; 117 females) were assessed with measures of symptom severity, neuro- and socio-cognitive abilities, functional capacity, social skills, and informant-reported real-world functioning outcomes, were analyzed.

Results: Active social avoidance, social skills, ASD symptoms, and emotion processing emerged as predictors of real-world interpersonal relationships. Cognitive performance, positive symptoms, and functional capacity emerged as predictors of real-world participation in daily activities. Cognitive performance, emotion processing, positive symptoms severity, and social skills emerged as predictors of real-world work outcomes.

Conclusion: Among other demographic, clinical, and functional capacity variables, increased ASD symptoms emerged as a significant predictor of poorer social relationships and may therefore represent a key factor in predicting real-world social functioning in schizophrenia.

Keywords: schizophrenia, autism spectrum disorder, social cognition, PANSS Autism Severity Score, real-world outcomes

INTRODUCTION

Background

The overlap between autism spectrum disorders (ASD) and schizophrenia spectrum disorders is a topic that has recently been of increasing interest and lately has been the focus of a growing body of literature, with data highlighting various similarities in pathophysiological, genetic, neuroimaging, and clinical characteristics between the two spectra (1, 2). Deficits in social interactions are considered one of the key features of ASD (3), and deficits in social cognition have been demonstrated both in patients with ASD (4, 5) and schizophrenia (6–8), with similar levels of impairment across disorders (9). Social cognition deficits have been associated also with older age, lesser education, poorer cognitive performance (10), and more severe functional impairment (11).

The presence of ASD features in patients with schizophrenia spectrum disorders has recently been investigated, leading to the development of specific instruments for the assessment of ASD symptoms in patients with schizophrenia (12). The PANSS Autism Severity Score (PAUSS) (13), a scale derived from the Positive and Negative Syndrome Scale (PANSS) (14), is one of such measures and has been shown to be able to evaluate ASD symptoms in schizophrenia patients with an accuracy comparable to that of more elaborate and time consuming tools (15). Being based on behavioral observation and symptoms severity, the PAUSS, rather than investigating "schizophrenic autism", a construct of more experiential nature (16–18), represents a valid and practical tool for the assessment of ASD features in patients diagnosed with schizophrenia in clinical settings (15).

Recent studies show that greater severity of ASD symptoms in patients with schizophrenia spectrum disorders predicts poorer performance on different social cognitive tests, both in the emotion processing and in the mental state attribution/theory of mind domains (19). Some authors have also hypothesized that schizophrenia patients with prominent ASD symptoms may represent a subpopulation with specific clinical characteristics (12), including poorer real-world functioning and greater impairments in the ability to judge the quality of their everyday functioning (20).

Impairment in real-world settings remains one of the most problematic issues that patients with schizophrenia have to face. These deficits are likely related to difficulties in various everyday functional skills, such as initiating and maintaining social relationships, entering and maintaining paid jobs, living independently in the community, and managing self-care, health-care, and basic financial resources (21, 22). Treatments that are effective in reducing the symptoms of schizophrenia do not consistently show a parallel improvement in real-world functioning (23), and the relationship between schizophrenia symptom severity and functioning is not linear: some patients with severe symptoms may function relatively well, while others with milder symptoms may show an important functional impairment (24). Thus, in order to understand functional impairment in schizophrenia, it is likely necessary to look beyond the impact of traditional psychotic symptoms. Cognitive impairment, reduction of functional capacity, and health status, as well as other factors, appear to have a considerable impact on the everyday functioning (25, 26). In addition, recent data demonstrate that social cognition has an important influence on functional outcomes in patients with schizophrenia, and may indeed be a central factor in determining real-world outcomes (27–29), particularly when combined with consideration of both social cognitive ability and self-assessments of that ability (30). Despite the identification of these contributors, a good portion of the variance in functional outcomes remains unaccounted for (31), suggesting that the search for determinants of outcomes should continue. Given that greater ASD symptoms in schizophrenia have been independently linked to poorer social cognition and poorer functioning, it is necessary to evaluate the importance of these factors when examined concurrently with each other and with other known predictors (e.g., cognitive impairment, etc.). Doing so could yield valuable information regarding those targets that should be prioritized in treatment efforts.

Aims of the Study

The aim of the present study was to identify the role of autism spectrum disorder symptoms, social cognitive performance, neurocognitive performance, functional capacity, and social skills in predicting real-world everyday outcomes in a sample of patients with schizophrenia spectrum disorders. Our primary hypothesis is that ASD symptoms will account for significant amounts of variance in outcomes and therefore represent an important and novel individual predictor of real-world functioning among individuals with schizophrenia. Since a possible partial overlap between negative symptoms severity and ASD features investigated by the PAUSS might be observed, active social avoidance was also included as an indirect measure of negative symptomatology, and all the analyses were performed also considering only patients with a low level of active social avoidance (PANSS G16 ≤ 3).

METHODS

Participants

Data analyzed in the present study were obtained by merging the datasets originally elaborated for two previously published studies (32, 33). In both of these studies, patients diagnosed with schizophrenia or schizoaffective disorders were assessed with clinical, psychosocial, neuro-cognitive and social-cognitive measures. These studies are part of a larger research project, the Social Cognition Psychometric Evaluation (SCOPE). Data included from the first dataset were gathered from the third phase of the whole research project, SCOPE Phase 3 (32), while data included from the second dataset were gathered for the fifth and final part of the project, SCOPE Phase 5 (33). For the SCOPE 3 study a total of 179 patients were recruited at two sites, the Southern Methodist University and the Miami Miller School of Medicine, while the SCOPE 5 study included a total of 218 patients recruited at three sites, the University of Texas at Dallas,

the University of Miami Miller School of Medicine, and the University of North Carolina at Chapel Hill.

Both studies used identical inclusion and exclusion criteria. To be included in the studies, patients had to satisfy the following criteria: (I) diagnosis of Schizophrenia or Schizoaffective Disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (34), confirmed with the Mini International Neuropsychiatric Interview (35) and the Structured Clinical Interview for DSM Disorders Psychosis Module (36), (II) patients had to be clinically stable, without any hospitalization occurring in the previous two months, without any change in the medication regimen for a minimum of 6 weeks, and without any medication dosage change for a minimum of 2 weeks.

Patients were excluded from the studies if they presented one of the following: (I) presence or history of pervasive developmental disorder, including ASD, or of mental retardation with an IQ < 70, as defined by the diagnostic criteria reported in the DSM-IV, (II) presence or history of any medical or neurological illness that could have a negative impact on the functioning of the central nervous system, including epilepsy and seizures, neoplasms of the central nervous system structures, inflammatory or autoimmune disorders affecting the central nervous system, (III) presence of visual or hearing impairment severe enough to limit the participation of the patients in the assessment, (IV) no or very limited proficiency with English language, (V) presence of substance abuse in the past month, (VI) presence of active substance dependence in past six months.

A number of different tests were administered to asses social cognition in the SCOPE 3 and the SCOPE 5 studies. Only the measures of social cognition included in both studies were utilized in the current analyses. Additionally, a small number of patients participated in both SCOPE 3 and SCOPE 5. To maintain the independence of the data, any SCOPE 5 data from repeat participants were removed from the final sample. The resulting sample size is therefore smaller than the sum of the number of patients recruited in the two SCOPE studies.

Measures

Social Cognition

For the assessment of social cognition, the following tests, used in both SCOPE 3 and SCOPE 5, were used for this study and included in the analyses. The *Bell Lysaker Emotion Recognition Task* (BLERT) (37) is a test measuring the ability to recognize seven basic emotional states: happiness, sadness, fear, disgust, surprise, anger, or no emotion. A series of 21 short video clips, presenting a male actor providing dynamic facial, vocal-tonal, and upper-body movement cues, is presented to the participant, who has to identify the emotion represented by the actor after each videoclip. The total number of correctly identified emotions represents the final score, ranging from 0 to 21.

The *Penn Emotion Recognition Text* (ER-40) (38) is a test composed of 40 color photographs of static faces. Each picture expresses one of four basic emotions (happiness, sadness, anger, or fear) or a neutral expression, and are balanced for model's sex, age, and ethnicity. For each emotion, four high-intensity and four low-intensity expressions are provided. The total number of correctly identified emotions represents the final score, ranging from 0 to 40.

The *Reading the Mind in the Eyes Test* (Eyes) (39) is a test designed to assess the ability to understand the mental state of other people form the expression of the eye region of the face. A set of 36 pictures of the eye region of different faces is presented to the participants, who have to identify the mental state presented among four different choices. The number of correct answers represents the final score, ranging from 0 to 36.

The *Awareness of Social Inferences Test, Part 3* (TASIT) (40) is a test assessing the capacity to detect and identify social exchanges, such as lies and sarcasm. Participants are shown a series of videos representing everyday social interactions and have to answer four standardized question concerning the intentions, beliefs, and meaning of the speakers and their interactions. The number of correct answers represents the final score, ranging from 0 to 64.

The *Hinting Task* (Hinting) (41) is a test assessing the ability to infer the true intent of indirect speech. Ten short passages, depicting an interaction between two fictional characters, are read by the experimenter, and each passage ends with one of the two characters dropping a hint to the other one. The participant is asked to explain what the character dropping the hint truly meant. If an incorrect answer is provided by the participant, a second hint is presented, allowing the possibility to earn partial credit. The total score ranges from 0 to 20.

Neurocognition

The neurocognitive assessment was composed of a subset of the tests from the MATRICS Consensus Cognitive Battery (MCCB) (42): Trail Making Test—Part A (TMT-A); BACS Symbol Coding; BACS Category Fluency (Animal Naming); Letter–Number Span; and Hopkins Verbal Learning Test—Revised (HVLT-R). These test are designed to evaluate different cognitive domains that appear to be impaired in patients with schizophrenia (43) such as processing speed, working memory, and verbal memory (44–46). Following the recommendation of the developers of the battery, a global composite score was calculated by averaging the t-scores of all the tests (47). Patients' premorbid IQ was also taken into account and was assessed with the Wide Range Achievement Test-3 Reading subscale (WRAT-3) (48). The WRAT-3 Standard Score was included in the analyses.

Clinical Symptoms

All patients were evaluated with the Positive And Negative Syndrome Scale (PANSS) (14). The PANSS Autism Severity Score (PAUSS), a scale derived from the PANSS for the measure of autistic symptoms in patients with schizophrenia (13), was used and included in the analyses. The PAUSS is calculated by summing eight different PANSS items: N1 ("blunted affect"), N3 ("poor rapport"), N4 ("social withdrawal"), N5 ("difficulties in abstract thinking"), N6 ("lack of spontaneity and flow of conversation"), N7 ("stereotyped thinking"), G5 ("mannerism"), and G15 ("preoccupation").

PANSS item G16, "active social avoidance", was also used and included in the analyses as a measure of potential social deficits. This PANSS item does not contribute to the PAUSS total score.

The PANSS positive subscale was also used and included in the analyses, based on the previous results of analyses of the PANSS (49). The PANSS positive subscale is composed of the sum of the following items: P1 ("delusions"), P2 ("conceptual disorganization"), P3 ("hallucinations"), P4 ("excitement"), P5 ("grandiosity"), P6 ("suspiciousness/persecution") and P7 ("hostility").

Functional Skills

Functional capacity was assessed with the UCSD Performance-Based Skills Assessment, Brief (UPSA-B) (50). The UPSA-B is a brief and widely used scale that assesses financial and communication skills involved in community tasks. The total score ranges from 0 to 100.

Social competence was assessed with the Social Skills Performance Assessment (SSPA) (51). The SSPA is a role-play measure in which participants have to start and maintain a conversation in two different social situations: meeting a new neighbor and negotiating with a landlord to fix a leak. Roleplay sessions are recorded and coded by an expert rater blind to participant diagnosis. The following variables are rated during the evaluation: interest, fluency, clarity, focus, overall abilities, and social appropriateness for both sessions, and negotiation ability and persistence are also rated for the landlord session only. The final total score is the mean score across both role-plays, ranging from 1 to 5.

Real-World Outcomes

Finally, real-world functional outcomes were assessed with the Specific Level of Functioning Scale (SLOF) (52). The SLOF is an informant-rated measure and, in its 24-item form, is composed of three subscales, one for social functioning (interpersonal relationships) and two for community-living skills (participation in activities and work skills). Informants were identified by the participants and were either high-contact clinicians, close friends, or family members. Each item is rated from 1 to 5, with higher scores indicating better functioning, and the final score of every subscale is the mean of the scores of every item composing the scale. The SLOF has been found to be a reliable and valid instrument to assess real-world functioning in patients with schizophrenia, with good construct validity and internal consistency (22, 53).

Statistical Analysis

To identify predictors of real-world functional outcome, multivariate linear regression analyses were performed, including the Interpersonal Relationships, Activities, and Work subscales of the SLOF as dependent variables, and demographic variables, PANSS positive symptoms score, PAUSS total score, PANSS item G16 ("Active Social Avoidance"), social cognitive performance, global cognitive composite score, UPSA-B score, and SSPA score as potential predictors. Potential predictors were included in the regression if they were found to be significant in univariate exploratory analyses, performed by correlating continuous variables with the dependent variables, and by using t-test for dichotomous potential predicting variables (*i.e.*, sex). Parametric statistics were adopted regardless of the distribution of the data due to the large size of the investigated sample. This conservative approach was used in order to avoid false negatives (or type II errors) (54, 55). Multiple linear regressions were conducted using a stepwise procedure. As the number of potential predictors in each model was lower than one for every twenty observed subjects, the number of the included predictors was considered appropriate (56, 57).

As active social avoidance has been shown to be a strong predictor of social competence and social functioning in patients with schizophrenia (28, 58), high levels of active social avoidance have been considered a possible confounder that could override the influence of other variables in the analyses. Therefore, all the analyses were also performed on a subgroup of the whole sample composed of patients with a score on PANSS G16 ("active social avoidance") ≤3, numbering a total of 296 patients and representing 81% of the total sample.

Statistical analyses were performed using SPSS 15.0 software. P-values < 0.05 (2-tailed) were considered significant.

RESULTS

Full Sample

Correlational Analyses

The characteristics of the sample are presented in **Table 1**. The univariate correlations are shown in **Table 2**. Potential predictors of better real-world interpersonal relationships outcomes (as measured by SLOF: Interpersonal relationships subscale) that emerged at the univariate analyses were: more education years, higher premorbid IQ (WRAT-3 standard score), better neurocognitive performance (Neurocog), better functional capacity (UPSA-B), better social skills (SSPA), less severe ASD features (PAUSS), less severe positive symptoms (PANSSpos), less severe active social avoidance (PANSS-G16), better emotion processing performance (as measured by both BLERT and ER-40), and better theory of mind (TASIT).

Potential predictors of better real-world participation in daily activities outcomes (as measured by SLOF: Activities subscale) that emerged at the univariate analyses were: more education years, higher premorbid IQ (WRAT-3 standard score), better neurocognitive performance (Neurocog), better functional capacity (UPSA-B), better social skills (SSPA), less severe ASD features (PAUSS), less severe positive symptoms (PANSSpos), less severe active social avoidance (PANSS-G16), better emotion processing performance (as measured by both BLERT and ER-40), and better theory of mind (as measured by both HINTING and TASIT).

Potential predictors of better real-world work outcomes (as measured by SLOF: Work subscale) that emerged at the univariate analyses were: younger age, more education years, higher premorbid IQ (WRAT-3 standard score), better neurocognitive performance (Neurocog), better functional capacity (UPSA-B), better social skills (SSPA), less severe ASD

features (PAUSS), less severe positive symptoms (PANSSpos), better emotion recognition skills (as measured by both BLERT and ER-40) and better theory of mind (as measured by EYES, HINTING and TASIT). All statistically significant relationships across the three outcomes represented small to medium effect sizes.

No differences between males and females emerged in any of the SLOF subscales analyzed at the univariate t-tests (**Table 3**).

Regression Analyses

Table 4 shows the individual predictors of real-world functional outcomes. Individual predictors of real-world social functioning, as measured by the SLOF Interpersonal Relationships subscale, were less severe Active Social Avoidance (PANSS-G16) ($p < 0.001$), better social skills (SSPA) ($p = 0.011$), less severe ASD symptoms (PAUSS) ($p < 0.001$), and better emotion processing performance (BLERT) ($p = 0.001$) (Model: $F = 33.755$, $R^2 = 0.290$, $p < 0.001$).

Real-world community living skills, as measured by the SLOF Activities subscale, were predicted by better global cognitive performance (Neurocog) ($p = 0.003$), less severe positive symptoms severity (PANSSpos) ($p = 0.029$), and better functional capacity (UPSA-B) ($p= 0.039$) (Model: $F = 11.267$, $R^2 = 0.093$, $p < 0.001$).

Finally, real-world work outcomes, as measured by the SLOF Work subscale, were predicted by better global cognitive performance (Neurocog) ($p < 0.001$), better emotion processing performance (BLERT) ($p = 0.001$), less severe positive symptoms (PANSSpos) ($p = 0.001$), and better social skills (SSPA) ($p = 0.044$) (Model: $F = 21.224$, $R^2 = 0.205$, $p < 0.001$).

Low Active Social Avoidance Subsample

Correlational Analyses

Univariate correlations for patients with low active social avoidance, as identified by PANSS item G16 (PANSS-G16 ≤ 3; n = 296), are shown in **Table 5**. In this subgroup of patients, potential predictors of better real-world interpersonal relationships outcomes (as measured by SLOF: Interpersonal relationships subscale) that emerged at the univariate analyses were: more education years, better neurocognitive performance (Neurocog), better functional capacity (UPSA-B), better social skills (SSPA), less severe ASD features (PAUSS), less severe positive symptoms (PANSSpos), less severe active social avoidance (PANSS-G16), better emotion processing performance (as measured by both BLERT and ER-40), and better theory of mind (as measured by EYES, HINTING and TASIT).

In patients with low active social avoidance, potential predictors of better real-world participation in daily activities outcomes (as measured by SLOF: Activities subscale) that emerged at the univariate analyses were: more education years, better neurocognitive performance (Neurocog), better functional capacity (UPSA-B), better social skills (SSPA), less severe ASD features (PAUSS), less severe positive symptoms (PANSSpos), better emotion processing performance (as measured by both BLERT and ER-40), and better theory of mind (TASIT).

TABLE 1 | Characteristics of the Sample.

Variable	N, Mean ± SD
N	361
M:F	244:117
Age (Years)	41.7 ± 12.0
Education (Years of Education)	12.9 ± 2.3
WRAT-3 Standard Score (Premorbid IQ)	94.4 ± 15.2
PAUSS total score (Autism)	15.3 ± 5.4
PANSS Positive Score (Positive Symptoms Severity)	16.14 ± 5.4
Active Social Avoidance (PANSS-G16)	2.2 ± 1.4
Global Cognitive Composite Score (t-score)	38.2 ± 7.1
UPSA-B (Functional Capacity)	69.7 ± 14.1
SSPA (Social Skills)	4.1 ± 0.5
BLERT (Social Cognition–Emotion Processing)	13.5 ± 4.0
ER-40 (Social Cognition–Emotion Processing)	30.2 ± 5.1
EYES (Social Cognition–Mental State Attribution)	20.6 ± 5.4
HINTING (Social Cognition–Mental State Attribution)	13.3 ± 3.8
TASIT (Social Cognition–Mental State Attribution)	44.4 ± 7.5

In patients with low active social avoidance, potential predictors of better real-world work outcomes (as measured by SLOF: Work subscale) that emerged at the univariate analyses were: more education years, higher premorbid IQ (WRAT-3 standard score), better neurocognitive performance (Neurocog), better functional capacity (UPSA-B), better social skills (SSPA), less severe ASD features (PAUSS), less severe positive symptoms (PANSSpos), better emotion processing performance (as measured by both BLERT and ER-40), and better theory of mind (as measured by EYES, HINTING and TASIT). As in the full sample, all statistically significant relationships across the three outcomes represented small to medium effect sizes.

No differences between males and females emerged in any of the SLOF subscales analyzed at the univariate t-tests in patients with low active social avoidance (**Table 6**).

Regression Analyses

Table 7 shows the individual predictors of real-world functional outcome in this subgroup of patients. In patients with low active social avoidance, individual predictors of real-world social functioning, as measured by the SLOF Interpersonal Relationships subscale, were less severe ASD symptoms (PAUSS) ($p < 0.001$), better emotion processing performance (BLERT) ($p < 0.001$), less severe Active Social Avoidance (PANSS-G16) ($p < 0.001$), better social skills (SSPA) ($p = 0.037$) (Model: $F = 22.473$, $R^2 = 0.251$, $p < 0.001$).

In patients with low active social avoidance, real-world community living skills, as measured by the SLOF Activities

TABLE 2 | Correlations between SLOF scales and demographic, cognitive, clinical, and social cognitive variables.

Variables	SLOF Inf: Interpersonal Relationships	SLOF Inf: Activities	SLOF Inf: Work
Age	–0.053	0.023	–0.142**
	(p = 0.021)	(p = 0.666)	(p =0.007)
Education Years	0.143**	0.160**	0.225**
	(p = 0.007)	(p = 0.002)	(p = < 0.001)
Premorbid IQ	0.121*	0.120*	0.236**
(WRAT-3 Standard Score)	(p = 0.022)	(p = 0.023)	(p = < 0.001)
Neurocog	0.191**	0.248**	0.344**
	(p = < 0.001)	(p = < 0.001)	(p = < 0.001)
UPSA-B	0.155**	0.219**	0.293**
	(p = 0.005)	(p = < 0.001)	(p = < 0.001)
SSPA	0.286**	0.176**	0.287**
	(p = < 0.001)	(p = 0.001)	(p = < 0.001)
PAUSS	–0.387**	–0.114*	–0.184**
	(p = < 0.001)	(p = 0.031)	(p = < 0.001)
PANSSpos	–0.204**	–0.149**	–0.191**
	(p = < 0.001)	(p = 0.005)	(p = < 0.001)
PANSS-G16	–0.414**	–0.104*	–0.095
	(p = < 0.001)	(p = < 0.049)	(p = < 0.071)
BLERT	0.221**	0.140**	0.303**
	(p = < 0.001)	(p = 0.008)	(p = < 0.001)
ER40	0.122*	0.119*	0.181**
	(p = 0.021)	(p = 0.024)	(p = 0.001)
EYES	0.103	0.076	0.218**
	(p = 0.052)	(p = 0.149)	(p = < 0.001)
HINTING	0.095	0.122*	0.203**
	(p = 0.073)	(p = 0.021)	(p = < 0.001)
TASIT	0.145**	0.159**	0.327**
	(p = 0.006)	(p = 0.003)	(p = < 0.001)

Pearson's r (p values).
**p < 0.05.*
***p < 0.01.*

subscale, were predicted by better global cognitive performance (Neurocog) ($p < 0.001$), and less severe positive symptoms severity (PANSSpos) ($p = 0.024$) (Model: $F = 10.579$, $R^2 = 0.073$, $p < 0.001$).

Finally, in this subgroup of patients, real-world work outcomes, as measured by the SLOF Work subscale, were predicted by better global cognitive performance (Neurocog) ($p < 0.001$), better emotion processing performance (BLERT) ($p < 0.001$) and less severe positive symptoms (PANSSpos) ($p = 0.011$) (Model: $F = 20.720$, $R^2 = 0.188$, $p < 0.001$).

DISCUSSION

The current study examined multiple potential predictors of real-world functioning in schizophrenia spectrum disorders and specifically sought to determine whether increased ASD symptoms would emerge as an independent and important contributor to functioning even when considering the influence of well-established predictors such as cognition and social cognition. Different clinical, neurocognitive, and social-cognitive variables emerged as individual predictors of real-world functioning, with specific factors predicting different functioning outcomes.

In particular, ASD symptoms emerged as predictors of real-world social functioning. This finding confirms the hypothesis that increased ASD symptoms could play an important role in the poorer social relationships experienced by patients with schizophrenia spectrum disorders, not only for their influence on social cognitive abilities, as previously demonstrated (19), but also as an independent individual predictor. In contrast, ASD symptoms did not emerge as individual predictors of real-life

TABLE 3 | Functional outcome differences between male and female patients (t-test).

SLOF scale	Males (mean ± SD)	Females (mean ± SD)	t-test p	Cohen's d
SLOF: Interpersonal Relationships	3.32 ± 0.84	3.33 ± 0.91	0.891	0.011
SLOF: Activities	4.52 ± 0.82	4.49 ± 0.79	0.758	0.037
SLOF: Work	3.72 ± 0.82	3.75 ± 0.83	0.738	0.036

TABLE 4 | Predictors of functional outcome (Stepwise linear multivariate regressions).

Dependent variables	Individual predictors	Standardized Beta	T	P	Adj.R^2	Adj. R^2 Change
SLOF:	PANSS-G16	–0.354	–7.276	<0.001	0.164	
Interpersonal Relationships	SSPA	0.138	2.552	0.011	0.236	0.072
	PAUSS	–0.189	–3.526	<0.001	0.261	0.025
	BLERT	0.158	3.210	0.001	0.281	0.020
	Model F = 33.755, R^2 = 0.290, Adj. R^2 = 0.281			<0.001		
SLOF:	Neurocog	0.183	3.005	0.003	0.061	
Activities	PANSSpos	–0.116	–2.195	0.029	0.075	0.014
	UPSA-B	0.127	2.071	0.039	0.084	0.009
	Model F = 11.267, R^2 = 0.093, Adj. R^2 = 0.084			<0.001		
SLOF:	Neurocog	0.221	3.941	<0.001	0.119	
Work	BLERT	0.192	3.464	0.001	0.158	0.039
	PANSSpos	–0.166	–3.343	0.001	0.187	0.029
	SSPA	0.111	2.023	0.044	0.195	0.008
	Model F = 21.224, R^2 = 0.205, Adj. R^2 = 0.195			<0.001		

community living skills or working skills in the regression analyses despite emerging as potential predictors in the univariate analyses. This suggests a stronger impact of ASD symptoms on interpersonal relationships and social outcomes, than on other real-world functioning areas that may be less socially relevant.

Lower active social avoidance, as measured by the PANSS item G-16, emerged as another individual predictor of real-world social functioning, but not of real-life community living skills or working skills. The decision to use this PANSS item, was due to the fact that it's included in the PANSS negative subscale derived from PANSS factor analysis (49), but not in the PAUSS (13), so it was used as a measure of negative symptomatology, outside ASD symptoms. This helped to further corroborate the notion of a specific predicting role of ASD symptoms on interpersonal relationship skills.

TABLE 5 | Correlations between SLOF scales and demographic, cognitive, clinical, and social cognitive variables in patients with Low PANSS-G16 (3 or lower).

Variables	SLOF Inf: Interpersonal Relationships	SLOF Inf: Activities	SLOF Inf: Work
Age	–0.025	0.068	–0.109
	(p = 0.671)	(p = 0.245)	(p =0.062)
Education Years	0.133*	0.119*	0.225**
	(p = 0.023)	(p = 0.042)	(p = < 0.001)
Premorbid IQ	0.083	0.061	0.223**
(WRAT-3 Standard Score)	(p = 0.157)	(p = 0.301)	(p = < 0.001)
Neurocog	0.231**	0.232**	0.345**
	(p = < 0.001)	(p = < 0.001)	(p = < 0.001)
UPSA-B	0.164**	0.202**	0.279**
	(p = 0.006)	(p = 0.001)	(p = < 0.001)
SSPA	0.323**	0.201**	0.291**
	(p = < 0.001)	(p = 0.001)	(p = < 0.001)
PAUSS	–0.419**	–0.142*	–0.164**
	(p = < 0.001)	(p = 0.015)	(p = 0.005)
PANSSpos	–0.154**	–0.144*	-0.144*
	(p = 0.008)	(p= 0.014)	(p= 0.014)
PANSS-G16	–0.292**	–0.047	0.056
	(p = < 0.001)	(p = 0.418)	(p = 0.339)
BLERT	0.255**	0.124*	0.304**
	(p = < 0.001)	(p = 0.034)	(p = < 0.001)
ER40	0.171*	0.125*	0.189**
	(p = 0.003)	(p = 0.033)	(p =0.001)
EYES	0.124*	0.081	0.222**
	(p = 0.033)	(p = 0.166)	(p = < 0.001)
HINTING	0.151*	0.104	0.190**
	(p = 0.010)	(p = 0.076)	(p = < 0.001)
TASIT	0.172**	0.146*	0.313**
	(p = 0.003)	(p = 0.012)	(p = < 0.001)

*Pearson's r (p values). *p < 0.05.*
***p < 0.01.*

TABLE 6 | Functional outcome differences between male and female patients (t-test) in patients with Low PANSS-G16 (3 or lower).

SLOF scale	Males (mean ± SD)	Females (mean ± SD)	t-test p	Cohen's d
SLOF: Interpersonal Relationships	3.42 ± 0.83	3.55 ± 0.89	0.236	0.151
SLOF: Activities	4.56 ± 0.81	4.51 ± 0.80	0.576	0.062
SLOF: Work	3.78 ± 0.83	3.79 ± 0.86	0.984	0.011

Emotion processing, a domain of social cognition, as measured by the BLERT, emerged as a predictor of both social functioning and working skills. This finding confirms the hypothesis regarding the role of social cognition in influencing real-world functioning in patients with schizophrenia (27). In particular, deficits in social cognition appear to impact not only social functioning, but also working performance, a fact already demonstrated (29).

Moreover, among the different social cognitive measures employed, assessing the domains of both emotion processing and mental state attribution, only the BLERT task (emotion processing) emerged as a predictor of functional outcomes. This also confirms the utility of the BLERT among the different tests available for the assessment of social cognitive abilities in patients with schizophrenia: indeed, the SCOPE studies already identified the BLERT as one of the key social cognitive tasks available and recommended its use in the context of clinical research, as it also shows good test–retest reliability, limited potential for floor and ceiling effects, high practicality, and good tolerability for the patient (32, 33).

Global cognitive performance was linked to community-living outcomes, both in the participation of activities and in working skills. This finding is in line with those already reported in literature (25). However, global neurocognitive performance did not predict real-world social functioning, further underlying the notion that specific functioning domains are differentially predicted by neuro- and social-cognitive abilities. In a similar way, positive symptom severity predicted both work abilities and participation in daily activities, but not social outcomes, highlighting a more specific impact of positive symptom severity on less social real-world functioning outcomes.

Social skills, as evaluated by the roleplay in the SSPA, predicted both real-world social and working outcomes, whereas functional capacity (UPSA-B) predicted real-world participation in activities only. The role of social skills in determining real-world outcomes has been already demonstrated (28) as has the link between functional capacity and real-world community-living skills (21). The fact that both social skills and social cognition emerged as predictors not only of social, but also of working outcomes underlines the impact of these abilities on different aspects of functioning and may thus represent a key factor determining global outcomes in patients with schizophrenia.

When comparing the different linear regression models, more variance was explained for interpersonal relationships (Adjusted $R^2 = 0.281$) than participation in daily activities (Adjusted $R^2 = 0.084$) and working skills (Adjusted $R^2 = 0.195$). This could be due to a more direct relationship between social functioning and various explored potential predictors, in particular ASD symptoms and social cognitive performance. A considerable portion of variance remained to be explained, suggesting that other factors besides those investigated in this study could contribute to real-world outcomes. However, this was an expected observation, as real-world functioning is a complex construct to which many different elements may contribute (25).

Considering patients with low levels of active social avoidance, predictors of real-world social functioning did not differ in general from those found in the analysis performed on the whole sample. However, in these patients, representing a large proportion of the sample (81%), ASD features and social cognitive performance showed an even more prominent role as predictors, underlining their important function as determinants of real-world social functioning, when taking into account negative symptomatology.

This study has limitations. The social cognition measures available measured only two of the four recognized domains of

TABLE 7 | Predictors of functional outcome in patients with Low PANSS-G16 (3 or lower) (Stepwise linear multivariate regressions).

Dependent variables	Individual predictors	Standardized Beta	T	P	Adj. R^2	Adj. R^2 Change
SLOF:	PAUSS	–0.249	–3.890	<0.001	0.165	
Interpersonal Relationships	BLERT	0.201	3.576	<0.001	0.206	0.041
	PANSS-G16	–0.191	–3.304	0.001	0.230	0.024
	SSPA	0.129	2.094	0.037	0.240	0.010
	Model F = 22.473, R^2 = 0.251, Adj. R^2 = 0.240			<0.001		
SLOF:	Neurocog	0.233	3.970	<0.001	0.052	
Activities	PANSSpos	–0.133	–2.267	0.024	0.066	0.012
	Model F = 10.579, R^2 = 0.073, Adj. R^2 = 0.066			<0.001		
SLOF:	Neurocog	0.257	4.285	<0.001	0.120	
Work	BLERT	0.230	3.828	<0.001	0.162	0.042
	PANSSpos	–0.141	–2.558	0.011	0.179	0.017
	Model F = 20.702, R^2 = 0.188, Adj. R^2 = 0.179			<0.001		

social cognition, with no tasks assessing attributional style/bias and social perception. The psychometric proprieties of available measures for these two social cognitive domains are not completely satisfactory, and no test is currently recommended for use in clinical research settings (33). Moreover, attributional style also emerged as separate from other socio-cognitive skills in subjects diagnosed with schizophrenia in a recent factor analysis (59).

The SCOPE studies, from which the database for this study was derived, were not designed and conducted with the specific objective of assessing the role of potential predictors in determining real-world outcomes, or to specifically investigate ASD features in patients with schizophrenia spectrum disorders. Therefore, some aspects of global real-world functioning, included in the SLOF, such as physical functioning or self-care skills, were not assessed.

Finally, as the PAUSS scale includes various items from the PANSS negative subscale, only indirect measures of negative symptomatology, such as active social avoidance, could be included in the analyses. Further differentiating the role of negative symptoms severity and ASD features in influencing cognitive and functional outcomes of schizophrenia patients represents an important issue that should be addressed in future studies.

Nonetheless, the findings of the present study support the role of ASD features in influencing real-world social outcomes in patients with schizophrenia spectrum disorders, demonstrating that increased ASD symptoms are related to poorer social outcomes. The current findings also confirm the central role of social cognition in determining different aspects of global functioning. Future research should continue to explore the impact of ASD symptoms in patients with schizophrenia spectrum disorder, considering the hypothesis that patients with prominent ASD features could represent a particular subpopulation, with specific clinical, neuro- and social cognitive and functioning characteristics, with possible specific illness trajectories.

DATA AVAILABILITY STATEMENT

The datasets used in this study are available from Dr. Philip Harvey at the following e-mail address: pharvey@miami.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics Committees at the University of Miami, University of Texas at Dallas, and the University of North Carolina at Chapel Hill. The University of Miami IRB has agreed the current analyses are exempt from review as human subjects because of the de-identified nature of the data. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PH designed the project, reviewed and discussed the data and statistical analyses and the final version of the paper. AP and DP participated in the design of the study. GN prepared the database and participated in the analyses. GD participated in the analyses and wrote the paper. AV participated in the design of the project and discussion of the data and manuscript. All authors contributed to and approved the final manuscript.

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Machine Learning for Differential Diagnosis Between Clinical Conditions With Social Difficulty: Autism Spectrum Disorder, Early Psychosis, and Social Anxiety Disorder

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Differential diagnosis in adult cohorts with social difficulty is confounded by comorbid mental health conditions, common etiologies, and shared phenotypes. Identifying shared and discriminating profiles can facilitate intervention and remediation strategies. The objective of the study was to identify salient features of a composite test battery of cognitive and mood measures using a machine learning paradigm in clinical cohorts with social interaction difficulties. We recruited clinical participants who met standardized diagnostic criteria for autism spectrum disorder (ASD: n = 62), early psychosis (EP: n = 48), or social anxiety disorder (SAD: N = 83) and compared them with a neurotypical comparison group (TYP: N = 43). Using five machine-learning algorithms and repeated cross-validation, we trained and tested classification models using measures of cognitive and executive function, lower- and higher-order social cognition and mood severity. Performance metrics were the area under the curve (AUC) and Brier Scores. Sixteen features successfully differentiated between the groups. The control versus social impairment cohorts (ASD, EP, SAD) were differentiated by social cognition, visuospatial memory and mood measures. Importantly, a distinct profile cluster drawn from social cognition, visual learning, executive function and mood, distinguished the neurodevelopmental cohort (EP and ASD) from the SAD group. The mean AUC range was between 0.891 and 0.916 for social impairment versus control cohorts and, 0.729 to 0.781 for SAD vs neurodevelopmental cohorts. This is the first study that compares an extensive battery of neuropsychological and self-report measures using a machine

learning protocol in clinical and neurodevelopmental cohorts characterized by social impairment. Findings are relevant for diagnostic, intervention and remediation strategies for these groups.

Keywords: autism spectrum disorder, cognition, differential diagnosis, early psychosis, machine learning, social anxiety disorder

INTRODUCTION

Machine learning (ML) paradigms have facilitated the evaluation of complex datasets (1, 2) and provide a dynamic framework to enhance comparisons between groups that may share neurodevelopmental, clinical or cognitive profiles (3). In contrast to the traditional multiple regression methods, the ML algorithms are also capable of including many input variables with relatively smaller sample sizes (4, 5) and can handle both linear and non-linear interactions between variables. In medicine and psychology, the resultant algorithms have led to insights in clinical classification within (6) and between clinical cohorts (7), transdiagnostic subtyping of mental health symptoms (8) and comparative lifetime health outcomes (9). Such research may contribute to improved profiling of cohorts such as Schizophrenia (SCH) and Autism Spectrum Disorder (ASD) given shared genetic liability (10) and theorized common etiologies associated with social cognition (11) and executive function (EF) (12) processes.

The clinical sub-groups of SCH and ASD have drawn much debate about similarities and differences that might exist between the two diagnoses (13, 14). There is considerable empirical support of shared genetic, neurocognitive, and behavioral pathways between SCH and ASD (15–17). In both, co-morbidities appear higher than expected population outcomes (18) and impairments in cognitive function appear similarly in domains of social cognition (19) and EF (20). For ASD, diagnosis may be made as early as 18 months of age, however a proportion is diagnosed in adolescence/adulthood (21). The developmental course of psychosis is different, with a slow progression beginning with social withdrawal and early psychosis (EP) (22) that typically begins in later adolescence and early adulthood. In these cases, a third of people who develop EP will go on to develop SCH (23). There has been limited research exploring cognitive markers that may assist differential diagnosis. Such comparisons are particularly useful in early adulthood prior to the chronic manifestation of SCH symptoms to permit early differentiation of these disorders.

In this study we adopted the cognitive domains framework outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (24). The DSM-5 (24) defines six cognitive domains as key domains for the assessment of neurocognitive disorders. These are complex attention, EF, learning and memory, language, perceptual–motor function, and social cognition. Within this framework complex attention refers to the processes of sustained attention (capacity to maintain attention on a discrete task over prolonged period), divided attention (focusing on two tasks simultaneously), selective attention (focusing on a specific task and ignoring others) and information processing speed. While acknowledging the considerable debate on the conceptualization of executive function (EF) (25, 26), research presented in this paper adopts the fractionated view of EF as noted in the DSM-5. Specifically, EF is characterized by discrete domains representing higher order cognitive processes. The EF domains include mental/cognitive flexibility (ability to shift between concepts), inhibition (ability to inhibit a previously learned or prepotent response), planning (ability to execute a sequence of actions so that a desired goal is achieved) and working memory (ability to store and dynamically manipulate information in temporary STM) (27).

In studies of complex attention, impairment in sustained attention has been reported in ASD (28) and on a composite battery of attention measures in EP (29). A recent comparison between EP and ASD (20) showed the former was significantly more impaired on attentional processes. Complex or top/down attentional processes have been shown to be guided by frontal neural circuitry (30), impairment noted above may reflect atypical processing in the prefrontal cortex in the ASD and EP groups, respectively.

Empirical findings in cognitive domains—other than EF and social cognition—are mixed and, in part dependent on the modality studied (verbal versus visuospatial). Studies with participants diagnosed with ASD have reported impaired performance in verbal learning (31), visuospatial short term memory (STM) (28), whilst others, noted superior visual (32) and comparable verbal STM (31, 32). In populations with psychosis, verbal STM and learning have also been noted to be impaired (12, 33, 34) but there have been mixed results for visual learning (33, 34). A study examining language domain measures in ASD with a neurotypical comparison group (35) found no differences between them. For the perceptual-motor domain difficulties have been reported for EP (34) and ASD (36).

There is, a larger body of research examining social cognition and EF domains and their contribution to symptoms and disability in each of the ASD and EP cohorts. Lower- and higher-order social cognition (37) performance has been shown to be reduced in participants diagnosed with either EP or ASD. These include performance on tests of emotion recognition (38, 39) and theory of mind tasks (34, 40, 41). Reduced performance on neurocognition has been reported for EP (22, 42) and ASD (36, 43, 44). Specifically, in relation to EF, impairment in EP has been reported in attentional shifting (20) with mixed findings across other domains including working memory and abstract thinking (33, 45). A recent meta-analysis in ASD across six EF domains (44) points to broad executive

problems, likely characterized by aberrant neural network connectivity (46).

While there is evidence of difficulties across some of these cognitive domains for EP/SCH and ASD, respectively, few studies have directly compared EP with ASD. There is however, a greater body of literature comparing ASD and SCH. The overall findings on shared and distinct pathways remain equivocal and are to some degree moderated by the type of assessment used (e.g. behavioral, imaging, physiological). Greater commonalities are observed when comparing ASD and SCH on behavioral measures of social cognition and EF. Using an extensive battery of social cognition and EF tasks (47) comparable impairment was reported between the two clinical groups that was significantly worse than the neurotypical control group. Similar findings were reported in a recent study (48) on a battery of social cognition tests across the domains of emotion recognition, social perception, mental state attribution, and attributional style. The comparison between a group with ASD and a mixed cohort with SCH or schizoaffective disorder revealed comparable levels of impairment. It was further noted that the few significant differences between groups were mediated by symptom severity. Findings of comparable performance on behavioral measures of social cognition tasks however are mixed. Highlighting the importance of using stimuli with greater ecological validity, comparable performance was observed between ASD and SCH on emotion recognition tasks when stimuli were presented within a realistic contextual background. Furthermore, both groups were impaired compared to the neurotypical control group (49). Despite these similarities it was noted that IQ was a significant moderator for SCH but not for the ASD group. Findings suggest different cognitive processes may mediate the observed outcomes. Further evidence of differences between the two conditions on a behavioral attribution style task were reported in a meta-analysis (50). Greater impairment was observed in the ASD cohort compared to SCH. It was further observed that the transition from first episode psychosis to SCH resulted in greater impairment in the use of mental states in the SCH group compared to the EP group.

More differences between ASD and SCH emerge when underlying neural mechanisms are investigated even when the two cohorts are comparable on behavioral task performance. Using a task of perspective taking, (51) comparable performance was reported between ASD and SCH on behavioral tasks. Imaging data however, revealed that the two groups were distinguished by different functional connectivity outcomes with greater local orbitofrontal connectivity in ASD compared to SCH. Similar discrepancy between behavioral and neural outcomes were reported in a study utilizing a social judgment task (52). Comparable performance on the behavioral measure was guided by distinct neural mechanisms in the amygdala and associated neural circuit clusters and differentiated between individuals with ASD and schizotypal personality disorder. In two studies Ciarramidaro and associates examined intention attribution (53) and facial affect recognition (54) comparing individuals with ASD and paranoid SCH. In the former study, different neural mechanisms were observed, verifying the hyper-hypo connectivity hypothesis (55), despite comparable difficulties in making attributions between the two groups. In contrast, the latter study did not identify significant neural or behavioral differences between the two groups on the task used (implicit negative affect recognition task).

These findings highlight that methodological design including diagnostic subtypes, transition stage of SCH (early or chronic psychosis), type of task and assessment mode, may contribute to the observed behavioral phenotype and underlying neural mechanisms. ML provides a methodology that allows for multiple variates to be assessed in a single design and can thus make a significant contribution to this field. Applying this methodology to a comparison between ASD and EP, prior to transition to psychosis and entrenchment of chronic symptomatology could provide significant insights on the neurodevelopmental basis of SCH and shared and distinct profiles between the two groups.

Furthermore, the ML methodology and focus on conditions with social impairment adopted in this study presents a novel approach for guiding research in this area. In particular, ML allows for the evaluation of multifactorial assessment outcomes, this is particularly important given potential biases in self/informant assessments (20, 56). Identifying discriminating behavioral profiles can provide a framework for investigating mechanisms underlying the reported shared and distinct phenotypes.

Few studies (19, 20) compared the EP and ASD groups with a clinical group that shares the social impairment phenotype but has generally intact cognitive and EF (57) such as Social Anxiety Disorder (SAD). The SAD group presents an important comparison cohort given that EP (58) and ASD (59) are both associated with substantially elevated levels of social anxiety reported at 25% and 50%, respectively. In addition, there is a period of prodromal features that are difficult to distinguish between SAD and early psychosis (60). A comparison between the three groups could facilitate discriminating profiles and aid diagnosis.

The broad goal of this study was to use ML on a large dataset of multiple cognitive domain measures and mood self-appraisals. The aims were to identify differentiating profiles between neurodevelopmental (EP, ASD), clinical (SAD) and neurotypical (TYP) comparison groups. Identifying discriminating profiles between these conditions would facilitate diagnosis and early intervention.

Our assessment battery included multiple measures across the domains of complex attention, executive function, learning and memory, perceptual-motor function, and social cognition. Self-report measures of depression, anxiety, and stress were also included in the study given research evidence demonstrating high levels of co-morbid depression in SAD (48%) (61) with reported range between 35% and 70% (62, 63). Comparable rates of depression comorbidities (54%) have been reported for EP (64). In adults with ASD, the rate of depression disorders range from 38% to 70%, while the rate of anxiety disorders ranges from 50% to 65% (65, 66). To our knowledge, this is the first study to

compare EP and ASD with SAD and a non-clinical comparison group across broad cognitive domains and affective states.

The first aim was to identify a profile that may distinguish between the combined social impairment cohort and control group. The second aim was to identify variables that differentiated the neurodevelopmental cohort from the SAD group. The third aim was to determine whether each of the EP, ASD, and SAD groups could be distinguished on a subset of measures from the other clinical groups and from each other. We predicted that the neurotypical control group would be distinguished from the social impairment cohort on self-appraisal measures of depression and anxiety, given the reported high comorbidity rates in the clinical groups. Second, we predicted that the neurodevelopmental cohort would be distinguished from the clinical comparison group on measures of attention, psychomotor speed, social cognition, EF, and visuomotor performance. This is based on literature findings that these domains are generally intact in SAD (57) but impaired in ASD (28, 31) and EP (34). Third, we predicted that the EP and ASD groups would be distinguished from each other on measures of complex attention given empirical support for impaired neural circuitry underpinning attention networks in EP (67). In their review, Wood and associates showed that attentional switching predicted transition from EP to SCH. This may be a useful marker for differential diagnosis. No specific predictions were made for the comparisons of ASD versus SAD/EP and EP versus SAD/ASD.

METHODS

Ethics

Ethics approval was given by the University of Sydney Ethics Committee (Protocol number 2013/352). Informed consent was obtained from each of the participants by postgraduate research students and trained clinicians.

Participants

Our dataset consisted of clinical participants who have met standardized diagnostic criteria for ASD (N = 62), EP (N = 48) or SAD (N = 83). Participants were sequential referrals from the Autism Clinic for Translational Research, Anxiety Clinic, and headspace clinics, at the Brain and Mind Centre, University of Sydney. Neurotypical control study volunteers (TYP = 43), were recruited separately through advertising at university websites. Clinical diagnoses were based on standardized diagnostic instruments (ADOS (68), ADIS-IV/V (69), SCID-I (70), PANS (71), and IQ was assessed based on scores on the WASI (72) or WTAR (73). Participants were excluded if IQ was below 70, prospective TYP participants were excluded if they reported past or current mental health diagnosis, or of they scored above cut-offs on screening instruments of depression, anxiety/social anxiety, stress or autism, [DASS-21 (74), SIAS (75), AQ-10] (76). Details of the diagnostic and assessment batteries and associated cognitive domains are presented in **Table 1**.

Assessment Battery

In this study, we utilized both neuropsychological (objective) and self-report (subjective) measures of social cognition, cognitive, and executive function, as well as self-report measures of affective states (depression, anxiety, and stress).

Data Selection

Patients and variables with more than 50% missing values were removed from the data set and the remaining missing data values were imputed with multivariate imputation with chained equations (MICE) (90) with 10 iterations using predictive mean matching for missing values. As shown in **Figure 1**, 10-fold cross-validation was applied to empirically assess the performance of the model built in imputed data sets. In each fold, 90% of the samples were used as the training set, and the remaining 10% were used for testing the generalizability of the models on unseen data. Ten-fold cross validation was used because it has been shown empirically to yield a reasonably low bias and modest variance (91, 92). Plausibility and consistency of the imputed values were visually inspected through density plots of the observed and imputed data, and the first imputed dataset was selected for downstream analysis.

Machine Learning

We applied five different ML algorithms to build models that can classify between our groups of interest, because there is no best algorithm for all problems (93). A great model for one problem may not hold for another problem. In particular, we selected five algorithms that can also perform variable selection in order to ascertain a variable's contribution to the model: Area Under the Curve Random Forests (AUCRF) (94), Boruta (95), Lasso regression (96), Elastic net regression (97) and Bayesian Additive Regression Trees (BART) (98).

The performances of the ML models were assessed using the Area Under the Curve (AUC) and Brier Scores. The AUC represents the probability that a classifier will ranks a randomly chosen negative example lower than a randomly chosen positive example (99). The AUC is a widely used performance measure in machine learning, and is often used as the primary performance measure for binary classification (100). In the evaluation of ML algorithms, the AUC has been shown to be a statistically consistent and more informative metric as compared to other traditionally used metrics, such as accuracy, precision, and recall (101–103). AUC is known to be a more complete performance metric as compared to other traditionally used metrics. AUC values < 0.5 suggest no discrimination, 0.7 to 0.8 are considered acceptable, 0.8 to 0.9 are considered good, and ≥ 0.9 are considered outstanding (104). As the AUC only represents the ability of a prediction model to distinguish between classes (discrimination), the Brier score was additionally used to evaluate the magnitude of the error of the probability estimates (calibration and discrimination) for complementing the AUC (105). Brier scores range between 0 (perfect accuracy) and 1 (perfect inaccuracy). Higher AUC and lower Brier scores indicate which model is the most informative. For those with similar scores, repeatedly identified features would be the reliable and

TABLE 1 | Summary of assessment measures.

Assessment Type	Domain	Assessment Test	Outcome Measures and Interpretation
Clinical and screening measures			
Semi-structured, standardized assessment of autistic symptoms	• Social Interaction and Communication • Restricted and Repetitive Behaviors	**ADOS-2 (**68**)** Autism Diagnostic Observation Schedule – 2nd edition	symptom severity
Self-report measure of autistic traits and capacity to identify and understand social cues and engage in social interaction	• Social Awareness • Social Cognition • Social Communication • Social Motivation • Restricted Interests and Repetitive Behavior	**SRS-2 (**77**)** Social Responsiveness Scale	Outcome measures on overall score and on each of the clinical scales -Higher scores, more autistic traits
	Social Anxiety	**ADIS-IV (**69**)** Anxiety Disorders Interview Schedule for DSM-IV.	–
	Schizophrenia	**SCID-I (**70**)** The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)	–
	Schizophrenia	**PANS (**71**)** Positive and Negative Symptoms Scale	–
Symptom severity measures (self-report)			–
	• Depression • Anxiety • Stress	**DASS-21 (**74**)** Depression Anxiety Stress Scale	Outcome measures on total score and on each of the scales -Higher scores, greater severity
	• Emotional Reactivity • Cognitive Empathy • Social Skills	**EQ (**78**)** Cambridge Behavior Scale Abbreviated Empathy Quotient	Outcome measures on total score and on each of the scales -Higher scores reflect higher levels of social cognition.
Performance and self-report measures of social cognition			-
		Faux Pas Recognition Task (79**)**	Outcome measures are: -Faux Pas Hit Rate -Faux Pas False Alarm Rate -D-Prime, a ratio of hits to false alarms -Faux Pas Questions Total Correct -Faux Pas Control Questions Correct -No Faux Pas Questions Total Correct -No Faux Pas Control Questions Correct -Higher scores, better social cognition -False rate,
	Emotion Recognition	**FEEST (**80**)** Facial Expressions of Emotions: Stimuli and Tests	Outcome measures are: -Total score -Score on each of the six basic emotions (happiness, surprise, fear, sadness, disgust, anger) Higher scores reflect higher levels of emotion recognition
Presentation of two series of social scenes, the first series without facial expressions and the second series with facial expressions	Emotion Recognition	**Movie Stills task (**81**)**	-Higher scores, better social cognition
	Emotion Recognition	**False Belief Picture Sequencing Task (**82**)**	Outcome measures are: -False belief -Social script -Capture -Mechanical Higher scores, better social cognition

(Continued)

TABLE 1 | Continued

Assessment Type	Domain	Assessment Test	Outcome Measures and Interpretation
	Emotion Recognition	**RMET (**83**)** Reading the Mind in the Eyes Test	-Higher scores, better emotion recognition
Reading of 50 words and assessment of correct pronunciation, may be subject to regional language variations in pronunciation	Overall Cognitive Ability	**WTAR (**73**)** Wechsler Test of Adult Reading	–
	Overall Cognitive Ability	**WASI (**72**)** Wechsler Abbreviated Scale of Intelligence	–
Neuropsychological and self-report measures of cognitive function and cognitive domain per DSM-5 (24**) framework**			–
Complex Attention involves sustained attention, divided attention, selective attention, and information processing speed			–
Executive function involves planning, decision making, working memory, responding to feedback, error correction, overriding habits, and mental flexibility			
Learning and memory involves immediate memory, recent memory (free recall, cued recall and recognition memory) and long term memory			
Language involves expressive 0language (naming, fluency, grammar, and syntax) and receptive language			
Social cognition involves recognition of emotions and behavioral regulation			
Executive function (self-report measure)		**BRIEF (**84**)** Behavioral Rating Inventory of Executive Function	-Higher score indicates negative self-report of EF
Executive function[1] **Language**[1] [1] DSM-5 defines fluency as a component of language but Fluency is generally accepted as an EF domain and was assessed as part of the EF battery	*Phonemic fluency *Semantic fluency	**COWAT (**85**)** Controlled Oral Word Association Test	-Higher score, better performance
Executive function	Cognitive flexibility	**TMT-B (**86**)** Trail Making Test-B	Outcome measure is completion time in seconds -Higher score worse performance
Complex attention	Attentional switching	**IED (**87**) Intra-Extra Dimensional Shift Test**	-Stages completed, higher score better performance -errors, higher score worse performance
Complex Attention	Sustained attention	**RVP (**87**)** Rapid Visual Processing Test	-Score range 0–1, score of "1" indicates perfect detection of target
Complex Attention	Information processing speed	**TMT-A (**86**)** Trail Making Test-A	Outcome measure is completion time in seconds -Higher score, worse performance
Learning and Memory	Verbal learning and memory	**LM – WMS-III (**88**)** Logical Memory Test Wechsler Memory Scale 3rd edition	-Higher score better performance
Learning and Memory	Visuospatial learning and memory	**PAL (**87**)** Paired Associate Learning	-Total errors, higher score worse performance
Learning and Memory	Verbal learning and memory	**RAVLT (**89**)** Rey Auditory Verbal Learning Test	-Higher score better performance
Learning and Memory	Visuospatial learning and memory	**SSP (**87**)** Spatial Span Test	-Total correct - higher score better performance -Total errors – higher score worse performance

clinically informative discriminatory features. Furthermore, to provide additional insights and make the results comparable to other studies that report accuracy, precision (positive predictive value), and recall (sensitivity) as performance evaluation measures, we have included these three measures in our analysis (refer to **Table 3**).

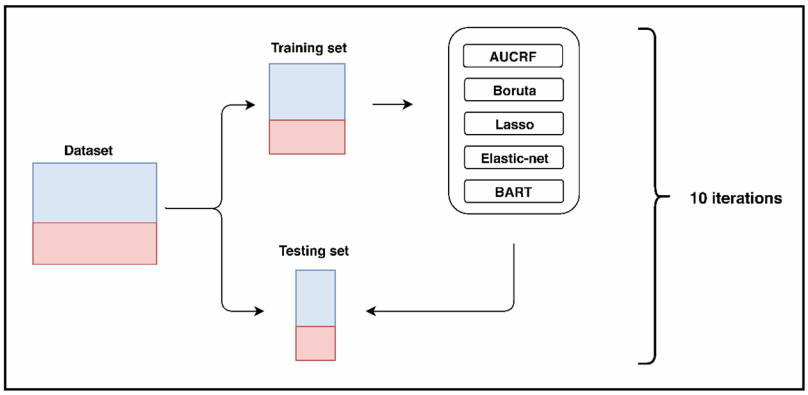

FIGURE 1 | Data selection flowchart.

Machine Learning Algorithms

The AUCRF (94) and Boruta (106) algorithms are both based on the Random Forest (RF) (107) algorithm. RF uses bootstraps of samples to build a forest of decision trees with variables as nodes of the tree. Furthermore, RF has an internal variable importance ranking system that describes the decrease in node impurity. A higher-ranking variable is one that splits the samples into more pure groups.

AUCRF recursively builds RF models whilst eliminating the lowly ranked variables. The optimal set of variables is those used in the RF model with the best performance. For AUCRF, the metric for performance is the AUC which describes the model's true positive rate (sensitivity) and false positive rate (1-specificity) across different thresholds for binary classification.

Boruta uses RF to compare a variable's original importance score to its importance score from a permutation of that variable. Permutations break the relationship between the predictor and the response variables and, hence, are expected to decrease the predictive value of a variable. Variables with higher importance scores than in its permuted form are considered important. RF models were built with the optimal sets of variables as identified by AUCRF and Boruta, and tested to obtain performance metrics. For each RF model in AUCRF and Boruta and for each final RF model, we generated 1000 decision trees. The best variable for splitting at each level of each decision tree was identified from a random set of $\sqrt{p}$ variables where p is the total number of variables. We also used internal 5-fold cross validation and a parameter tune length of 10 to identify the optimal value for λ (lambda). Lambda controls the strength of the penalization in Lasso and Elastic net and the balance between L1- and L2-regularization in Elastic net. Lasso (96) regression uses L1-regularization that penalizes coefficients with large absolute values in order to reduce overfitting. Lasso regression shrinks the coefficient of unimportant variables to zero and hence, effectively, performs variable selection. In contrast, Elastic net regression (97) employs a linear combination of L1-regularization and L2-regularization, which penalizes coefficients with large squared values. We used internal five-fold cross validation and a parameter tune length of 10 to identify the optimal value for λ which controls the strength of the penalization in Lasso and Elastic net, and α which controls the balance between L1- and L2-regularization in Elastic net.

In contrast to RF where trees are built from random bootstraps and independently, BART (98) employs a sum-of-trees approach. The Bayesian foundations of BART allows for the specification of regularization priors that ensures that each tree is weak and the use of Bayesian back-fitting (108) to fit trees iteratively. Variable selection with BART involves comparing the variable's inclusion proportions, which reflects the frequency of which the variable is chosen to be the split node, against a null distribution created from multiple permutations of the variable.

RESULTS

Sample Description

Demographic characteristics are summarized in **Table 2**. In total, 236 participants were included in the study with mean age X = 22.7 years (SD 5.8), 96 (40.7%) were female. No significant differences were observed between the cohorts with regard to age, gender, and years of education ($p > 0.05$).

Model Performance

Classification performance for classifying between neurotypical controls and social impairment cohorts was good with mean AUCs greater than 0.87 (**Table 3**). All five algorithms performed similarly well with BART providing the highest mean AUC (0.92) and Boruta providing the lowest mean Brier Score (0.14).

For classification between clinical and neurodevelopmental groups, the mean AUCs were lower than that between neurotypical controls and the combined social impairment cohort, which reflects the challenge in developing a classification tool between disorders. Mean AUCs for discrimination between the EP and ASD groups ranged from 0.72 to 0.76 with BART providing the highest mean AUC (0.76) and Boruta the lowest mean Brier Score (0.21).

TABLE 2 | Demographic descriptive statistics by diagnosis.

	All (n = 236)	Control (n = 43)	SAD (n = 83)	ASD (n = 62)	EP (n = 48)	Significance
Age in years	22.72 (5.83)	23.21 (5.84)	22.34 (6.15)	22.63 (5.55)	23.08 (5.76)	H(3) = 2.567, p = 0.463
Gender female (%)	96 (40.7%)	21 (48.8%)	28 (33.7%)	21 (33.9%)	26 (54.2%)	$\chi 2(3) = 7.654$, p = 0.054
Education in years	13.02 (2.19)	12.86 (2.00)	12.85 (2.30)	13.37 (2.45)	13.07 (1.81)	H(3) = 1.714, p = 0.634

H: Kruskal-Wallis Test for non-normal data.

Variable Selection

Figure 2A illustrates the frequency that each variable was selected across the five algorithms with repeated cross-validation in the social impairment vs neurotypical control group. Self-report measures of depression, anxiety, and stress (DASS), social cognition measures of EQ-social skills, and the cognitive measure of visuospatial STM, best discriminated between the groups.

Figures 2B–E and **Table 4** present the top variables identified from the variables input into the three models for differentiating diagnosis between the disorders of social impairments by all five algorithms. Discriminating variables were identified across cognitive domains and affective states. A summary of the key discriminating variables is presented in **Figure 3**.

Performance metrics like AUC and Brier scores represent how well the model differentiates between patients with different mental health problems. Based on the AUC and Brier scores, the most informative model can be identified. For example, the model for differentiating diagnosis between the SAD and neurodevelopmental group, the BART model showed the highest AUC = 0.781 and the lowest Brier score (0.198). However, other models also showed similar AUC and Brier scores. Features that are consistently selected by the best-performing model and these similarly performing models can be the recommendations for diagnosis and intervention strategies.

DISCUSSION

In this study, we used ML algorithms on a composite assessment battery to identify cognitive profiles that discriminate between clinical, neurodevelopmental, and neurotypical comparison groups. Our three hypotheses were that firstly, self-appraisal measures of depression and anxiety will differentiate the neurotypical group from the cohorts with social impairment. Second, the neurodevelopmental cohort will be distinguished from the SAD group on measures of attention, information processing, social cognition, EF, and visuomotor performance and third, the ASD and EP groups will be differentiated based on their performance on tasks of complex attention.

Our results showed that a reduced set of assessment measures differentiated between the comparison groups with good discriminative ability (AUC ≥ 0.7 and Brier score = 0.14–0.24). Our first hypothesis was confirmed in that depression, anxiety, and stress discriminated the combined social impairment cohort from the comparison control group. Two measures drawn from the social cognition and learning/memory domains (social skill and visuospatial short-term memory) complemented this profile. Our second hypothesis received partial support. Three of the predicted five cognitive domains (visual learning, social cognition, and EF), featured in the optimized profile discriminating between the neurodevelopmental groups and the SAD group. Depression was the other distinguishing feature. Finally, contrary to our third hypothesis, psychomotor speed rather than complex attention distinguished between the EP and ASD groups. Taken together, our research outcomes support and extend literature findings on distinguishing features of the SAD and neurodevelopmental (ASD/EP) groups. The results are particularly compelling given the high discriminative performance of the optimized profiles that emerged from an extensive battery across multiple cognitive domains and affective states.

The first finding of interest is that other cognitive domains in addition to EF and social cognition featured in the optimized profiles. The learning/memory domain measure of visuospatial memory contributed to the combined social impairment cohort versus control discriminating profile. This is surprising given that cognitive function in SAD (57) is generally intact, and thus not expected to differentiate this cohort from a neurotypical control group. The finding suggests that our combined social impairment cohort shares atypicalities in maintaining visual information in short term memory. There is evidence of reduced visual working memory capacity in EP (109) and ASD (110, 111) and our findings may in part reflect this. The shared profile with SAD however, points to more complex processes. A number of cognitive models predict that anxiety attenuates cognitive control and impairs working memory processes (112) including visual working memory (113). Our combined social impairment cohort is characterized by high levels of anxiety, and our findings may reflect the influence of anxiety on executive control.

Measures from learning, attention, and psychomotor speed domains featured in the optimized profiles that discriminated between clinical cohorts. Visual associative learning contributed to discriminating the neurodevelopmental from the SAD cohort. A closer examination of this profile indicated that although all groups were comparable on overall visual learning performance, the neurodevelopmental cohort made more errors. This may reflect impaired processes specific to EP and ASD including impaired visual working memory (109, 110) and slow processing speed (114, 115). Attentional processes were the most salient features that discriminated the EP group from the combined ASD/SAD cohort and EP from the SAD groups. Attentional neural circuitry in EP is clearly impaired in the course of illness (30) and indicates that it may have a unique role in early detection and differentiation. Psychomotor processing speed was the only distinguishing feature discriminating between EP

TABLE 3 | Classification performance on repeated cross-validation test sets.

	Control vs Clinical	SAD vs Neurodevelopmental (ASD and EP)	ASD vs SAD and EP	EP vs ASD and SAD	EP vs ASD	EP vs SAD	SAD vs ASD
Test set AUC's mean (SD)							
AUCRF	0.891 (0.081)	0.752 (0.092)	0.676 (0.141)	0.776 (0.123)	0.747 (0.156)	0.825 (0.114)	0.741 (0.135)
Boruta	0.900 (0.076)	0.759 (0.090)	0.661 (0.137)	0.771 (0.124)	0.742 (0.163)	0.833 (0.117)	0.746 (0.133)
Lasso	0.871 (0.092)	0.729 (0.112)	0.718 (0.134)	0.712 (0.151)	0.724 (0.149)	0.746 (0.144)	0.780 (0.136)
Elastic-net	0.893 (0.076)	0.754 (0.099)	0.749 (0.118)	0.727 (0.143)	0.724 (0.141)	0.792 (0.139)	0.808 (0.125)
BART	0.916 (0.069)	0.781 (0.101)	0.735 (0.124)	0.777 (0.129)	0.759 (0.146)	0.827 (0.109)	0.782 (0.118)
Test set Brier Scores mean (SD)							
AUCRF	0.146 (0.042)	0.206 (0.037)	0.234 (0.046)	0.196 (0.042)	0.207 (0.056)	0.173 (0.044)	0.213 (0.051)
Boruta	0.138 (0.040)	0.204 (0.033)	0.237 (0.042)	0.197 (0.042)	0.206 (0.057)	0.170 (0.043)	0.209 (0.048)
Lasso	0.181 (0.058)	0.226 (0.047)	0.231 (0.058)	0.234 (0.046)	0.239 (0.061)	0.214 (0.068)	0.203 (0.052)
Elastic-net	0.153 (0.045)	0.208 (0.044)	0.224 (0.050)	0.234 (0.074)	0.237 (0.072)	0.194 (0.060)	0.185 (0.050)
BART	0.150 (0.026)	0.198 (0.032)	0.211 (0.028)	0.204 (0.028)	0.210 (0.032)	0.180 (0.034)	0.196 (0.034)
Test set Accuracy's mean (SD)							
AUCRF	0.790 (0.096)	0.690 (0.094)	0.639 (0.109)	0.719 (0.103)	0.663 (0.142)	0.745 (0.115)	0.674 (0.115)
Boruta	0.801 (0.092)	0.685 (0.093)	0.625 (0.087)	0.707 (0.106)	0.668 (0.134)	0.747 (0.113)	0.693 (0.118)
Lasso	0.760 (0.094)	0.660 (0.115)	0.655 (0.110)	0.659 (0.114)	0.661 (0.130)	0.703 (0.121)	0.710 (0.130)
Elastic-net	0.784 (0.097)	0.689 (0.096)	0.684 (0.095)	0.681 (0.126)	0.654 (0.134)	0.735 (0.110)	0.732 (0.114)
BART	0.819 (0.079)	0.706 (0.095)	0.702 (0.103)	0.724 (0.102)	0.693 (0.143)	0.756 (0.109)	0.723 (0.105)
Test set Precision's mean (SD)							
AUCRF	0.801 (0.210)	0.676 (0.129)	0.654 (0.144)	0.721 (0.126)	0.656 (0.221)	0.768 (0.197)	0.650 (0.183)
Boruta	0.810 (0.198)	0.682 (0.136)	0.635 (0.121)	0.707 (0.129)	0.643 (0.220)	0.757 (0.192)	0.681 (0.194)
Lasso	0.831 (0.209)	0.619 (0.151)	0.663 (0.147)	0.660 (0.139)	0.670 (0.220)	0.670 (0.196)	0.704 (0.193)
Elastic-net	0.817 (0.201)	0.644 (0.144)	0.706 (0.132)	0.683 (0.150)	0.666 (0.212)	0.705 (0.195)	0.707 (0.178)
BART	0.525 (0.142)	0.787 (0.107)	0.817 (0.093)	0.895 (0.075)	0.673 (0.192)	0.669 (0.169)	0.689 (0.150)
Test set Recall's mean (SD)							
AUCRF	0.480 (0.145)	0.763 (0.107)	0.786 (0.099)	0.888 (0.076)	0.634 (0.195)	0.652 (0.162)	0.630 (0.158)
Boruta	0.501 (0.148)	0.756 (0.110)	0.782 (0.093)	0.884 (0.079)	0.645 (0.203)	0.655 (0.166)	0.657 (0.163)
Lasso	0.438 (0.134)	0.755 (0.132)	0.801 (0.099)	0.856 (0.088)	0.618 (0.168)	0.602 (0.165)	0.664 (0.171)
Elastic-net	0.472 (0.150)	0.786 (0.115)	0.810 (0.085)	0.866 (0.084)	0.619 (0.181)	0.659 (0.170)	0.701 (0.157)
BART	0.844 (0.188)	0.678 (0.139)	0.730 (0.117)	0.720 (0.125)	0.701 (0.207)	0.768 (0.183)	0.703 (0.178)

and ASD groups. Research supports that processing speed is impaired in both groups (34, 114) however, different patterns of reaction time changes may apply. There is some evidence that processing speed in EP/SCH deteriorates in later age (116) whilst in ASD, processing speed has matured by adolescence (117) and is significantly impaired compared to neurotypical controls (114). The discriminating profile identified here may reflect different trajectory changes. The absence of measures from other cognitive domains in the EP/ASD comparison support that these two groups have a shared phenotype across most cognitive domains.

The second finding of interest is that phonemic fluency was the only EF measure that contributed to a profile discriminating between SAD and the neurodevelopmental cohort. Phonemic fluency performance is thought to be positively associated with intact frontal lobe function (118) and results may indicate frontal lobe alterations in EP (67) and ASD (119). Given that impairment in EF is noted for both EP (22) and ASD (36, 120) cohorts, greater prominence of EF measures would be expected. The limited role of our other EF measures in differentiating between the clinical groups suggests EF may have greater relevance as a transdiagnostic dimension of neurodevelopment (121).

Social cognition was a distinguishing feature for a number of optimized profiles. These measures featured in all profiles that included participants diagnosed with ASD, except for the ASD/EP direct comparison. Self-appraisals for social skill (a sub-scale of the EQ questionnaire that measures difficulty in social situations), differentiated the clinical cohort from the control group. Co-morbidity with SAD has been reported for each of the EP (122) and ASD (59) groups, and our finding of a shared profile feature likely reflects this. The neurodevelopmental cohort was distinguished from the SAD group on measures of basic emotion recognition (RMET task), identifying emotions in the absence of salient cues (movie stills task) and, in experiencing an appropriate emotion in response to another (self-appraisal of emotional reactivity/empathy). Finally, the ASD versus SAD profile distinguished between the two groups on the overall level of empathy (EQ questionnaire). These findings highlight the salience of social cognition in the neurodevelopmental cohort and particularly for the ASD group. Considered together with the limited prominence of EF features despite known EF deficits, it suggests that social cognition is a more important domain for discriminating the ASD group from other cohorts.

The prominence of mental health features (depression, anxiety, and stress) in the profile discriminating between the combined social impairment cohort and the control group, reflects the high levels of co-morbid depression (61, 64) and anxiety (122) reported for ASD, EP, and SAD. The inclusion of depression and stress self-appraisals in discriminating between the three clinical cohorts warrants further discussion and suggests that nuanced differences differentiate between the groups. The SAD group reported the highest levels of

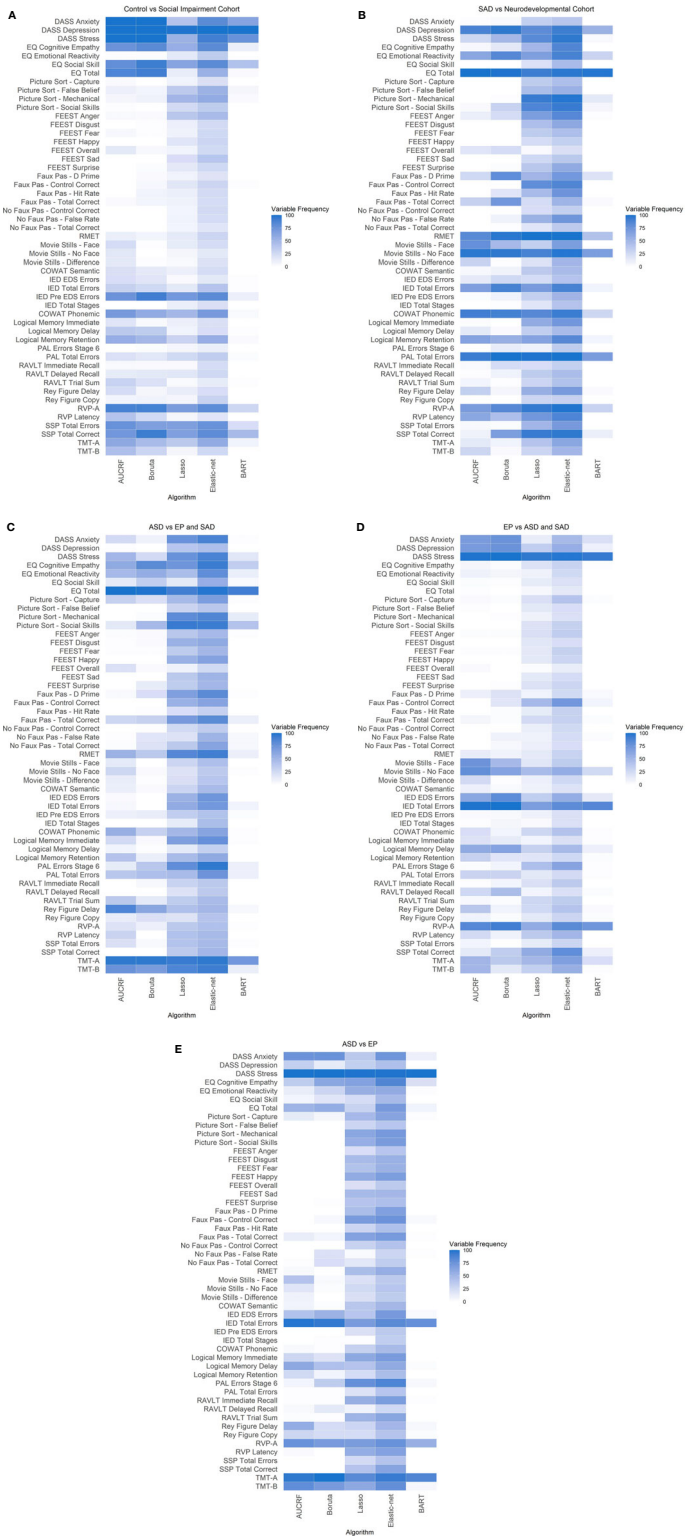

FIGURE 2 | (A) Heatmap of Neurotypical Control vs Social Impairment Cohort. **(B)** Heatmap of SAD vs Neurodevelopmental Cohort. **(E)** Heatmap of ASD vs EP and SAD. **(D)** Heatmap of EP vs ASD and SAD. **(E)** Heatmap of ASD vs EP. **(A–E)** Variable frequency. Plot shows the frequency that each variable was selected for differentiating Control and Social impairment cohorts across the five algorithms with 10 times repeated 10-fold cross-validation. The darker color represents high frequency, while the lighter color represents low frequency.

TABLE 4 | Variables discriminating between ASD, EP, SAD, and neurotypical controls.

Cohort	N	Variables
TYP ∩ ASD/EP/SAD	5	DASS Depression, DASS Anxiety, DASS Stress, EQ Social Skill, SSP, RVP-A
SAD ∩ ASD/EP	6	EQ emotional reactivity, Movie Stills—No Face, RMET, DASS Depression, PAL total errors, COWAT phonemic
EP ∩ ASD/SAD	3	IED Total Errors, IED EDS Errors, DASS Stress
ASD ∩ EP/SAD	2	EQ Cognitive Empathy, Picture Sort—Social Script
ASD ∩ SAD	1	EQ Total
ASD ∩ EP	1	TMT-A
EP ∩ SAD	1	RVP-A

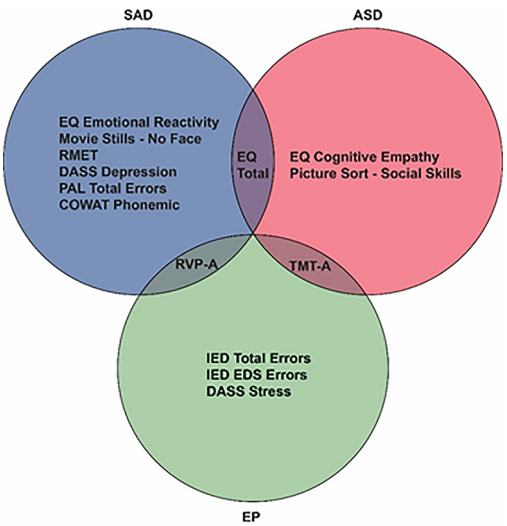

FIGURE 3 | Venn diagram of distinguishing features.

depression in our clinical cohort and EP the lowest levels of stress. Depression was the only affective state that discriminated the SAD versus neurodevelopmental cohort. This may reflect the high levels of co-morbid depression characterizing SAD (61). The lower levels of stress differentiating the EP group from ASD/SAD may reflect differences in symptom severity levels on presentation to our services. Acute positive psychotic symptoms in the EP cohort were controlled prior to inclusion in our services. The ASD and SAD participants however, would be experiencing a more acute profile of their respective symptoms. This may translate to the lower levels of distress reported by the EP group. Alternatively, lower stress in EP may reflect different levels of insight. There is research support that individuals with EP, (particularly those with more impaired cognitive function) have lower levels of insight (123) and may therefore report lower levels of stress.

Limitations

There are a number of limitations in our study. First, although the sample size used in this study was larger than the suggested sample sizes of 75 to 100 for reasonable precision (4) the relatively small sample size of our cohort may reduce the parameters for trainability and cross-validations of our data. A larger sample size would be of benefit to further research. We also acknowledge the resources required to collect the detailed data we have. This is one of the largest studies with detailed information in the field to date. Second, our findings can only be attributed to individuals without intellectual disability, as we did not include any participants with an IQ below 70. Third, our findings include a number of features based on self-appraisals, and there is some question whether self-report appraisals by individuals with ASD are comparable to other cohorts (19, 20). Fourth, a number of participants in the diagnostic groups were being treated with medication, however, we were not able to control for medication use in this study. Fifth, we used 10-fold cross-validation to evaluate the classification performance of models and to identify the discriminating profiles between clinical, neurodevelopmental, and neurotypical comparison groups. Although this approach is considered as the most robust resampling technique to assess the accuracy and generalizability of models (124), the need for a more rigorous approach (external validation) has been emphasized to ensure the model generalizability (125). The present findings, therefore, need to be replicated in future studies with an independent large test set of completely unseen data in order to assess the generalizability of our ML models.

CONCLUSIONS

The optimized profiles identified in our study highlight the importance of evaluating multiple cognitive domains when determining discriminating profiles between clinical groups. Further, they demonstrate that our combined social impairment cohort (ASD, EP, and SAD) is characterized by both shared and discriminating features. This has implications for diagnostic, intervention, and remediation strategies. The discriminating profiles can thus facilitate differential diagnosis particularly when clinical cohorts are characterized by comorbid mental health conditions and shared phenotypes. Conversely, the shared profile features, provide a framework for identifying transdiagnostic dimensions for intervention and remediation programs. The unique discriminating features (attention and empathy) that respectively characterized our EP and ASD cohorts potentially identify key target areas for early intervention programs. To-date there has been promising research on the effectiveness of

intervention programs in improving social and non-social cognition in populations with ASD (126), EP (127) and SCH (128). In a study investigating cognitive support training in early psychosis (127) improvements were identified, however it was uncertain whether these were restorative or compensatory in nature. In cohorts with ASD, a recent study identified that higher levels of cognitive empathy mediated the positive influence of affective empathy on personal well-being (129). The researchers suggested that training programs on cognitive empathy could contribute to improvements in quality of life in ASD. Taken together these findings suggest that early intervention programs that target attention and empathy in the respective cohorts could contribute to improved functioning and potentially attenuation of symptoms.

To our knowledge, this is the first study that utilized measures across multiple cognitive domains and affective states. Our findings provide a framework for further research on shared and differentiating profiles of neurodevelopmental cohorts and cohorts characterized by social impairment.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The University of Sydney Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ED—conceptual design, literature review, data collection, manuscript preparation, manuscript revision. SP—conceptual design, data analysis, manuscript preparation, manuscript revision. NH—conceptual design, data analysis, manuscript preparation, manuscript revision. KP—data collection, manuscript revision. YS—manuscript revision. SN—manuscript revision. ET—data collection. IH—manuscript revision. AG—conceptual design, manuscript revision.

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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.2020.00545/full#supplementary-material

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Conflict of Interest: IH is a Commissioner in Australia's new National Mental Health Commission from 2012. He was a director of headspace: the national youth mental health foundation until January 2012. He was previously the chief executive officer (till 2003) and clinical adviser (till 2006) of beyondblue, an Australian National Depression Initiative. He is the Co-Director, Health and Policy at the Brain and Mind Centre that operates two early-intervention youth services under contract to headspace. He has led a range of community-based and pharmaceutical industry-supported depression awareness and education and training programs. He has led projects for health professionals and the community supported by governmental, community agency and pharmaceutical

industry partners (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) for the identification and management of depression and anxiety. He has received honoraria for presentations of his own work at educational seminars supported by a number of non-government organisations and the pharmaceutical industry (including Servier, Pfizer, AstraZeneca and Eli Lilly). He is a member of the Medical Advisory Panel for Medibank Private and also a Board Member of Psychosis Australia Trust. He leads an investigator-initiated study of the effects of agomelatine on circadian parameters (supported in part by Servier) and has participated in a multicentre clinical trial of the effects of agomelatine on sleep architecture in depression and a Servier-supported study of major depression and sleep disturbance in primary care settings.

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REVIEW
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A Review of Default Mode Network Connectivity and Its Association With Social Cognition in Adolescents With Autism Spectrum Disorder and Early-Onset Psychosis

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Recent studies have demonstrated substantial phenotypic overlap, notably social impairment, between autism spectrum disorder (ASD) and schizophrenia. However, the neural mechanisms underlying the pathogenesis of social impairments across these distinct neuropsychiatric disorders has not yet been fully examined. Most neuroimaging studies to date have focused on adults with these disorders, with little known about the neural underpinnings of social impairments in younger populations. Here, we present a narrative review of the literature available through April 2020 on imaging studies of adolescents with either ASD or early-onset psychosis (EOP), to better understand the shared and unique neural mechanisms of social difficulties across diagnosis from a developmental framework. We specifically focus on functional connectivity studies of the default mode network (DMN), as the most extensively studied brain network relevant to social cognition across both groups. Our review included 29 studies of DMN connectivity in adolescents with ASD (Mean age range = 11.2–21.6 years), and 14 studies in adolescents with EOP (Mean age range = 14.2–24.3 years). Of these, 15 of 29 studies in ASD adolescents found predominant underconnectivity when examining DMN connectivity. In contrast, findings were mixed in adolescents with EOP, with five of 14 studies reporting DMN underconnectivity, and an additional six of 14 studies reporting both under- and over-connectivity of the DMN. Specifically, intra-DMN networks were more frequently underconnected in ASD, but overconnected in EOP. On the other hand, inter-DMN connectivity patterns were mixed (both under- and over-connected) for each group, especially DMN connectivity with frontal, sensorimotor, and temporoparietal regions in ASD, and with frontal, temporal, subcortical, and cerebellar regions in EOP. Finally, disrupted DMN connectivity appeared to be associated with social impairments in both groups, less so with other features distinct to each condition, such as repetitive behaviors/restricted interests in ASD and hallucinations/delusions in EOP. Further studies on demographically well-matched groups of adolescents with each of these conditions

are needed to systematically explore additional contributing factors in DMN connectivity patterns such as clinical heterogeneity, pubertal development, and medication effects that would better inform treatment targets and facilitate prediction of outcomes in the context of these developmental neuropsychiatric conditions.

Keywords: functional connectivity, default mode network, social cognition, autism spectrum disorder, early-onset psychosis

INTRODUCTION

Autism spectrum disorder (ASD) and schizophrenia are heterogeneous conditions that share several phenotypic and genomic features (1–4). For instance, deficits in social interaction, emotional reciprocity, pragmatic speech, and theory of mind (ToM) are postulated to be central to both disorders (5). While early detection and clinical diagnosis of both disorders has improved over the past decade, frequent challenges still arise in differential diagnosis (e.g., in the event of later diagnosis of ASD) especially if predominant symptoms for both involve social difficulties and unusual social thinking (2, 6). Recent behavioral studies of adults with ASD and schizophrenia highlighted not only the similarities but also some divergent patterns of social impairments in the two disorders—with ASD characterized by lower social motivation, poorer social reciprocity, and undermentalizing, and schizophrenia characterized by greater reciprocity but poor expressiveness (7, 8). Moreover, these social impairments are associated with difficulties in the work setting (9, 10), social relationships (11, 12), and overall reduced quality of life (13, 14) across both groups. While several studies have demonstrated genetic overlap between ASD and schizophrenia (2–4, 15), the neural mechanisms underlying the pathogenesis of the social impairments observed in these disorders are still not well understood. Given the public health significance of social disability and social isolation (16), it is crucial to explore the neurobiological mechanisms underlying social deficits across both groups, as well as to understand how they relate to real-world behaviors. Exploring the shared and distinct neural underpinnings in ASD and schizophrenia could advance our understanding of social cognitive deficits across these conditions, which will ultimately help better inform treatment. Although antipsychotics have been shown to be effective in reducing positive symptoms in schizophrenia, they are not effective in addressing the devastating social disability associated with the disorder which contributes to chronic functional impairment (17, 18). It is thus imperative to identify behavioral interventions for children and adolescents that have already shown promise in other clinical groups such as ASD. By enhancing our understanding of the neurobiological underpinnings of social impairments in ASD and how they compare to those observed in schizophrenia, we will be able to refine treatment targets and predict outcomes for each group. Hence, here we conduct a narrative review of the existing neuroimaging literature on functional connectivity of a key social brain network (default mode network; DMN) in ASD and schizophrenia, in order to elucidate the shared and unique neural mechanisms underlying social impairments across diagnosis from a developmental framework.

Adolescence or youth (ages 10–24; 19, 20) is a particularly critical window for social development and thus is an important time to investigate neural mechanisms implicated in social functioning. Adolescence is a developmental period classified by gaining independence and autonomy from caretakers (21), with marked changes in identity, self-consciousness, and cognitive flexibility (22–24). As a part of this process of developing as an independent individual, there is typically an increase in peer-directed social interactions (21, 23, 25). As a result of this increase in sociality, adolescence is a time when the social demands change most dramatically, requiring individuals with social deficits to work harder. Prior research has shown that social deficits become even more apparent during this period as social contexts increase in complexity and pose higher social expectations (24, 26). Consequences of poor social skills include peer rejection or victimization, poor friendship quality, lack of social support, experiences of loneliness, poor academic and vocational outcomes, and the development of anxiety, depression, or other psychopathologies (27–29). For individuals with ASD, adolescence may be a particularly difficult developmental period as they are also experiencing increased motivation to engage with peers, yet likely have a greater awareness of their social deficits (30). For individuals with psychotic disorder, negative symptoms including social withdrawal, reduced communication, and general apathy often precede positive symptoms and are linked more strongly to poor prognosis (31–34). The fact that social deficits often precede full-blown positive symptoms in schizophrenia implies that there are likely neural changes occurring during adolescence that precede manifestation of psychotic symptoms in early adulthood. While social impairment is a hallmark of both ASD and psychosis, these difficulties may have distinct origins: for example, the hypo-hyper-intentionality hypothesis (1, 35) postulates that individuals with ASD may under-attribute intentions to others or "undermentalize", whereas those with schizophrenia may over-attribute intentions to others or "overmentalize", parlaying into symptoms of suspiciousness and paranoia.

In addition to contextual changes in the social environment, adolescence is also a period marked by significant neural changes, particularly in the prefrontal cortex, a major hub in several brain networks associated with social functioning (23, 36–41). Evidence suggests that while sensory and motor brain regions are fully myelinated within the first several years of an infants' life, neurons in the frontal cortex continue to be myelinated through adolescence (21, 23, 40). This increased

myelination as well as white matter density is coupled with decreases in cortical thickness and gray matter in social brain hubs in frontal and parietal lobes (38, 40). Additionally, synaptic pruning—the process of eliminating unused neural connections, and the reorganization of strengthened pathways—is occurring actively in the prefrontal cortex during puberty (23, 25, 42–44). As a result, adolescents experience a net decrease in synaptic density during this time (23) along with increased long-distance and decreased short-distance functional connections in the brain, indexing better network integration and segregation during this period (45, 46). Increases in functional activation of prefrontal cortex are also observed in typical adolescents compared to adults in response to social tasks (25, 38). Increased functional connectivity between prefrontal cortex and temporal brain regions during adolescence is also related to increased social information processing during this age (39).

Although the social brain is not a specifically defined network, there is general consensus in the literature that the medial prefrontal regions, the temporoparietal junction, anterior and lateral temporal regions, anterior insula, and the posterior cingulate cortex/precuneus subserve several crucial social functions (25, 40, 47). Of note, the aforementioned brain regions are all highly represented within the DMN—a large-scale brain network with hubs in the medial prefrontal cortex (mPFC), posterior cingulate cortex/precuneus (PCC), inferior parietal lobe (IPL), and temporal lobe structures (48–50). The DMN is one of the most extensively studied functional networks, and it shows substantial overlap with several other "social brain" networks such as the mentalizing network and emotion recognition network (47, 51, 52). It has been proposed that the DMN is specifically involved in self-referential thinking (53–56), thoughts about self versus others and theory of mind (50, 52, 57, 58), and autobiographical memory (55, 56). Prior studies investigating DMN connectivity in health adolescents have suggested that there is a strengthening of connectivity in this network with age, particularly between anterior and posterior hubs from childhood to late adolescence, indicating increased integration in typical development (36, 37, 41, 45). Additionally, these same studies have suggested that DMN connectivity with other functional networks such as the central executive network becomes sparse from childhood to late adolescence, suggestive of increased autonomy and segregation of the DMN from task-related networks in typical development.

Disrupted DMN functional connectivity has been implicated in several psychiatric conditions with associated social difficulties (47, 59–61), including ASD (62) and schizophrenia (63). With such a rich literature, investigation of DMN function in adolescence offers a window into understanding how these social brain regions are functionally connected, how they are altered in disorders affecting social function, and their relationship to real-world social deficits. Much of this existing literature on the social brain and DMN connectivity has, however, focused on children (for ASD) and adults (for schizophrenia/psychosis), with fewer studies focusing on adolescents. While ASD may be diagnosed earlier in life, there is evidence to suggest that functional connectivity patterns in individuals with this condition undergo substantial changes from childhood to adulthood, likely influenced by factors such as puberty and/or access to treatment interventions over the years (64). In contrast, the age of onset for psychotic disorder peaks in adolescence, but more subtle cognitive and socio-emotional disturbances are present in early childhood (65). It is posited that overt symptom onset of psychosis during adolescence may be related to underlying changes in brain connectivity patterns affected by hormonal changes and increased stress response during this period (40). Due to the importance of this developmental period for brain development in general, as well as the relevant changes to social contexts, examining brain networks implicated with social cognition such as the DMN in adolescence requires substantial attention to further our understanding of the shared and distinct neural mechanisms underlying the social cognition deficits present in each group.

Hence, the current article aims to further explore cross-sectional studies on DMN connectivity in ASD and early-onset psychosis (EOP) during the adolescent years. For this purpose, we reviewed the literature available through April 2020 in PubMed, Google Scholar, and PsycINFO on DMN connectivity in adolescents with ASD and/or EOP, using search terms including "default mode network, functional connectivity," combined with "adolescence, autism, ASD, Asperger's" or "psychosis, adolescent-onset psychosis, adolescent-onset schizophrenia, first-episode psychosis, early-onset psychosis, early-onset schizophrenia". The initial literature search revealed 160 relevant studies in ASD and 46 in EOP. Studies were subsequently included in the review based on age-range spanning adolescence and patient groups meeting diagnostic criteria for either ASD or EOP. All included studies were also required to have a control group of typically developing adolescents. Additionally, we focused only on empirical studies that included either: 1) static resting-state analysis or dynamic functional connectivity (DFC) analysis that examines temporal variations in connectivity patterns across the duration of the scan (66–68), and 2) provided information about the directionality of their findings. The methods used for these studies included:

1. Traditional seed-based analysis (SBA), wherein the time-series from a seed-region are correlated with all other voxels in the entire brain or a mask of the DMN (69, 70).
2. SBA that quantify the amplitude of low-frequency fluctuations (ALFF), i.e., the magnitude of signal intensity of spontaneous fluctuations for a given brain region. In ALFF analyses, the time-series from a given seed-region are transformed into a frequency domain from which the power spectrum are obtained (70, 71).
3. Independent component analyses (ICA), a data-driven method wherein whole-brain signal are decomposed to identify spatially and temporally independent components. Software templates of the DMN are then used to identify components that correspond to this network (70).
4. Support vector machines (SVM) are data-driven supervised machine-learning methods using pattern recognition algorithms to automatically classify neuroimaging data into typical or atypical categories (72).

5. Self-organizing map (SOM) algorithm, a clustering analysis technique wherein voxels are organized on a two-dimensional matrix with each node representing clusters of voxels that are highly correlated and nodes that are closer together on matrix representing neural networks (72, 73).
6. Regional Homogeneity (ReHo), a voxel-based approach to measuring brain connectivity wherein the similarity between the time-series of a given voxel and its nearest neighbors within a network is evaluated (74).
7. Granger Causality Analysis (GCA), a statistical method that allows for prediction of causality between functional connectivity of two seed-regions/nodes from time-series data (75).
8. Network Homogeneity (NH), a voxel-wise measurement of homogeneity and cohesiveness of each voxel within a functional network that provides an index of network integrity (76).

Our final review included 29 studies of DMN connectivity in adolescents with ASD (mean age range = 11.2–21.6 years; see **Table 1** for demographic details), and 14 studies in adolescents with EOP (Mean age range = 14.2–24.3 years; see **Table 2** for demographic details). Our goal is to synthesize the findings of altered DMN connectivity from the existing literature for each clinical population within a developmental framework and discuss how the potential commonalities or differences in underlying neural mechanisms may relate to characteristic symptomatology. We conclude by providing some insights into gaps within the extant literature and highlighting future directions for research.

DMN CONNECTIVITY IN ADOLESCENTS WITH ASD

The past few years have witnessed a proliferation of resting-state connectivity studies in adolescents with ASD, facilitated in part by the availability of open-access multinational datasets such as the Autism Brain Imaging Data Exchange (ABIDE; 118). Approximately 52% of the studies in adolescents with ASD presented in our review (**Table 1**) have utilized the ABIDE dataset to investigate DMN connectivity (81, 84, 86–91, 93, 95, 98–100, 102, 103), using a combination of traditional SBA, SVM, ICA, ALFF, and DFC analytic techniques. These studies appear to be using a largely overlapping, although not exactly the same, set of ABIDE participants. About half of the studies (15 out of 29) in adolescents with ASD have found a global pattern of underconnectivity both within the DMN hubs (77, 78, 80, 87, 88, 90, 96, 98, 102), as well as between the DMN and other brain regions such as insula, subcortical regions, fronto-parietal regions, and visual cortex (73, 81, 84, 90, 95, 99), regardless of analytic methods used. Relatively fewer studies (five out of 29) have observed over-connectivity between the DMN and task-positive regions within the fronto-parietal, visual, and sensorimotor regions, as well as the salience network (79, 86, 94, 101, 104). Some studies (nine out of 29) have additionally found mixed patterns involving under- and over-connectivity of ASD youth relative to typically developing (TD) controls, largely highlighting a pattern of within-DMN underconnectivity, with overconnectivity between DMN and other networks such as task-positive or sensorimotor networks (82, 83, 85, 89, 91–93, 97, 100, 103). Of the studies using the ABIDE dataset, one reported predominant DMN overconnectivity with task-positive regions (86), while nine collectively reported DMN underconnectivity both within its hubs (87, 88, 90, 98, 102) as well as with other brain regions (81, 84, 90, 95, 99). Another five studies using the ABIDE dataset reported mixed DMN connectivity findings (89, 91, 93, 100, 103) using a range of analytic techniques (see **Table 1** for main results from each study).

Additional perspectives on DMN connectivity in ASD have been offered by new and emerging studies investigating whole brain DFC. Functional connectivity of neural networks are not static (temporally nor spatially); hence, functional connectivity of a network can vary in terms of connectivity strength and directionality during different temporal "windows" or timepoints of a scan (67, 119), Additionally, DFC clustering analysis allows for the identification of recurring patterns of connectivity among networks that is consistent with those observed during tasks. This coupling of specific functional networks during various timepoints of a resting-state scan are often referred to as "states" or state-dependency" of neural activity (67, 120). While some of these studies have found broader temporal variability of DMN connectivity across states in adolescents with ASD (87, 101), others show predominant patterns of underconnectivity between the DMN and salience, attentional, and visual networks, which is state-dependent and may be related to social cognition states (90, 99). Since DFC is a relatively new realm of functional connectivity research, additional investigations of dynamic DMN connectivity as it relates to adolescents with ASD is warranted to further delineate such state-dependent patterns. In addition to static versus dynamic models, one study also examined lateralization of the DMN and its relationship to language networks in adolescents with ASD (81), and found that the ASD group had significantly less left lateralization of these networks compared to TD controls, suggesting that these language and social cognition networks may not be as functionally specialized in ASD. They additionally found that this reduced left-lateralization was associated with higher ASD symptom severity.

A few studies have also explored the maturational trajectory of DMN connectivity in individuals with ASD (73, 84, 100). Wiggins et al. (73) looked at age-related patterns of DMN connectivity cross-sectionally, and found that the ASD group did not demonstrate typical age-related increases in connectivity between the precuneus/PCC hub of the DMN and frontal regions. Nomi and Uddin (84) further looked at differences in DMN connectivity between children and adolescents with ASD cross-sectionally, and found that children with ASD showed a pattern of within-DMN overconnectivity and between-network DMN underconnectivity relative to controls. Comparatively, adolescents with ASD did not differ from age-matched controls in within-DMN connectivity but demonstrated

TABLE 1 | Summary of demographic details and results for studies on DMN functional connectivity in adolescents with ASD.

Study	Sample Size	Age		Sex (F%)	IQ	Dataset	Analysis	Results for ASD group
	N (ASD/TD)	ASD Mean (SD)	TD Mean (SD)	ASD/TD				
77	30 (15/15)	15.7 (3)	17.1 (3.6)	6.7%/ 13.3%	ASD IQ=113.3 ± 15.0 TD IQ=117.1 ± 16.9		ICA	Underconnectivity within DMN hubs of precuneus (PCUN), and medial prefrontal cortex (mPFC).
78	31 (16/15)	15(1.45)	16(1.44)	12.5%/ 6.7%	No Full-Scale IQ ASD VIQ=114 ± 18.58 ASD NVIQ=117 ± 13.82 TD VIQ=113 ± 14.10 TD NVIQ=106 ± 12.53		SBA	Underconnectivity between posterior cingulate cortex (PCC) hub of DMN and 9 of 11 other DMN regions – retrosplenial cortex, and bilateral mPFC, superior frontal gyri (SFG), temporal lobe, parahippocampal gyri (PHG).
73	80 (39/41)	14(2.08)	15.3(2.4)	17.9%/ 19.5%	No Full-Scale IQ ASD VIQ=108.2 ± 19.04 ASD NVIQ=111.54 ± 15.97 TD VIQ=116.5 ± 13.34 TD NVIQ=105.4 ± 11.51		SOM	Underconnectivity between posterior hubs of DMN and right (r) SFG.
79	28 (14/14)	17.8(1.9)	17.7(1.8)	0%/0%	ASD IQ=116.9 ± 13.7 TD IQ=119 ± 9.6		SBA	Overconnectivity between anterior (a) MPFC hub of the DMN and right lateral parietal (rLP) seed.
80	50 (24/26)	14.9(1.4)	14.8(1.7)	25%/ 26.9%	ASD IQ=107.3 ± 16.9 TD IQ Not Reported		ICA	Underconnectivity between anterior and posterior DMN subnetworks.
81	964 (447/517)	16.6(8.1)	16.9(7.56)	11.4%/ 17.6%	ASD IQ=105 ± 17.4 TD IQ=112 ± 13.3	ABIDE	SBA	Reduced left lateralization in connectivity between PCC hub of DMN and language regions (Wernicke's area).
82	115 (71/44)	12.3(3.1)	12.2(3.8)	0%/0%	ASD IQ=97.8 ± 19.7 TD IQ=117.2 ± 9.7		SBA	Mixed results with underconnectivity between left PCC hub of DMN and left (l) MPC, right inferior temporal gyrus (rITG), and bilateral angular gyri (AG). In contrast, overconnectivity between PCC hub and inferior parietal lobule (IPL), superior parietal gyri (SPG), SFG, middle frontal gyri (MFG) and precentral gyri (PreCG).
83	39 (22/17)	13.8(2.0)	12.8(3.6)	23.5%/ 13.6%	ASD IQ=107.8 ± 18.7 TD IQ=107.8 ± 14.3		ICA/SBA	Mixed results with local overconnectivity in dorsal (d) anterior cingulate cortex (ACC) but underconnectivity between dACC and PCC/PCUN hub of DMN.
84	56 (28/28)	13.71(1.79)	14.01(1.74)	17.9%/ 17.9%	ASD IQ=103.57 ± 15.45 TD IQ=105.18 ± 9.90	ABIDE	ICA	Children showed within-DMN overconnectivity but not adolescents; Adolescents showed underconnectivity between DMN and subcortical/insular network.
85	75 (37/38)	13.9(2.6)	13(2.6)	13.5%/ 21%	No Full-Scale IQ ASD VIQ=105 ± 19.3 ASD NVIQ=104 ± 16.0 TD VIQ=107.8 ± 11.8 TD NVIQ=107.5 ± 12.5		SBA	Mixed results with underconnectivity within mPFC and PCC hubs of the DMN and overconnectivity between PCC and right ventrolateral prefrontal cortex (rVLPFC) and rIPL, mPFC and rVLPFC, and lAG and right dorsolateral prefrontal cortex (rDLPFC) and rIPL.
86	185 (90/95)	13.1(3.3)	13.2(3.1)	0%/0%	Not Reported	ABIDE	SBA	Overconnectivity between bilateral mPFC hub of DMN with bilateral IPL and right anterior insula (AI).

(Continued)

TABLE 1 | Continued

Study	Sample Size	Age		Sex (F%)	IQ	Dataset	Analysis	Results for ASD group
	N (ASD/TD)	ASD Mean (SD)	TD Mean (SD)	ASD/TD				
87 (Study 1)	152 (76/76)	16.1(4.9)	15.8(4.5)	11.8/ 15.8%	**Study 1:** ASD IQ=106.6 ± 18.1	ABIDE	DFC/SBA	Greater temporal variability across windows, as well as predominant underconnectivity within DMN regions such as PCC with mPFC, ACC, and right hippocampus, and mPFC with lLP.
87 (Study 2)	64 (32/32)	14.3(2.4)	13.5(2.7)	12.5%/ 15.6%	TD IQ=108.1 ± 12.4 **Study 2:** ASD IQ=106.3 ± 18.0 TD IQ=109.5 ± 11.1			
88	134 (51/40) 43 Unaffected Siblings	ASD M 14.5 (1.7) ASD F 14.5(2.0) M Sib 15.0(2.1) F Sib 14.6(2.2)	M 14.8(1.7) F 15.3(5.3)	31.4%/ 50% Siblings 69.8%	ASD M IQ=108 ± 16.1 M Sib IQ=113.5 ± 11 ASD F IQ=97.6 ± 10.7 F Sib IQ=112 ± 9.6 TD M IQ=114 ± 11.4 TD F IQ=110.7 ± 10.9	ABIDE	SBA	Underconnectivity within-DMN network in both males and females with ASD even compared to unaffected siblings.
89	46 (22/24)	13.1(3.1)	15.4(1.6)	31.8%/ 29.2%	ASD IQ=95.2 ± 22.1 TD M=104 ± 18.3	ABIDE	SVM	Atypical connectivity within DMN and salience network in both ASD and EOP. Distinct atypical connectivity for ASD was within-salience network.
90	213 (91/122)	14.87(1.61)	15(1.61)	0%/0%	ASD IQ=107.45 ± 12.11 TD IQ=109.30 ± 11.08	ABIDE	DFC/SBA	Underconnectivity within-DMN regions, between DMN and visual as well as ventral attention network in lower frequency bands (slow-4, slow-5).
91	54 (28/26)	13.79(1.79)	14.46(1.45)	17.9%/ 19.2%	ASD IQ=108.06 ± 13.86 TD IQ=110.11 ± 7.87	ABIDE	ALFF	Mixed results with lower ALFF values in rPCUN hub of DMN, and higher ALFF values in mPFC hub of DMN only for adolescents.
92	31 (15/16)	21.6(3.7)	21.9(3.5)	0%/0%	ASD IQ=111 ± 10 TD IQ=123 ± 9.2		SBA	Mixed results with underconnectivity between mPFC hub of DMN and bilateral AG region, and overconnectivity between DMN coupling with task positive fusiform face are (FFA) and supramarginal gyri (SMG).
93	92 (50/42)	13.34(2.41)	13.05(1.82)	10%/ 14.3%)	ASD IQ=99.73 ± 14.40 TD IQ=107.21 ± 10.94	ABIDE	ICA	Mixed results with underconnectivity within anterior hubs of the DMN of mPFC, inferior frontal gyrus-triangularis (IFGtriang) and overconnectivity with posterior hubs of the DMN (PreCG, SPG, PCUN).
94	102 (49/53)	17.39(3.1)	16.8(2.95)	12.2%/ 23.3%	ASD IQ=103.65 ± 14.46 TD IQ=108.81 ± 10.76		SBA	Overconnectivity between DMN and salience as well as frontoparietal network.
95	718 (369/349)	13.53	13.54	0%/0%	Not reported	ABIDE	SVM	Underconnectivity between DMN and salience network and lower coupling of DMN and right temporoparietal junction (rTPJ) node of dorsal attention network.
96	150 (62/10)	16.16(1.21)	16.16(1.21)	45.2% F	ASD IQ=100.5 ± 16.05		SBA	Underconnectivity between DMN (PCC, vmPFC) and salience network (ACC, rAI) hubs in adolescents.
97	51 (22/29)	17.45(3.29)	18.48(2.82)	18.2%/ 34.5%	ASD IQ=99.77 ± 9.5 TD IQ=105.83 ± 9.64		SBA	Mixed results with underconnectivity between PCC hub and executive control component of DMN (ACC, IFG, SFG, middle temporal regions), and overconnectivity between mPFC hub and sensorimotor

(Continued)

TABLE 1 | Continued

Study	Sample Size	Age		Sex (F%)	IQ	Dataset	Analysis	Results for ASD group
	N (ASD/TD)	ASD Mean (SD)	TD Mean (SD)	ASD/TD				
								component of DMN (amPFC, bilateral Pre-and Post-CG).
98	98 (49/49)	14.35(1.77)	14.35(1.77)	0%/0%	Not reported but groups matched for IQ (± 10 points)	ABIDE	SBA	Underconnectivity between rPCUN hub of DMN and right middle temporal gyrus (rMTG) as well as bilateral Post-CG.
99	507 (209/298)	16.5(6.2)	16.8(6.2)	0%/0%	ASD IQ=110.6 ± 13.4 TD IQ=110.2 ± 11.4	ABIDE	DFC/SBA	Underconnectivity within vmPFC and PCC hubs of the DMN with rAI in social cognition dynamic states (state 3, state 5).
100 (Time 1)	38 (16/22)	12.5(0.8)	12.9(0.9)	6.3%/0%	ASD IQ=101.3 ± 17.7 TD IQ=107.8 ± 13.5	ABIDE II	SBA	Atypical developmental trajectory with lower negative connectivity between DMN and central executive network longitudinally from early to late adolescence.
100 (Time 2)	38 (16/22)	15.5(0.8)	16.0(0.9)	6.3%/0%				
101	119 (62/57)	13.7(2.5)	13.1(2.9)	16.1%/ 19.3%	ASD IQ=103 ± 18 TD IQ=108 ± 12		DFC/ICA	Overconnectivity between DMN and visual, sensorimotor, frontoparietal, and executive network in static state; along with increased variability in DMN across dynamic states.
102	88 (44/44)	11.2(2.7)	10.9(2.8)	~22%/ ~22%	Low ASD IQ=77 ± 6 High ASD IQ=123 ± 8 Average TD IQ=99 ± 7 High TD IQ=124 ± 8	ABIDE II	SBA	Underconnectivity within-DMN in lower-functioning participants more prominent than higher-functioning participants.
103	260 (83/177)	11.2(5.3)	11(4)	16.9%/ 24.9%	No Full-Scale IQ ASD NVIQ=105.0 ± 15.7 TD IQ=106.1 ± 11.2	ABIDE II	ICA	Mixed results with underconnectivity within-DMN regions, and overconnectivity between DMN and somatomotor network.
104	102 (52/50)	13.7(2.6)	13.6(2.6)	15.38%/ 16%	ASD IQ=104 ± 16.4 TD IQ=107 ± 11		SBA	Overconnectivity between PCC hub of DMN and IFG and visual cortex bilaterally

underconnectivity between DMN and the salience network and subcortical regions. In a longitudinal study, Lawrence et al. (100) looked at changes in DMN connectivity between ASD and TD controls from early to late adolescence, and found that TD controls had an age-associated increase in *negative* functional connectivity between the DMN and the task-positive central executive network, not observed in adolescents with ASD. These findings support the theory of a crucial maturational shift in DMN connectivity patterns during adolescence which is likely significantly impacted in individuals with ASD such that the typically expected strengthening and honing of DMN connectivity is disrupted in this population during this age period. However, the mechanism underlying the shift in DMN connectivity patterns after the onset of puberty is not fully understood in ASD yet, and requires further exploration to elucidate differential trajectories and their impact on symptomatology.

So far, only one study has systematically examined sex differences in DMN connectivity in ASD (88). This study spanned a wide age range from childhood to adulthood, but in the adolescent subset female TD controls demonstrated stronger within-DMN connectivity relative to male TD controls; comparatively, ASD females and males showed similar within-DMN connectivity strength, that in turn was significantly lower than their TD counterparts. Notably, this DMN hypoconnectivity appeared to be an endophenotype, as it was also observed in the unaffected siblings of ASD cases, relative to TD controls. These findings suggest aberrant DMN connectivity may underlie a broader continuum of autism-relevant traits in the general population.

Intellectual functioning is another variable of interest relevant to DMN connectivity in adolescents with ASD, given the wide range of cognitive abilities in this population (121). Most of the studies included in this review focused on adolescents within the normative intellectual functioning range; however, one recent study (101) examined the differences in within-DMN connectivity between low (Mean IQ=77 ± 6) and high-IQ ASD participants (Mean IQ=123 ± 8) and found that the low cognitive functioning group demonstrated significant within-DMN underconnectivity compared to the high-functioning group, even after controlling for symptom severity.

Lastly, several of the studies (12 out of 29) included in our review have examined the relationship between aberrant DMN connectivity in adolescents with ASD and behavioral measures of

TABLE 2 | Summary of demographic details and results for studies on DMN functional connectivity in adolescents with EOP.

Study	Sample Size	Age		Sex (F%)	IQ	Patient Characteristics	Analysis	Results for EOP group
	N (EOP/TD)	EOP Mean (SD)	TD Mean (SD)	EOP/TD				
105	64 (32/32)	16.2(1.2)	16.4(0.9)	53.1%/50%	EOP=9.4 ± 1.5 TD=9.7 ± 0.7	Youth with first-episode schizophrenia < 2 years illness onset	ICA/ ALFF	Overconnectivity between mPFC and other areas of the DMN.
106	67 (37/30)	15.5(1.8)	15.3(1.6)	54.1%/43.3%	EOP=8.5 ± 1.48 TD=8.7 ± 1.42 IQ > 70 both groups	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset	SBA	Underconnectivity between rMTG seed region of DMN and lITG, lFFA, lPHG, as well as between DMN and visual network regions.
107	102 (31/37) UHR 34	20.61(4.42) UHR 21.50 (3.53)	20.76(3.08)	38.7%/51.4% UHR 38.2%	EOP=6.26 ± 4.27 UHR =6.26 ± 4.13 TD=5.46 ± 1.87	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset UHR included brief intermittent psychotic syndrome, attenuated positive symptom syndrome, and genetic risk and deterioration syndrome	SBA	Overconnectivity between DMN (PCUN/PCC, mPFC) and cerebellum in both EOP and UHR groups; with UHR group showing stronger patterns of cerebellar-DMN connectivity than EOP group.
108	65 (35/30)	15.5(1.8)	15.3(1.6)	42.9%/56.7%	EOP=8.5 ± 1.48 TD=8.7 ± 1.42	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset	SBA/ ALFF	Lower ALFF values in vPCUN, along with underconnectivity between vPCUN and dPCUN as well as midcingulate cortex (MCC).
89	66 (35/31)	15.6(1.8)	15.4(1.6)	42.86%/ 58.06%	Not Reported	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset	SVM	Atypical connectivity within DMN and salience network in both EOP and ASD. Distinct atypical connectivity for EOP was between DMN-salience connectivity.
109	51 (32/19)	AVH 21.24 (3.85) Non-AVH 22.53(4.07)	23.79(3.75)	AVH 41.18% Non-AVH 46.67% TD 47.37%	AVH=13.71 ± 1.93 Non-AVH= 13.40 ± 1.55 TD=14.74 ± 2.26	Patients with schizophrenia experiencing AVHs vs. Patients with schizophrenia not experiencing AVHs	ICA/ ALFF	Higher signal amplitude within-DMN regions (mPFC, ACC, PCC, AG, rSPG) along with increased prefrontal cortex-DMN coactivation in patients with AVHs versus non-AVH patients. AVH patients also demonstrated more atypical ALFF values in PCUN than non-AVH patients.
110	65 (35/30)	15.5(1.8)	15.3(1.6)	42.9%/56.7%	EOP=8.5 ± 1.48 TD=8.7 ± 1.42	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset	DFC	Underconnectivity in PCUN hub of DMN in slow-4 frequency band, but no significant group differences in slow-5 frequency band.
111	79 (48/31)	15.79(1.64)	15.42(1.52)	56.3%/54.8%	EOP=8.88 ± 1.95 TD=8.44 ± 1.56 IQ > 70 both groups	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset	SVM/ ReHo	Decreased ReHo values in rPre-CG, lPost-CG, rIPL, rMFG, bilateral PCUN, left superior temporal gyrus (lSTG), left paracentral lobule regions of the DMN. Reho values in bilateral PCUN and rIPL especially discriminated patients with 91.67% sensitivity, 87.1% specificity, and 89.87% accuracy.
112	79 (48/31)	15.79(1.64)	15.42(1.52)	56.3/54.8%	EOP=8.88 ± 1.95 TD=8.44 ± 1.56 IQ > 70 both groups	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset	SVM	Mixed results with underconnectivity of both long- and short-range networks involving posterior DMN hubs, and overconnectivity of both long- and short -range networks involving anterior DMN hubs.

(Continued)

TABLE 2 | Continued

Study	Sample Size	Age		Sex (F%)	IQ	Patient Characteristics	Analysis	Results for EOP group
	N (EOP/TD)	EOP Mean (SD)	TD Mean (SD)	EOP/TD				
113	79 (48/31)	15.79(1.64)	15.42(1.52)	56.3/54.8%	EOP=8.88 ± 1.95 TD=8.44 ± 1.56	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset	SVM/ ReHo	Mixed results with increased ReHo values in mPFC hub of DMN, and decreased ReHo values in lSTG, rPre-CG, rIPL, and left paracentral lobule; this combination was able to discriminate patients from controls with the sensitivity of 88.24%, specificity of 91.89%, and accuracy of 90.14%.
114	86 (48/38)	AVH 24.32 (8.46) Non-AVH 24.35(6.94)	25.44(7.52)	AVH 53.5% Non-AVH 50% TD 55.3%	AVH=11.29 ± 3.00 Non-AVH= 11.70 ± 2.60 TD=13.34 ± 3.58	Drug-naïve patients with first-episode schizophrenia experiencing AVHs vs. Drug-naïve patients with first-episode schizophrenia not experiencing AVHs < 2 years illness onset for both groups	GCA	Mixed results with underconnectivity between DMN hubs (mPFC, PCC) and left inferior temporal gyrus (lITG), lSTG, bilateral cingulate gyrus, bilateral thalamus, left insula, and left cerebellum, with overconnectivity between hub regions and left cingulate gyrus, right putamen, rMFG, right thalamus, and left cerebellum. AVH patients demonstrated underconnectivity between aMPFC and lITG, as well as PCC to left cerebellum, lITG, and rMFG compared to non-AVH patients.
115	65 (35/30)	15.5(1.8)	15.3(1.6)	42.9/56.7%	EOP=8.5 ± 1.48 TD=8.7 ± 1.42	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset	DFC	Mixed results with underconnectivity between lPCUN hub of DMN and lMTG in state2, and overconnectivity in rPCUN, rSMG, and right putamen in state 4.
116	68 (27/41)	18.1(1.6)	17.8(1.6)	59.3%/56.1%	EOP=92.8 ± 15.7* TD=104.1 ± 9.8*	Youth with early onset psychosis including schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, bipolar spectrum disorders, and psychosis not otherwise specified < 2 years illness onset	ICA	Underconnectivity of mPFC hub of DMN in EOP group compared to TD controls, and connectivity additionally decreased with age in EOP where it increased with age in TD controls.
117	79 (48/31)	15.79(1.64)	15.42(1.52)	56.3%/54.8%	EOP=8.88 ± 1.95 TD=8.44 ± 1.56 IQ > 70 both groups	Drug-naïve patients with first-episode schizophrenia < 2 years illness onset	SVM/NH	Mixed results with higher NH values in left mPFC and lower NH values in bilateral PCC/PCUN in EOP group compared to TD controls.

**Study reported IQ scores instead of education in years for demographic characteristics.*

symptom severity such as the Autism Diagnostic Observation Schedule (ADOS; 122, 123), the Autism Diagnostic Interview-Revised (ADI-R; 124), and the Social Responsiveness Scale (SRS; 125, 126). Studies looking at the association of within-DMN network connectivity with behavioral measures of symptom severity (N=6 studies) found mixed effects, with most (five out of six studies) reporting greater within-DMN network underconnectivity associated with higher social impairment scores on the ADOS (77, 90, 91), ADI-R (78, 103), and SRS (77); while one of the six found greater within-DMN overconnectivity to be associated with higher social impairment scores on the SRS (83), and one (using the ADOS) reporting a mixed pattern (91). Studies looking at the association of DMN between-network connectivity with behavioral measures of symptom severity (N=7) mostly found that greater overconnectivity between DMN and other brain regions (mostly in the frontal and temporal lobes; four out of seven studies) was associated with higher social impairments on the ADOS (89), ADI-R (trend level; 97), and SRS (85, 86). Interestingly, in one of the first studies to report DMN overconnectivity in adolescents with ASD, Redcay et al. (79) found that greater DMN overconnectivity with the right lateral parietal region was associated with less impairment on the social-communication domain of the ADOS, suggesting the possibility of an underlying

compensatory mechanism in this particular brain network. Only two out of seven studies looking at the association of DMN between-network connectivity with behavioral measures of symptom severity found that greater underconnectivity between DMN hubs and other brain regions (salience, attention networks) in ASD was associated with higher symptom severity on the ADOS (90, 99). Additionally, Doyle-Thomas et al. (82) and Ypma et al. (88) found that anomalous DMN connectivity patterns in adolescents with ASD (mixed within-DMN connectivity results in the former study, and within-DMN underconnectivity in the latter study) were associated with poorer performance on the "Reading the Mind in the Eyes" Test (RMET; 127), a measure of affective theory of mind (ToM). Of the studies (all 12 reporting associations between DMN connectivity and behavioral measures of symptom severity) that looked at both the social interaction domain and the repetitive behaviors/restricted interests domain of the ADOS-2 and ADI-R (77–79, 83, 85, 86, 89–91, 97, 99, 103), only one study (78) reported a significant relationship for DMN within-network underconnectivity patterns and measures of repetitive behaviors/restricted interests (ADI-R) in ASD adolescents. Hence, it appears that aberrant DMN connectivity may play a larger role in the social functioning deficits experienced by this population rather than other features of ASD.

DMN CONNECTIVITY IN ADOLESCENTS WITH EOP

Prior research on adults with schizophrenia spectrum disorders suggests that disrupted DMN connectivity may play an important role in the pathophysiology of schizophrenia (63). Specifically, findings in adults with schizophrenia frequently include within-DMN overconnectivity, as well as mixed findings of under- and over-connectivity between DMN and task-positive networks; in turn, these disruptions have been associated with positive symptoms, poor social functioning, as well as poor cognitive functioning in schizophrenia (63). Additionally, DMN connectivity has been found to become more "normative" in response to anti-psychotic treatment in adults with schizophrenia (128, 129). Some of the inconsistencies found in the literature on DMN connectivity patterns in schizophrenia, with both under- and over-connectivity involving this network being associated with symptom severity, as well as social and cognitive functioning, could be attributed to the heterogeneity of patient characteristics within schizophrenia spectrum disorders. For instance, studies thus far have included individuals with first-episode schizophrenia, chronic patients, drug-naïve patients, as well as patients treated with antipsychotic medications which may have impacted the results across these studies. Hence, how disease progression as well as treatment status impacts DMN connectivity and its relationship with behavioral outcomes in schizophrenia is not yet clear.

More recent studies of DMN connectivity in adolescents with EOP offer some insight into neural anomalies in the earlier stages of this disorder (**Table 2**). Several EOP studies (11 out of 14) have focused on drug-naïve adolescent patients with psychotic disorder with illness onset within two years (89, 106–108, 110–115, 117). Of these, the majority (eight out of 11) appear to report on the same (or at least, largely overlapping) cohort (106, 108, 110–113, 115, 117). Other EOP studies (three out of 14) have involved independent cohorts of adolescents with recent-onset psychotic disorder receiving anti-psychotic treatment (105, 109, 116). Collectively, results suggest a mixed pattern of under- and over-connectivity involving the DMN, similar to that observed in adults with schizophrenia (63) and regardless of analytic method or cohort used (see **Table 2** for main results from each study).

One study comparing adolescents at clinical high risk for psychosis (CHR) to drug-naïve adolescents with a diagnosed psychotic disorder suggested that while both groups showed increased connectivity between DMN and cerebellum compared to TD control groups, the connectivity strength was attenuated in those with overt illness (107). On the other hand, some studies of drug-naïve adolescents with psychotic disorder have reported underconnectivity within the DMN (108, 110, 111) relative to healthy controls, and between DMN and other brain areas such as prefrontal cortex, temporal gyrus, parietal cortex, and limbic regions (106). However, six out of 14 studies investigating DMN connectivity in youth with EOP indicate a mixed pattern of connectivity, both within the DMN as well as between the DMN and other brain regions such as temporal lobe, subcortical regions, and cerebellum (89, 112–115, 117). One interesting perspective offered by Wang et al. (112) from their examination of short versus long-range DMN connectivity is that there is potentially a pattern of overconnectivity involving the anterior hubs of the DMN, compared to underconnectivity involving the posterior hubs of the DMN in drug-naïve adolescents with psychotic disorder. This perspective is further supported by recent findings of higher network homogeneity in anterior hubs of the DMN but lower in posterior hubs of the DMN in drug-naïve adolescents with psychotic disorder compared to controls (117). In the past few years, studies investigating whole-brain DFC in adolescents with EOP have also emerged (110, 115). These studies have been largely consistent with the mixed connectivity findings of the DMN for drug-naïve adolescents with a diagnosed psychotic disorder (110, 115) and suggested that over- or under-connectivity of the DMN could be state-dependent, with the precuneus hub of the DMN especially demonstrating differential state-dependent connectivity patterns with other brain regions.

Studies of youth with EOP receiving anti-psychotic medication mostly showed overconnectivity relative to healthy controls within the DMN (105, 109), as well as increased co-activation between DMN and prefrontal cognitive control regions (109) with only one study reporting underconnectivity within the DMN (116). It is therefore tempting to speculate that prior to the introduction of anti-psychotic medication the DMN tends to be underconnected or mixed in its connectivity patterns, with changes occurring in the pattern of connectivity after implementation of a medication regimen or as the course of the disease progresses.

Current symptom severity may also impact DMN connectivity patterns in adolescents with EOP. Ten out of 14 studies reviewed

here examined the relationship between DMN connectivity and symptom severity on the Positive and Negative Syndrome Scale (PANSS), a widely used measure in schizophrenia (130). Out of these, four studies did not find any significant associations between DMN connectivity patterns and PANSS scores (89, 112, 115, 116). However, results from six out of 10 studies that found significant relationships between DMN connectivity and the PANSS revealed that aberrant within-DMN connectivity (105, 108, 110) as well as disrupted connectivity between DMN and other brain regions (106, 107, 114) in EOP tended to be more strongly associated with PANSS negative symptoms scores rather than positive symptom scores. Lastly, one recent study found that within-DMN underconnectivity accounted for ~16% of the variance in ToM performance measured by the RMET in adolescents with EOP treated with anti-psychotics (116). This suggests that the DMN may have a more crucial role in the social impairments observed in adolescents with EOP, rather than positive symptoms such as unusual thought content or perceptual disturbances.

SHARED AND DISTINCT DMN CONNECTIVITY PATTERNS IN ADOLESCENTS WITH ASD AND EOP

Figure 1 provides a schematic representation of findings from all the studies for each group, with yellow dots representing the DMN hub regions, blue (underconnected) or red (overconnected) dots representing connectivity with other brain regions, and thickness of lines connecting the dots representing frequency of findings across studies in each group. Here, we see that studies examining within-DMN connectivity (intra-DMN) found underconnectivity involving the posterior hub of the DMN or between the anterior and posterior hubs of the DMN more frequently in ASD (77, 78, 80, 82, 83, 85, 87, 88, 90, 91, 97, 102, 103), while overconnectivity involving the anterior hub or between the anterior and posterior hubs of the DMN was often found in EOP studies (105, 109, 112, 113, 117). Some studies reported intra-DMN underconnectivity in EOP involving the posterior hub of the DMN or between the medial and lateral hubs of the DMN (106, 108, 110, 117). However, it should be noted that all these studies reporting intra-DMN underconnectivity in EOP are based on the same or largely overlapping subjects. On the other hand, overconnectivity within the ASD group was most frequently seen between the anterior and lateral hubs of the DMN (79, 85, 86, 91, 97). For studies examining connectivity between DMN and other brain regions (inter-DMN), underconnectivity in ASD relative to TD controls mostly involved the posterior hub of the DMN and frontal regions as well as right anterior insula, a hub region of the salience network (73, 82, 84, 89, 93, 95–99). It should be noted that six out of 10 of these studies reporting inter-DMN underconnectivity involving the posterior hub in ASD are based on the same or largely overlapping ABIDE subjects (84, 89, 93, 95, 98, 99); as such, these cannot be considered independent findings. In contrast, inter-DMN underconnectivity for EOP relative to controls was seen most frequently between the anterior hub of the DMN and left temporal lobe (106, 111, 113–115). Overconnectivity for inter-DMN networks in the ASD group also involved the posterior hubs of the DMN, mostly with somatomotor and visual regions as well as anterior hubs of the DMN with the right anterior insula (82, 85, 86, 92–94, 97, 100, 101, 103, 104). In contrast, inter-DMN overconnectivity in EOP relative to controls was predominantly observed between DMN hubs (both anterior and posterior) and the subcortex and cerebellum (107, 114, 115). Hence, it appears that intra-DMN networks seem to be more frequently underconnected (between anterior and posterior hubs) in ASD adolescents, but mixed (i.e., underconnected for anterior hub, or between medial and lateral hubs, and overconnected for posterior hub or between anterior and posterior hubs) in EOP adolescents. On the other hand, inter-DMN connectivity patterns appear to be mixed for both groups, especially in its connectivity with frontal, sensorimotor, and temporoparietal regions in ASD, and with frontal, temporal, subcortical, and cerebellar regions in EOP.

Taken together, the findings reviewed thus far highlight that ASD and EOP have both convergent, as well as divergent, patterns of dysregulation of DMN networks. Convergently, the mixed findings reported to date suggest poor functional segregation and integration of the DMN in both ASD and EOP during adolescence. The only currently published study that has directly compared whole-brain connectivity patterns in adolescents with ASD and EOP (89) found that ASD and EOP youth shared a common pattern of disrupted connectivity compared to TD controls, mainly involving the prefrontal nodes of the DMN and salience networks, which is also implicated in social functioning (131, 132). In contrast, they found that disrupted connectivity *between* DMN and salience network was more characteristic of EOP, whereas in ASD the atypical connections were primarily found *within* the salience network. Studies examining the maturational trajectory of resting state networks in ASD suggest that DMN connectivity appears to decrease from childhood to adolescence (73, 84, 100), similar to the DMN "network pruning" found in studies of typically developing adolescents (36, 37, 41, 45). However, unlike typically developing adolescents, there is a lack of both strengthening between anterior and posterior hubs of the DMN and segregation from other brain regions reported during this developmental period in the reviewed ASD studies. There were no available studies examining longitudinal trajectories of DMN connectivity in EOP adolescents to address age-associated changes or medication effects in this group. Thus, more longitudinal studies are warranted to understand DMN connectivity changes as a function of development and disease progression in both ASD and EOP groups.

Additionally, the studies reviewed here that reported brain-behavior associations have mostly used symptom severity measures (such as the ADOS, ADI-R, SRS, PANSS) rather than measures of social functioning or social cognition per se. One reason for the absence of specific social cognition measures across studies might be the use of shared datasets which provides researchers with large sample sizes, but a limited amount of common behavioral data

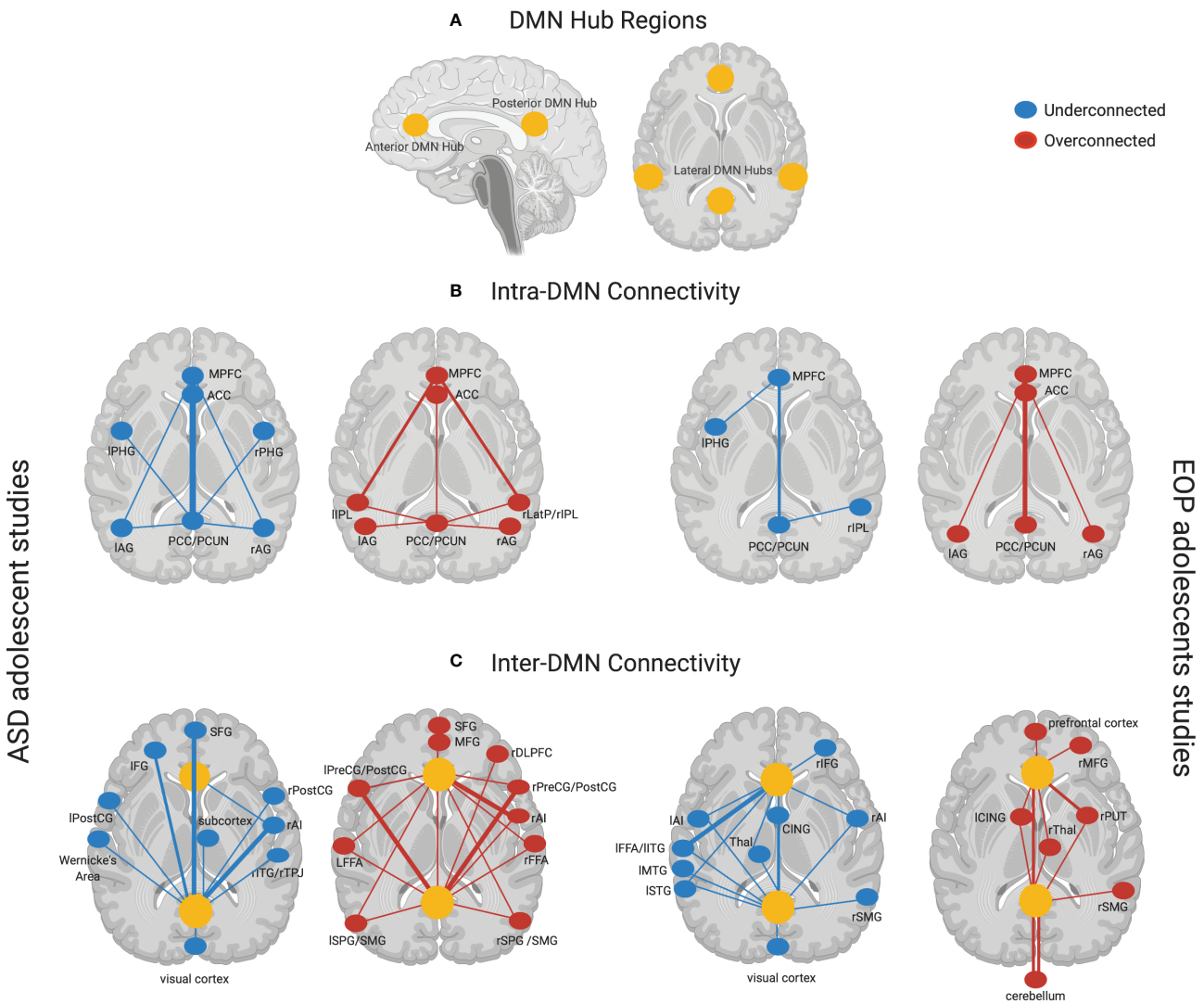

FIGURE 1 | (A) DMN hub regions included in analyses across most studies in the present review denoted in yellow circles—anterior hubs include medial prefrontal regions (mPFC) and anterior cingulate cortex (ACC), posterior hubs include the posterior cingulate cortex (PCC) and precuneus (PCUN), lateral hubs include inferior parietal lobule (IPL), angular gyrus (AG), and medial temporal regions such as parahippocampal gyrus (PHG); **(B)** Intra-DMN connectivity findings across ASD adolescent studies (left panel)—Underconnectivity findings (denoted by blue dots) mostly involve the posterior hubs of the DMN. Thicker lines such as between the PCC/PCUN and the anterior hubs of the DMN (mPFC, ACC) denote overlapping findings across multiple studies, with thinner lines indicating underconnectivity within DMN regions found in fewer studies. Overconnectivity findings (denoted by red dots) for the ASD group involve the anterior hubs of the DMN slightly more prominently than the posterior hubs on the DMN. Thicker lines such as between the mPFC and left and right IPL denote overlapping findings across multiple studies, with thinner lines indicating overconnectivity within DMN regions found in fewer studies. Intra-DMN connectivity findings for EOP adolescent group are depicted in the right panel—Underconnectivity within the DMN regions (blue dots) was found by fewer studies for this group indicated by thinner lines, while overconnectivity (red dots) was mostly found within the anterior and posterior hubs of the DMN; **(C)** Inter-DMN connectivity findings across ASD adolescent studies (left panel)—Underconnectivity findings (denoted by blue dots) mostly involve the posterior hub (PCC/PCUN) of the DMN especially in its connectivity with prefrontal regions and the right anterior insula (rAI) hub of the salience network denoted by thicker lines with additional findings of underconnectivity between DMN and other brain regions denoted by thinner lines. Overconnectivity findings (denoted by red dots) for the ASD group also involve the posterior hubs of the DMN mostly with somatomotor regions as well as anterior hubs of the DMN with the salience network hub (rAI) denoted by thicker lines. Other regions demonstrating overconnectivity with the DMN for the ASD group are denoted by thinner lines. Inter-DMN connectivity findings for EOP adolescent group are depicted in the left panel—Underconnectivity between anterior DMN hubs and left temporal lobe was most prominently found across studies depicted by thicker lines, with additional findings of underconnectivity between both the anterior and posterior hubs of the DMN and other brain regions denoted by thinner lines. On the other hand, overconnectivity in the EOP group was predominant between DMN hubs (both anterior and posterior) and the subcortex and cerebellum highlighted by thicker lines, with additional overconnectivity between DMN hubs and other brain regions denoted by thinner lines. Additional abbreviations used in figure: PHG, parahippocampal gyrus; AG, angular gyrus; LatP, lateral parietal lobule; SFG, superior frontal gyrus; IFG, inferior frontal gyrus; PreCG, precentral gyrus; POSTCG, postcentral gyrus; ITG, inferior temporal gyrus; TPJ, temporoparietal junction; MFG, middle frontal gyrus; DLPFC, dorsolateral prefrontal gyrus; FFA, fusiform face area; SPG, superior parietal gyrus; SMG, supramarginal gyrus; CING, cingulate gyrus; Thal, thalamus; MTG, middle temporal gyrus; STG, superior temporal gyrus; PUT, putamen.

collected across all contributing sites. Another reason could be the absence of *a priori* hypotheses about the association between DMN connectivity and social functioning. Only two ASD studies (82, 88) and one EOP study (116) used the RMET to measure social cognition in these clinical populations. Notably, all three studies found a significant inverse association between intra-DMN connectivity and RMET performance in both patient groups (i.e., less intra-DMN connectivity was associated with poorer task performance). This might suggest that the strengthening of connectivity between anterior and posterior DMN hubs during adolescence plays a crucial role in social functioning, and disruptions to this process in these neuropsychiatric conditions may be pertinent to social impairments. Other studies reporting brain-behavior findings additionally suggest that disrupted DMN connectivity appears to be associated with social impairments in both ASD (using the ADOS, ADI-R, or SRS) and EOP (using the PANSS), rather than other features distinct to each condition (e.g., repetitive behaviors and restricted interests in ASD vs. presence of hallucinations or delusions in EOP). Collectively, these may be considered preliminary findings for the shared role of DMN connectivity specifically underlying social functioning deficits characteristic of both ASD and EOP. However, more comprehensive assessments of social cognition abilities are needed in future studies to better elucidate the shared and distinct role of DMN connectivity disruptions in the developing brain and its relevance to social functioning.

FUTURE DIRECTIONS

In this review, we have summarized resting state functional MRI studies of DMN connectivity from empirical studies in two different clinical populations involving marked social impairment, autism spectrum disorder and early onset psychosis, during the crucial developmental window of adolescence. While the literature thus far has helped shed some light on both the common and unique patterns of DMN connectivity across these two groups, several gaps remain in our understanding of how DMN connectivity might contribute to the unique pathophysiology of both neuropsychiatric conditions. First, there have been far fewer studies on DMN connectivity in EOP than ASD adolescents. This may be due in part to difficulties in ascertaining adolescents with EOP compared to adults with psychotic disorder, given its relatively lower prevalence (133, 134). Another reason is the wider availability of large, open-access imaging datasets of adolescents with ASD such as ABIDE. Given the difficulties of collecting neuroimaging data in unique clinical populations at single sites, it is advantageous for more researchers to combine their imaging datasets using a systematic and open-source forum to allow large-scale statistical analyses cross-diagnostically. However, at present, the extent of overlap in subjects is unclear in ASD studies using ABIDE data, as well as the EOP studies that used a similar cohort of drug-naïve adolescent patients. Additionally, differences in methodologies implemented across ASD and EOP studies preclude direct comparisons of effect size for the reviewed findings. Hence, we encourage future studies on DMN connectivity in these patient populations to provide greater transparency and consistency in reporting of methods and results. Furthermore, both these conditions are characterized as spectrum disorders of varying severity, heterogeneous etiologies, and comorbidities. Since the DMN connectivity patterns observed for each of these neuropsychiatric disorders did not appear to map on well to the symptom severity measures used to assess social functioning (ADOS, ADI-R, SRS, PANSS), future studies might want to examine dimensional relationships between symptoms, social cognition performance, and their neural correlates, rather than the traditional case-control designs implemented in the majority of studies to date. Such a dimensional approach can include multiple neural features of DMN connectivity and more detailed clinical assessments of social cognition, but will require larger samples to provide meaningful findings. Finally, the impact of factors such as genetic risk, symptoms endorsed, pubertal development, and treatment history on DMN connectivity have yet to be explored within both groups. For instance, few studies have examined the contribution of medication on DMN connectivity, despite evidence that antipsychotic medication can impact brain connectivity patterns (63, 128, 135). Similarly, more work examining the impact of disease progression in EOP on DMN connectivity is needed to understand if abnormal DMN connectivity within this population remains relatively stable across the duration of illness or if further declines are associated with longer-term illness. In the ASD population, imaging studies have generally focused on high-functioning individuals, with only one study so far exploring the differences in DMN connectivity between high-and low-functioning ASD adolescents (101). It would be important to explore the influence of such contributing factors to DMN connectivity anomalies to interpret the divergent findings across studies and develop a potential mechanistic model of how genetics, neural wiring, and environmental factors may cascade into the phenotypic features we observe in these neuropsychiatric conditions.

AUTHOR CONTRIBUTIONS

AN and CB took the lead role in reviewing papers and drafting the manuscript. MJ and SL assisted in reviewing papers and preparing tables. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Adding a Dimension to the Dichotomy: Affective Processes Are Implicated in the Relationship Between Autistic and Schizotypal Traits

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Introduction: There is a recognized increase in vulnerability to psychosis in autistic people (AP). However, the construct of psychosis (particularly schizophrenia) contains several distinct factors, making understanding the relationship between autism and psychosis complex. Previous research has suggested that affective lability may be particularly related to psychotic experiences for AP who have experienced psychosis (AP-P). There is also a suggestion that psychosis might be a state of extreme (over) empathizing, perhaps related to emotional processes.

Method: We recruited three groups: AP-P (N = 23), a group of AP who had not experienced psychosis (AP-NP; N = 59) and a neurotypical control group (NC, N = 41). Participants completed measures of autistic traits, schizotypal traits (as a proxy for psychosis-proneness), emotional processes, and perspective taking (as a proxy for the type of empathizing most theoretically likely to be linked to psychosis). As well as comparisons between groups, regression analyses were used to understand the influence of dependent variables on schizotypal traits.

Results: We found that AP-P had significantly higher rates of schizotypy (positive and disorganized), as well as higher rates of emotional difficulties. Across all groups, affective lability had a positive and significant association with positive and disorganized schizotypal traits. Differences in perspective taking between groups were small and generally non-significant, particularly in adjusted comparisons; additionally, its impact on schizotypy was small and non-significant.

Discussion: Our findings suggest that positive and disorganized schizotypy, in particular, have a relationship with affective lability. This, in turn, supports the idea of emotional processes as related to the development of schizotypal traits and psychosis across all

individuals, regardless of autism diagnostic status. We found no evidence of empathy relating to any subscale of schizotypy, or the total schizotypy score. We contend that emotional processes should be considered in exploration of the relationship between autism and schizotypy in future. This may help to explain some of the findings of overlap between these constructs in previous research. Factors known to affect neurodevelopment of emotion systems such as history of early trauma, challenges during pregnancy and birth, and early childhood experiences of adversity during critical windows of development need further consideration in future research.

Keywords: autism, schizotypy, psychosis, affect, emotion, empathy, executive functioning

INTRODUCTION

Autism spectrum disorders (ASDs) are life-long neurodevelopmental conditions affecting an individual's perception of, and interaction with, the world (1). ASD refers to a number of heterogeneous 'autisms' (2), conditions that share core features of unusual perceptual abilities (3), social communication difficulties (4), and difficulties interpreting social cues (5) but differ subtly from individual to individual. Since the first definition of autism, and Bleuler's description of what we would now label 'negative symptoms' of psychotic mental illness (6), there has been persistent debate about the relationship between experiences of autistic people (AP; individuals who meet diagnostic criteria for ASD[1]) and experiences of mental illness, particularly psychosis. This study is an attempt to further explore and clarify the relationship between these concepts, with reference to other relevant psychological processes.

Chisholm and colleagues (7) reviewed eight possible models of relationship between ASD and schizophrenia spectrums disorders (SSDs), and concluded that the evidence was strongest for four models: the increased vulnerability model (AP are more at risk of psychosis due to their ASD, but the conditions are separate); the diametrical model (ASD and psychosis are opposite ends of a continuum of overlapping constructs); associated liabilities model (factors that increase risk of one condition also increase risk of the other, but they remain separate); and the multiple overlapping etiologies model (some factors that lead to developing ASD also lead to developing psychosis, but others do not, leading to distinct but often similar or overlapping presentations). From the available evidence, the authors were not able to demonstrate that one model was clearly superior. They highlight that these models may not be mutually exclusive, and that there are likely to be subgroups for which one or other model may provide the greatest explanatory power. Thus, any research into an overlap between ASD and psychosis will be informed by, and influence, discussion of an explanatory model of that overlap.

In order to understand the relationship between ASD and psychosis, researchers have attempted to map ASD traits and psychotic traits into the same conceptual 'space'. A personality construct called schizotypy has been used as a proxy for 'psychosis-proneness' (8). Schizotypy is characterized by magical thinking, strange experiences, social withdrawal, and other features, and can broadly be categorized into factors called positive, negative, or disorganized (9). Like ASD, it can be considered a spectrum that blends into 'normality'—all people have schizotypal traits, but these are usually not clinically significant. In higher quantities, schizotypal traits might lead to a diagnosis of schizotypal personality disorder, a condition strongly linked to psychosis (10). This makes it perhaps easier to compare ASD (a collection of traits) to schizotypy (another set of traits), rather than psychosis (a state that changes over time and might at any time be considered present or absent). Research has found correlations between subscales of schizotypy and ASD. For example, there is a robust overlap between negative symptoms of schizotypy and autistic traits in adolescents with ASD (11). Social skill deficit seems specific to ASD, and positive schizotypy (for example, unusual experiences such as believing in magic or psychic phenomena), seems specific to schizotypy in high functioning adults (12). Executive functioning processes have been implicated as a causal neurobiological mechanism that might explain both (13).

Using factor analysis, two of the largest studies in this area drew differing conclusions about the relationship between autistic and schizotypal traits. Dinsdale et al. (14) favored a two-factor solution, and argued that there was a clear division between autistic and schizotypal traits, adding further support for a theory that defined ASD and schizophrenia as diametrical opposites (15). Ford and Crewther (16), however, defined a three-factor solution that presents a more complex relationship between the traits. While there were two factors that segregated between the measures, indicating separate autistic ('social disorganization') and schizotypal ('perceptual oddities') constructs, these explained much less variance than the third factor which included both autistic and schizotypal traits. They term the construct that this factor measures 'social rigidity' and postulate that this factor underlies many of the difficulties experienced by both AP and people who experience high levels of schizotypy. Other evidence from research on those dually-diagnosed with ASD and psychosis indicates high rates of major mood disorders such as schizoaffective disorder or bi-polar disorder (17). This

[1] Identity first language is used throughout this paper. For readers unfamiliar with this concept who wish to learn more about it, we would refer you to https://www.identityfirstautistic.org/ for an introduction.

finding is also supported by genetic studies (18) and prevalence data (19) showing higher rates of bi-polar disorder in AP.

A factor that may be involved in the relationship between schizotypal and autistic traits is empathy. Empathy is a complex skill that involves predicting and reacting to how you believe another person will feel. It has been conceptualized as having broadly two factors: cognitive empathy (broadly, this is defined as understanding other people's perspectives); and affective empathy (colloquially, feeling for another person). The diametric model of ASD and schizophrenia suggests that increased empathy may be linked to increased risk of psychosis, through a mechanism of overly empathizing with the perceived contents of others' minds (15, 20). Empathy is found to be impaired in AP in general (21), and has been linked to Theory of Mind deficits, which have a strong basis in both the mirror neuron and executive functioning systems of the brain (22). Harmesen (23) has highlighted that both AP, those with a diagnosis of BPD and those with a diagnosis of bipolar disorder all show impaired cognitive empathy. Conversely, individuals with schizophrenia show impaired affective empathy. However, one particular subtype of empathy, perspective taking, has been found to be impaired in both AP (24) and, separately, in individuals with schizophrenia (25). Previous research has shown that there are differences in empathizing between AP-P and AP-NP (26), but cognitive and affective empathizing have not been considered separately in this population. It might reasonably be predicted that perspective taking may be differentially experienced by AP-P and AP-NP, on the basis of the above research, and further that it could play a role in our understanding of autistic and schizotypal traits.

In order to contribute to better understanding of this area, and the potential interactions between emotion regulation difficulties, affective lability, schizotypy, and autistic traits, we have attempted to investigate these concepts in the same theoretical space. The following hypotheses were tested:

H1. AP-P will use less effective emotion regulation strategies and report more affective lability than AP-NP

H2. AP-P will be better at perspective taking than AP-NP

H3. Schizotypal traits will be higher in AP with a history of psychosis (AP-P) compared with AP who have no history of psychosis (AP-NP)

H4. Emotion regulation difficulties and affective lability will be associated with higher schizotypal scores across participant groups

MATERIALS AND METHODS

Ethical approval for the study was given by the North of Scotland NHS Research Ethics Committee in January 2016. The study was conducted between January 2016 and April 2017.

Design

An observational study comparing self-reported measures of autistic traits, schizotypal traits, and emotional processes between participant groups. Participants were recruited either *via* participation in previous research or *via* social media advertising, and were incentivized with the opportunity to participate in a prize draw.

Participants

Participants were all adults (aged 18 or older), and were required to have English as their first language. They were recruited to three groups.

Autistic People With No Psychosis (AP-NP)

Recruited *via* the Autism Research Centre's (ARC's) database (https://www.autismresearchcentre.net/), they were asked to confirm they had no significant mental health history. ASD diagnosis was not confirmed, but the database is maintained by a respected research group who check participant eligibility: thus, we considered this group representative of AP. A total of 59 participants were recruited.

Autistic People with Psychosis (AP-P)

Consisted of:

i. participants invited from previous research (17);
ii. new participants self-identified through the ARC database.

Participants from the ARC database were screened using the Diagnostic Interview for Psychosis (DIP-DM) (27), which generates diagnoses using the OPCRIT algorithm (28). Individuals meeting criteria for an SSD in DSM-IV-TR (29), ICD-10 (30), or Research Diagnostic Criteria (RDC) (31) systems were considered to have a confirmed history of psychosis. This replicates methods used in Larson et al. (17), and full details are given in Supplemental Materials.

A total of 23 participants were recruited from both sources.

Neurotypical Controls (NC)

Participants were recruited through social media advertising. Participants were not formally screened, but were asked to confirm they had neither history of ASD diagnosis nor any significant mental health history. A total of 41 participants were recruited.

Measures

The following self-report measures were used:

- *Autism Spectrum Quotient (AQ)* (32): A 50-item questionnaire that measures traits associated with ASD. It contains five subscales (Communication, Social, Imagination, Local Details, and Attention Switching). The minimum score is zero, indicating low ASD traits, and the maximum is 50. A cut-off of 32 is considered indicative of probable ASD. The AQ has been shown to have good reliability and construct validity by the original authors and in later studies (33, 34),

although subscale definitions have been questioned. Thus, we used the 'total AQ' summary score.

- *Schizotypal Personality Questionnaire—Brief Revised (SPQ-BR)* (35): A 32-item questionnaire measuring schizotypal traits. Contains nine subscales that can be categorized into three or four superordinate subscales: cognitive perceptual differences, interpersonal difference, and disorganized traits. SPQ-BR scores range from 32 (low overall schizotypy) to 160. Cognitive Perceptual (Positive Schizotypy) scores range from 14 to 70. Interpersonal (Negative Schizotypy) ranges from 10 to 50, and Disorganized ranges from eight to 40. It has been suggested that the Interpersonal subscale could be divided into two, separating out social anxiety (36); however, in line with previous studies we are seeking to replicate, we do not do so. The SPQ-BR as a whole has been shown to have reasonable reliability and validity in a large normative sample (36).
- *Affective Lability Scale-18 (ALS-18)* (37): This 18-item assesses the extent to which individuals switch between emotional states and comprises three subscales (anxiety/depression, depression/elation, and anger) assessing shifts between different emotional states. Higher scores indicate higher levels of affective lability, ranging from zero to 54. The anxiety/depression and anger subscales, each consisting of five items, have scores ranging from zero to 15. The depression/elation subscale consists of eight items and produces scores ranging from zero to 24. The measure has good psychometric properties (38).
- *Emotion Regulation Questionnaire-9 (ERQ-9)* (39): This is a nine item measure of the extent to which individuals utilize one of two distinct coping strategies to manage strong emotion: reappraisal and suppression. Results are given in relation to these two strategies. Individuals rate themselves from one to seven on each item, and some items are reverse-scored. Reappraisal is measured by five items, giving a score of five to 35. Suppression is measured by four items, giving a score of four to 20. Higher scores indicate higher levels of emotion regulation strategy use, and can be considered separately or as a total. The measure has good reliability and validity in community samples (40), and has improved psychometric properties compared to a previous, longer, version.
- Questionnaire of Cognitive and Affective Empathy (QCAE) (41), perspective-taking subscale: A 10-item subscale of a larger measure, it captures the cognitive empathy element related to the ability to imagine alternative perspectives other than one's own. Higher scores indicate higher levels of alternative perspective-taking ability, ranging from zero to 10. It has good reliability and construct validity in a student sample (41).

All participants were asked their age and gender. No other demographics were collected.

Analysis

Data were analyzed using R (R Core Team).

Descriptive Statistics and Univariate Comparisons

Initially, the AP-NP, AP-P and NC groups were compared in terms of gender, age and the measures introduced in *Measures* section. Univariate comparisons between AP-NP and AP-P were made using Fisher's Exact test and t-tests. Univariate comparisons across all three groups were made using Fisher's Exact test and one-way analysis of variance (ANOVA). Non-parametric versions (Wilcoxon and Kruskal–Wallis rank-sum tests) of these comparisons, along with appropriate descriptive statistics, are reported in the Supplementary Materials. These sets of analyses are compared to determine robustness of conclusions.

Group Comparisons of ALS-18, ERQ-9 and QCAE Perspective Taking

To begin examining our hypotheses, unadjusted comparisons of affective and empathy measures between groups were conducted as outlined in *Descriptive Statistics and Univariate Comparisons* section. Adjusted group comparisons were made using linear regression, with a separate regression for each scale. Independent variables (excluding the outcome scale in the corresponding regression) included: Participant Group; Gender; Age; ALS-18 Total; ERQ-9 Cognition Reappraisal; ERQ-9 Emotion Suppression; QCAE Perspective Taking.

Schizotypy Regressions

Linear regression models were used to look for adjusted relationships with SPQ-BR scales (Total and all subscales). In these models, the following independent variables were included: Participant Group; Gender; Age; AQ Total; ALS-18 Total; ERQ-9 Cognition Reappraisal; ERQ-9 Emotion Suppression; QCAE Perspective Taking. In each regression, multicollinearity was examined using variation inflation factors (VIFs).

For each regression, a key area of interest was the potential interaction between Participant Group and each of the dependent variables. To explore these interactions, we fitted a series of models that extended each base regression with all possible combinations of (first order) interactions between Group and other dependent variables. Fitted models were compared using the second-order Akaike Information Criterion (AICc) (42, 43), where lower values indicate a better fitting model. The AICc, as opposed to the standard AIC, was used given the sample size. We considered models with AICcs within two of the lowest AICc (details given in the Supplementary materials), as models within this range are not considered distinguishable. This allowed us to check the robustness of the fit of the best model. Where this set of models included the model with no interactions, we choose this model for greater parsimony. Residual plots of the finally selected models were reviewed to check model fit.

Where interactions were fitted, the Effects (44) package in R was used to plot their effect.

Secondary Analysis: Exploring ALS-18 Subscales

Having conducted the analysis outlined in the above sections, affective lability was highlighted as a key factor. Thus, we repeated the analyses described in *Descriptive Statistics and Univariate Comparisons*, *Group Comparisons of ALS-18, ERQ-9 and QCAE Perspective Taking* and *Schizotypy Regressions* sections, replacing ALS-18 Total with its subscales.

Effect Size Measures

Pearson's correlation coefficient (r) was used as the primary measure of effect size. Generally, Pearson's r was calculated from t-statistics (45), using a formula from Rosenthal (46). For the one-way ANOVA, eta-squared effect measures were converted to r using formulas from Cohen (47) and Rosenthal (46)—the common effect size measure easing comparison. Effect sizes for r were considered small (<0.1), medium (<0.3) and large (<0.5) (48). To further assist interpretation, regression models fit in the main paper were refitted in the **Supplementary Materials** with their continuous variables standardized to zero mean and unit variance.

RESULTS

Participant Group Size, Descriptive Statistics and Univariate Comparisons

Group sizes, descriptive statistics and tests of differences between groups (including confidence intervals, p-values and effect sizes) are reported in **Table 1** and non-parametric forms of these comparisons are reported in **Table S1**.

Gender split was similar between AP-NP and NC groups; however, there were significantly (proportionately) fewer women in AP-P compared to AP-NP. The AP-NP group was significantly older than the AP-P and NC groups. A large and significant difference in AQ scores was found between AP-NP and AP-P. As would be expected, the NC group had the lowest AQ score. Between AP-NP and AP-P groups, across SPQ-BR scales, the only significant difference was found on the Positive scale. NC had the lowest means across all SPQ-BR scales. The same differences between groups were found in the equivalent non-parametric analysis reported in **Table S1**.

Group Comparisons of ALS-18, ERQ-9 and QCAE Perspective Taking Scores

Detailed unadjusted comparisons of these measures are given in **Table 1** (including test statistics, 95% confidence intervals (CIs), p-values and effect sizes). Between AP-NP and AP-P, there were only significant unadjusted differences on ALS-18 Total. The NC group only significantly differed to the AP-NP and AP-P groups on QCAE Perspective Taking.

Detailed adjusted comparisons of these measures are given in **Table 2** (including 95% CIs, p-values and effect sizes; equivalent standardized versions are given in **Table S2**). The only significant adjusted differences included: the NC group scoring significantly higher than AP-NP group on ALS-18 Total; and NC had significantly higher QCAE Perspective Taking scores than both AP-NP and AP-P.

Schizotypy Regressions: Controlled Relationships With Schizotypy Scores

Regression models within two of the best AICc for each SPQ-BR scale (Total, Positive, Negative and Disorganized) are shown in **Table S3**. For three of the models (Total, Positive and Disorganized) the model including no interactions with Group gave the best fitting model (highlighted in yellow in **Table S1**); additionally, there were no consistently included interactions across the other models considered. For the Negative scale, the model with no interactions did *not* have the lowest AICc; however, its fit is only negligibly worse than the best fitting model (765.52 versus 764.38)—given this fit, and the lack of

TABLE 1 | Descriptive statistics.

	AP-NP		AP-P		NC		ASD comparison (AP-NP v AP-P)						All group comparison		
	Mean	SD	Mean	SD	Mean	SD	Stats comp	OR/diff	LCI	UCI	P-value	r	Stats comp	P-value	r
N=	59		23		41										
Gender (% W)	56%		26%		61%		Fisher's	0.28	0.08	0.88	***0.026***	0.33	Fisher's	***0.020***	–
Age (years)	44.3	12.8	33.5	11.0	31.5	9.4	t(47) = 3.8	10.9	5.1	16.6	***<0.001***	0.49	F(2,120) = 17.4	***<0.001***	0.47
AQ Total	39.0	8.2	31.0	9.9	19.4	9.1	t(35) = 3.4	8.0	3.3	12.7	***0.002***	0.51	F(2,120) = 59.3	***<0.001***	0.71
SPQ-BR Total	71.8	16.6	77.6	21.7	52.3	20.0	t(33) = –1.2	–5.8	–16.0	4.4	0.256	0.20	F(2,120) = 18	***<0.001***	0.48
SPQ-BR Positive	20.6	9.2	29.1	13.4	15.2	9.1	t(30) = –2.8	–8.5	–14.7	–2.3	***0.009***	0.45	F(2,120) = 14.1	***<0.001***	0.44
SPQ-BR Negative	28.4	7.6	26.8	8.1	19.4	8.9	t(38) = 0.8	1.6	–2.3	5.6	0.414	0.13	F(2,120) = 15.6	***<0.001***	0.46
SPQ-BR Disorganized	22.7	6.1	21.7	4.7	17.8	7.3	t(51) = 0.9	1.1	–1.5	3.6	0.398	0.12	F(2,120) = 7.6	***<0.001***	0.34
ALS-18 Total	19.2	13.3	26.0	10.8	17.8	12.8	t(49) = –2.4	–6.8	–12.5	–1.1	***0.021***	0.32	F(2,120) = 3.3	***0.041***	0.23
ALS-18 Anxiety/Depression	6.3	4.3	8.3	4.3	5.9	5.0	t(40) = –1.9	–2.0	–4.2	0.1	0.065	0.29	F(2,120) = 2.3	0.104	0.19
ALS-18 Depression/Elation	8.9	6.6	11.9	4.9	9.0	6.8	t(54) = –2.2	–3.0	–5.6	–0.3	***0.032***	0.29	F(2,120) = 2	0.142	0.18
ALS-18 Anger	3.9	4.2	5.7	4.2	3.0	3.5	t(40) = –1.8	–1.8	–3.9	0.3	0.088	0.27	F(2,120) = 3.6	***0.031***	0.24
ERQ-9 Cognitive Reappraisal	22.3	7.0	19.7	6.4	22.0	6.4	t(44) = 1.6	2.6	–0.6	5.9	0.110	0.24	F(2,120) = 1.3	0.270	0.15
ERQ-9 Emotion Suppression	16.3	6.4	17.3	5.9	14.5	5.7	t(43) = –0.7	–1.0	–4.0	2.0	0.500	0.10	F(2,120) = 1.8	0.171	0.17
QCAE Perspective Taking	20.3	7.0	22.2	6.7	29.2	5.8	t(42) = –1.2	–2.0	–5.3	1.4	0.246	0.18	F(2,120) = 23.1	***<0.001***	0.53

Means, standard deviation (SD) by participant group and comparisons between (i) AP groups (Fisher's exact test/two-sample t-test) and (ii) all three groups (Fisher's exact test/ANOVA). Bold/italic p-values indicate significant differences at the 5% level.

AP-NP, Autistic people with no psychosis; AP-P, Autistic people with psychosis; NC, Neurotypical controls; Stats. Comp, Statistical comparison; OR/diff, Odds ratio/difference; LCI/UCI, Lower/upper 95% confidence interval; W, Women; SPQ-BR, Schizotypal Personality Questionnaire; ALS-18, Affective lability scale-18; ERQ-9, Emotional regulation questionnaire-9; QCAE, Questionnaire of cognitive and affective lability. There are two separate sets of comparisons: the first compares the AP groups (middle set of columns) and the second compares all three groups (last set of columns).

TABLE 2 | Fitted regressions on ALS-18 Total, ERQ-9 and QCAE scales.

Variable	Cat. level	Adjusted comparison regressions (n = 123)																			
		ALS-18 Total (adjusted R^2 = 0.43)					ERQ-9 Cognitive Reappraisal (adjusted R^2 = 0.08)					ERQ-9 Emotion Suppression (adjusted R^2 = 0.43)					QCAE Perspective Taking (adjusted R^2 = 0.67)				
		b	95% CI		P-value	r	B	95% CI		P-value	r	b	95% CI		P-value	r	b	95% CI		P-value	r
Intercept	–	–6.0	–26.7	14.7	0.567	0.054	11.6	–1.8	25.0	0.090	0.160	4.7	–5.0	14.4	0.343	0.090	37.0	30.8	43.3	***<0.001***	0.743
Participant	AP-P	3.4	–2.6	9.3	0.266	0.105	–2.1	–6.0	1.8	0.289	0.101	0.7	–2.1	3.5	0.626	0.046	–2.3	–5.0	0.3	0.086	0.162
Group*	NC	7.1	1.1	13.1	***0.020***	0.218	–0.7	–4.7	3.3	0.723	0.034	2.4	–0.5	5.2	0.105	0.153	–1.4	-4.1	1.4	0.330	0.092
Gender†	W	0.9	–3.0	4.9	0.636	0.045	0.1	–2.5	2.7	0.945	0.007	–2.4	–4.2	–0.6	***0.008***	0.247	0.8	–1.0	2.5	0.392	0.081
Age (years)	–	–0.2	–0.3	0.0	***0.023***	0.213	0.0	–0.1	0.1	0.534	0.059	0.0	–0.1	0.1	0.659	0.042	0.0	-0.1	0.1	0.984	0.002
AQ Total	–	0.4	0.1	0.7	***0.025***	0.211	0.1	–0.1	0.3	0.484	0.067	0.0	–0.1	0.2	0.683	0.039	–0.5	–0.6	–0.3	***<0.001***	0.569
SPQ-BR Positive	–	0.5	0.3	0.7	***<0.001***	0.406	0.1	0.0	0.3	0.122	0.146	0.0	–0.1	0.1	0.411	0.078	0.1	0.0	0.2	0.243	0.111
SPQ-BR Negative	–	0.0	–0.3	0.4	0.826	0.021	0.0	–0.2	0.2	0.953	0.006	0.5	0.3	0.6	***<0.001***	0.503	–0.1	–0.3	0.0	0.122	0.146
SPQ-BR Disorganized	–	0.4	0.1	0.7	***0.012***	0.236	0.1	–0.2	0.3	0.632	0.045	–0.2	–0.3	0.0	***0.039***	0.195	–0.1	–0.2	0.1	0.508	0.063
ALS-18 Total	–						–0.1	–0.3	0.0	***0.022***	0.215	0.0	–0.1	0.1	0.894	0.013	0.0	0.0	0.1	0.354	0.088
ERQ-9 Cognitive Reappraisal	–	–0.3	–0.6	0.0	***0.022***	0.215						0.0	–0.2	0.1	0.580	0.053	0.2	0.0	0.3	***0.017***	0.224
ERQ-9 Emotion Suppression	–	0.0	–0.4	0.4	0.894	0.013	–0.1	–0.3	0.2	0.580	0.053						0.1	–0.1	0.2	0.554	0.056
QCAE Perspective Taking	–	0.2	–0.2	0.6	0.354	0.088	0.3	0.1	0.6	***0.017***	0.224	0.1	–0.1	0.3	0.554	0.056					

*Bold/italic p-values indicate significant terms at the 5% level. Gray cells indicate that the corresponding term has not been included in the regression. Cat., Categorical; SPQ-BR, Schizotypal Personality Questionnaire; CI, Confidence interval; AP-P, Autistic people with psychosis; NC, Neurotypical controls; W, Woman; AQ, Autism quotient; ALS-18, Affective lability scale-18; ERQ-9, Emotional regulation questionnaire-9; QCAE, Questionnaire of cognitive and affective lability. *'AP-NP' group taken as reference level. †'Man' taken as reference level.*

consistent interactions included across the other models, we chose the model with no interactions for reasons of parsimony. Residual plots indicate no substantial problems with model fit. Except for one variable, all VIFs are below four; the remaining variable has a VIF of just over five.

The fit of the final models is given in **Table 3** (including 95% CIs, p-values and effect sizes; the resulting fit with continuous variables standardized is given in **Table S4**). The amount of variation explained varied from its lowest in disorganized schizotypy to highest in negative schizotypy. In each of the four regression models, the test of overall regression is significant (p-values <0.001).

Between groups, schizotypy differences are minimal. For total schizotypy, there was a significant difference between NC and AP-P, with AP-P scoring approximately 11 units higher. On positive schizotypy, AP-P scored significantly higher than both AP-NP and NC. Other group differences were small and non-significant.

Across Positive, Negative and Disorganized scales, AQTotal was only significantly associated with negative schizotypy. This was the second largest effect on the Negative scale, and likely drives the significant relationship with AQTotal on the Total scale.

ALS-18 Total had a significant and the largest impact within each of the Positive and Disorganized scales. Accordingly, ALS-total significantly impacts on SPQ-BR Total and has the largest impact thereon. ERQ-9 Emotion Suppression had a significant effect on the Positive and Negative scales, and had the third and largest impact on these respectively. These relationships likely drive the significant impact of ERQ-9 Emotion Suppression on SPQ-BR Total.

There were no significant relationships between the SPQ-BR subscales and gender, age, ERQ-9 Cognitive Reappraisal, or QCAE Perspective Taking respectively.

With no interactions with Participant Group, we had no evidence for effects noted above differing by Participant Group (however, this is *not* proof for the contrary).

Secondary Analysis: Exploration of ALS-18 Subscales

Unadjusted comparisons between groups on the three ALS-18 subscales are detailed in **Table 1**. AP-P scores higher on all three subscales, but only significantly so on the ALS-18 Depression/Elation scale. Differences between NC and AP-P are greatest, but non-significant; differences between NC and AP-NP are smaller.

Adjusted comparisons between groups on the three ALS-18 subscales are detailed in **Table S4** (and standardized in **Table S5**). In the adjusted comparisons, all group differences were non-significant and small, including direct comparisons between NC and AP-P groups.

Regressions relating the ALS-18 subscales to SPQ-BR measures, alongside other variables, are reported in **Table 4**

TABLE 3 | Fitted Schizotypal regressions.

Variable	Cat. level	SPQ-BR regressions (n = 123)																			
		Total (adjusted R^2 = 0.61)					Positive (adjusted R^2 = 0.41)					Negative (adjusted R^2 = 0.68)					Disorganized (adjusted R^2 = 0.28)				
		b	95% CI		P-value	r	b	95% CI		P-value	r	b	95% CI		P-value	r	b	95% CI		P-value	r
Intercept	–	18.9	−8.0	45.8	0.167	0.130	−4.2	−21.5	13.0	0.629	0.045	7.7	−2.7	18.2	0.144	0.137	15.4	4.0	26.8	0.009	0.244
Participant	AP-P	6.2	−1.7	14.0	0.122	0.145	6.7	1.6	11.7	***0.010***	0.240	0.2	−2.8	3.2	0.895	0.012	−0.7	−4.0	2.6	0.673	0.040
Group*	NC	−4.7	−12.9	3.6	0.265	0.105	−3.6	−8.9	1.7	0.178	0.126	−0.1	−3.3	3.1	0.946	0.006	−0.9	−4.4	2.5	0.595	0.050
Gender†	Woman	−1.1	−6.4	4.2	0.672	0.040	−0.5	−3.8	2.9	0.790	0.025	0.0	−2.0	2.1	0.979	0.002	−0.7	−2.9	1.5	0.535	0.058
Age (years)	–	0.1	−0.2	0.3	0.545	0.057	0.1	−0.1	0.2	0.356	0.087	0.0	−0.1	0.1	0.740	0.031	0.0	−0.1	0.1	0.740	0.031
AQ Total	–	0.5	0.1	1.0	***0.018***	0.221	0.0	−0.2	0.3	0.728	0.033	0.3	0.2	0.5	***<0.001***	0.345	0.2	0.0	0.3	0.115	0.148
ALS-18 Total	–	0.7	0.5	0.9	***<0.001***	0.505	0.4	0.3	0.5	***<0.001***	0.484	0.1	0.0	0.2	0.058	0.177	0.2	0.1	0.3	***<0.001***	0.354
ERQ-9 Cognitive Reappraisal	–	0.3	−0.1	0.7	0.118	0.147	0.2	0.0	0.5	0.090	0.159	0.0	−0.1	0.2	0.706	0.036	0.1	−0.1	0.2	0.432	0.074
ERQ-9 Emotion Suppression	–	0.7	0.3	1.2	***0.002***	0.291	0.3	0.0	0.6	***0.045***	0.187	0.6	0.4	0.7	***<0.001***	0.517	−0.1	−0.3	0.1	0.198	0.121
QCAE Perspective Taking	–	−0.1	−0.7	0.4	0.691	0.037	0.1	−0.2	0.5	0.453	0.071	−0.2	−0.4	0.1	0.143	0.137	−0.1	−0.3	0.1	0.465	0.069

*Bold/italic p-values indicate significant terms at the 5% level. Cat., Categorical; SPQ-BR, Schizotypal Personality Questionnaire; CI, Confidence interval; AP-P, Autistic people with psychosis; NC, Neurotypical controls; AQ, Autism quotient; ALS-18, Affective lability scale-18; ERQ-9, Emotional regulation questionnaire-9; QCAE, Questionnaire of cognitive and affective lability. *'AP-NP' group taken as reference level. †'Man' taken as reference level.*

(standardized version given in **Table S8**). A detailed report on these regressions is given in the Supplementary Results. Results were broadly similar to those reported in *Schizotypy Regressions: Controlled Relationships with Schizotypy Scores*. ALS-18 Anxiety/Depression significantly impacted on positive and negative schizotypy. ALS-18 Depression/Elation significantly impacted on disorganized schizotypy. These relationships likely drive the relationships between the total schizotypy and both of Anxiety/Depression and Depression/Elation. ALS-18 Anger generally does not impact on schizotypy scales except for negative schizotypy, where there is an interaction with participant group, as depicted in **Figure 1**: increases on ALS-18 Anger is associated with *increases* on negative schizotypy for NCs, but *decreases* for the AP-NP and AP-P groups. There was also interaction between participant group and ERQ-9 Cognitive reappraisal, as depicted in **Figure S1**: increases on cognitive reappraisal are associated with increases for NC, decreases for AP-P and very little change for AP-NP.

DISCUSSION

Our study set out to examine whether there was a role for emotional factors to explain existing known relationships between ASD traits and schizotypal traits. In particular, we were interested in the role of emotion regulation, affective lability, and perspective taking/empathy in understanding the relationship between these constructs. Our results replicated those found in previous research in terms of the relationship between AP and NC groups on variables such as schizotypal traits, autistic traits, and empathy. We tested four novel hypotheses, finding that affective processes do appear to contribute to the model of interaction between schizotypal and autistic traits, but our results were not fully conclusive. Taking each hypothesis in turn:

H1. AP-P Will Use Less Helpful Strategies and Report More Affective Lability Than AP-NP

While in the uncorrected analysis the AP-P group reported significantly greater affective lability, particularly shifts between elation and depression, this difference was not found in the adjusted model. There was no effect found of group on emotion regulation strategy usage, either helpful or unhelpful, and the results provide no corroboration for this hypothesis. However, there is significant gender imbalance between groups, with the AP-P group having proportionally fewer women than the AP-NP group, which may have impacted our ability to identify differences even having controlled for gender. Female AP are known to present differently to male AP in multiple ways (49, 50), and it is unknown how they might differ in their emotion processing.

H2. AP-P Will Be Better at Perspective Taking Than AP-NP

We found no evidence to support this hypothesis. While AP in general reported worse perspective taking in our study than NC, there was no significant difference between AP groups. This combined with the results of H3, suggest that the psychotic experiences of AP-P are not linked with high levels of

TABLE 4 | Fitted Schizotypal regressions with ALS-18 subscales.

Variable	Cat. level	SPQ-BR regressions (with ALS-18 subscales) (n = 123)																			
		Total (adjusted R^2 = 0.62)					Positive (adjusted R^2 = 0.41)					Negative (adjusted R^2 = 0.74)					Disorganized (adjusted R^2 = 0.32)				
		b	95% CI		P-value	r	b	95% CI		P-value	r	b	95% CI		P-value	r	b	95% CI		P-value	r
Intercept	–	16.5	−11.2	44.2	0.239	0.112	−3.1	−21.0	14.9	0.734	0.032	5.3	−6.2	16.9	0.359	0.089	10.9	−0.6	22.4	0.063	0.175
Participant Group*	AP-P	6.1	−1.8	13.9	0.131	0.143	6.3	1.2	11.4	***0.016***	0.226	6.0	−3.1	15.1	0.196	0.125	0.0	−3.2	3.3	0.978	0.003
	NC	−4.9	−13.1	3.4	0.242	0.111	−4.0	−9.3	1.4	0.145	0.138	−9.9	−17.4	−2.5	***0.009***	0.248	−0.3	−3.8	3.1	0.851	0.018
Gender†	Woman	−2.6	−8.1	2.9	0.348	0.089	−0.9	−4.4	2.6	0.619	0.047	−0.9	−2.8	1.1	0.380	0.085	−0.9	−3.2	1.4	0.441	0.073
Age (years)	–	0.1	−0.1	0.3	0.476	0.068	0.1	−0.1	0.2	0.401	0.080	0.0	−0.1	0.1	0.900	0.012	0.0	−0.1	0.1	0.425	0.076
AQ total	–	0.6	0.1	1.0	***0.017***	0.225	0.0	−0.3	0.3	0.857	0.017	0.4	0.2	0.6	***<0.001***	0.400	0.2	0.0	0.4	***0.024***	0.212
ALS-18 Anxiety/ Depression	–	1.3	0.5	2.1	***0.002***	0.295	0.7	0.2	1.2	***0.009***	0.245	0.6	0.3	0.8	***<0.001***	0.364	0.1	−0.3	0.4	0.726	0.033
ALS-18 Depression/ Elation	–	0.6	0.1	1.2	***0.018***	0.223	0.3	−0.1	0.6	0.107	0.153	−0.1	−0.3	0.1	0.210	0.121	0.5	0.2	0.7	***<0.001***	0.364
ALS-18 Anger	–	0.0	−0.7	0.8	0.919	0.010	0.3	−0.2	0.9	0.184	0.126	−0.3	−0.6	0.1	0.145	0.140	−0.2	−0.5	0.2	0.302	0.098
ERQ-9 Cognitive Reappraisal	–	0.3	−0.1	0.7	0.089	0.161	0.2	0.0	0.5	0.082	0.164	0.0	−0.2	0.2	0.794	0.025	0.1	−0.1	0.2	0.392	0.081
ERQ-9 Emotion Suppression	–	0.7	0.3	1.2	***0.002***	0.282	0.3	0.0	0.6	***0.046***	0.188	0.6	0.4	0.7	***<0.001***	0.540	−0.2	−0.3	0.0	0.105	0.153
QCAE Perspective Taking	–	−0.1	−0.6	0.5	0.820	0.022	0.1	−0.2	0.5	0.492	0.065	−0.1	−0.3	0.1	0.441	0.075	0.0	−0.3	0.2	0.811	0.023
Participant Group × ALS-18 Anger	AP-P: Anger											−0.3	−0.9	0.3	0.304	0.099					
	NC : Anger											0.7	0.2	1.3	***0.006***	0.263					
Participant Group × ERQ-9 Cog. Reapp.	AP-P: ERQ-9 CR											−0.2	−0.6	0.2	0.338	0.093					
	NC : ERQ-9 CR											0.4	0.1	0.7	***0.018***	0.226					

*Bold/italic p-values indicate significant terms at the 5% level. Cat., Categorical; SPQ-BR, Schizotypal Personality Questionnaire; CI, Confidence interval; AP-P, Autistic people with psychosis; NC, Neurotypical controls; AQ, Autism quotient; ALS-18, Affective lability scale-18; ERQ-9, Emotional regulation questionnaire-9; QCAE, Questionnaire of cognitive and affective lability; CR, Cognitive reappraisal. *'AP-NP' group taken as reference level. †'Man' taken as reference level.*

empathizing after the onset and resolution of their acute episodes of mental ill-health. We cannot say whether their self-reported empathizing skills would have been at the time of their illness. It is also possible that our study was under-powered to detect differences, as previous research has shown differences between AP-P and AP-NP in empathizing, using a different measure (26). Finally, it is possible that differences might have been found in different types of empathy, and that we simply selected a type of empathy which does not have significant links to psychosis.

H3. Schizotypal Traits Will Be Higher in AP-P Compared With AP-NP

While this was not true for overall schizotypal traits, it was supported for Positive Schizotypy. Both autistic groups had higher mean levels of schizotypy across the three subscales (Positive, Negative, and Disorganized) than NC, although not all of these comparisons were statistically significant.

H4. Emotion Regulation Difficulties and Affective Lability Will Be Associated With Higher Schizotypal Scores Across Participant Groups

The premise of this hypothesis is that emotional processes are involved with or impacted by schizotypy, regardless of other factors. This hypothesis was supported. Affective lability has a significant and positive association with overall schizotypy (as one increases, so does the other); further, this is also the strongest association with schizotypy among the variables considered here (r = 0.5, a large effect). This suggests an important relationship between these constructs. Exploratory analysis of the subscales of the ALS-18 suggests that different affective processes may be related to different schizotypal traits. For example, we found that switches between anxiety and depression (ALS-18 anxiety/depression) were more strongly associated with Positive and Negative schizotypy. Switches between depression and elation

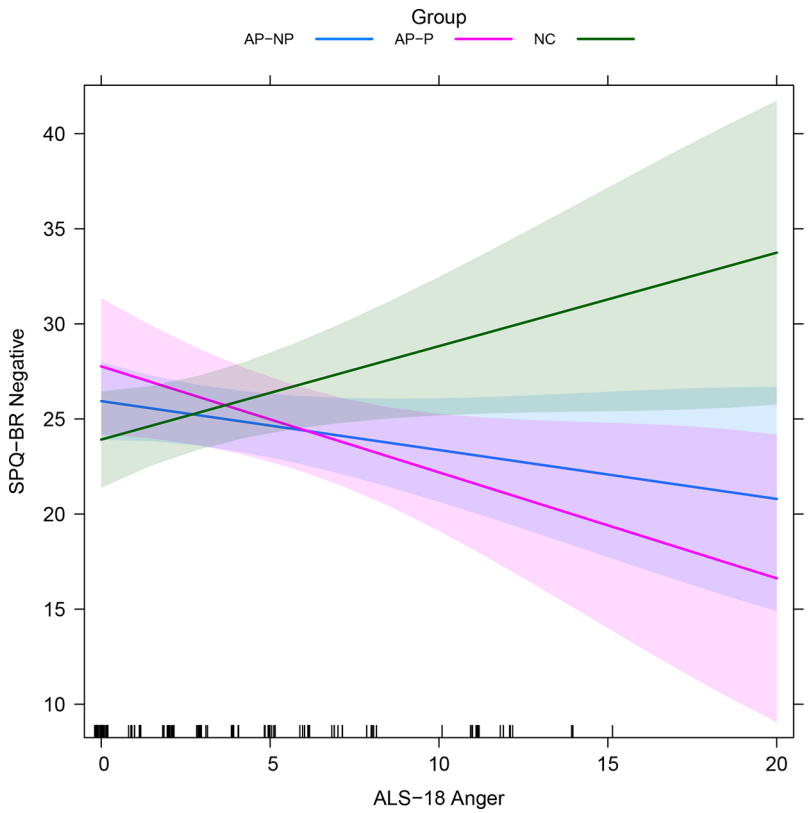

FIGURE 1 | Fitted interactions between participant group and ALS-18 Anger in SPQ-BR Negative regression with ALS-18 subscales (see *Secondary Analysis: Exploration of ALS-18 Subscales*; averaged across other variables). Colored regions indicate the 95% confidence intervals. AP-NP, Autistic people with *no* psychosis; AP-P, Autistic people *with* psychosis; NC, Neurotypical controls; SPQ-BR, Schizotypal Personality Questionnaire; ALS-18, Affective lability scale-18.

associated more with Disorganized schizotypy. We also found that, as predicted, Emotional Suppression is significantly associated with greater overall schizotypy, and specifically Positive and Negative schizotypy.

It is important to note that the relationship between emotional processes and negative schizotypy is complex and appears to be affected by the presence of an ASD diagnosis. The two group by measure interactions that we found in the analyses both related to negative schizotypy, and in both cases, the AP groups showed a different relationship between affective lability, emotion regulation, and negative schizotypy, when compared to NC. This suggests that there may be something fundamentally different in the way that AP report experiencing and managing anger. It is also interesting to consider how AP, who show more negative schizotypal traits, report better use of an emotion regulation strategy that relies on logically appraising the situation (Cognitive Reappraisal). The finding may indicate a specific relevance of or different understanding of the descriptions of Cognitive Reappraisal between AP and NC, for example. This requires further investigation.

Limitations

Potentially impacting on generalizability, this study's sample sizes were small. This was partially a by-product of selecting a rare dual diagnostic group such as AP-P, and also the nature of the study as exploratory investigation of a novel hypothesis. The sample size particularly impacts on the statistical power to detect interactions. Conclusions, particularly based on interactions, should be interpreted with caution given the small sample size. It may be helpful to consider our results as preliminary in light of these limitations, and further research is clearly required to confirm and expand on them.

Recruitment methods varied between groups, potentially introducing bias: for example, mental status relating to autism and psychosis were retrospectively determined, which may produce bias and impact on the results of the study. Additionally, further screening of individuals may have been useful: AP-NP and NC groups were not screened, and so may have mis-represented their diagnostic status. Psychopathology screening would have helped rule out other confounding relationships. However, additional screening would have added to participant burden and so may have not been as useful as hoped as we are not aware of evidence to suggest research participants have been found to under-represent their mental health status.

Given the limitations of the small sample and limited screening, but the interesting relationships highlighted, future research replicating these results would be valuable. Increased

screening of participants to confirm group diagnoses and rule out general psychopathology would help reduce bias from unmeasured confounders. Controlling for additional demographic variables may also further reduce bias. Other designs—such as matching—might also be considered.

Conclusions

As found in previous research, there appears to be a complex relationship between negative schizotypy, disorganized schizotypy, and autistic traits, and our results have suggested that these traits correlate with emotional processing differences. Future studies would benefit from comparing AP-P to other populations with psychosis to further understanding in this area.

It seems plausible to us that emotional processes, particularly affective lability, add to the model of relationship between autistic and schizotypal constructs. To our knowledge, these factors have not previously been considered in this research field. Lability involving anxious emotional states is associated with positive and negative schizotypy, while lability involving elated emotional states is associated with disorganized schizotypy, suggesting that different emotional experiences may give rise to or be caused by different patterns of thought or behavior. AP as a whole in our study reported significantly higher negative schizotypal traits than NC, replicating previous findings. However, this difference was complicated by interactions with euthymia/anger lability and use of cognitive reappraisal as an emotion regulation strategy, which require further research to replicate and explore further.

Clinically, we would hypothesize that individuals with emotion regulation difficulties and affective lability are likely to be those with either underlying neurobiological differences and/or histories of traumatic experiences such as difficulties during pregnancy/birth [e.g. (51)], insecure early attachments [e.g. (52, 53)], or traumatic events during childhood/adolescence [e.g (54, 55)] which affect neurodevelopmental trajectories. We posit that this would therefore be a potential relevant factor in the development of schizotypal traits that should be further investigated. While differences in attachment have been found between autistic and non-autistic children, these differences seem to be mediated by cognitive ability and level of autistic traits (56), meaning this may not be a risk factor that is greater than in the general population. Little is known about the childhood experiences of AP, including pregnancy and birth issues, and this is an area that would benefit from future study.

We believe that our finding could be considered a development of the stress-vulnerability theory of psychosis (57), and that AP might be particularly at risk due to a combination of neurobiology and life experiences influencing the development of emotion regulation difficulties. In particular, Ford and Crewther's (16) proposal of a social rigidity factor could be representing the same processes at work in emotional suppression—primarily avoidance and control, as contrasted with openness and flexibility. Understanding the impact of something like social rigidity or other stressors would be key to supporting a program of prevention/strengthening of emotional regulation skills in the at-risk population of teenagers/young AP [see (58) for a possible model]. We believe this is an exciting and transdiagnostic direction for understanding in this field to take, which will ultimately benefit patients through identification of treatment targets and risk markers.

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 study involved human participants and was reviewed and approved by North of Scotland NHS Research Ethics Committee. All patients/participants provided informed consent to participate in this study, either written or electronic.

AUTHOR CONTRIBUTIONS

FL led design of the study, with contributions from AW, SW, RR, and KC. FL gathered the data. AW conducted data analysis in collaboration with FL. 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.2020.00712/full#supplementary-material

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Lifetime and Momentary Psychotic Experiences in Adult Males and Females With an Autism Spectrum Disorder

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Background: Existing research shows that adults with an autism spectrum disorder (ASD) are more vulnerable to develop overt psychosis. However, studies investigating (subclinical) psychotic experiences (PE) in ASD are scarce, and it is unknown if PE are accompanied with more distress in adults with ASD compared to the general population. This study examined lifetime PE and accompanying distress, momentary PE levels, and the impact of daily life stress and negative affect (NA) on momentary PE in males and females with ASD compared to controls.

Methods: In 50 adults with ASD (males N= 26, females N= 24) and 51 adults without ASD (males N= 26, females N= 25), the Community Assessment of Psychic Experiences (CAPE) was used to analyze group differences in frequency and distress of lifetime subclinical positive, negative, and depressive symptoms. The Experience Sampling Method (ESM) was used to measure momentary PE, NA, and stress (activity-related, event-related, and social stress) for 10 days. Multilevel analyses were conducted to test whether stress and NA were associated with momentary PE and whether these associations were modified by group or sex.

Results: Adults with ASD reported more lifetime CAPE negative and depressive symptoms, but similar levels of PE, than controls. Higher levels of accompanying distress were found in participants with ASD for each subscale. With respect to ESM momentary PE, higher levels were reported by adults with ASD and a stronger association between event-related stress and momentary PE was found compared to controls. This was not the case for NA, activity-related, and social stress. Overall, no significant differences between male and female outcomes were found.

Conclusion: Adults with ASD are more prone to encounter lifetime subclinical negative and depressive symptoms and accompanying distress compared to adults without ASD. Similar levels of lifetime PE in both groups were still accompanied with more distress in the ASD group. Furthermore, higher levels of ESM momentary PE were found in participants

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with ASD. Additionally, event-related stress may act as a risk factor for PE in both females and males with ASD, with a stronger risk-increasing effect than in their control counterparts.

Keywords: autism spectrum disorder, stress, psychotic experiences, negative affect, momentary assessment

INTRODUCTION

Individuals with an autism spectrum disorder (ASD) are more prone to develop overt psychosis relative to those without ASD (1, 2). General population studies have shown that psychotic experiences (PE) are an important risk factor for a psychotic disorder (3, 4), psychopathology (5, 6), and suicidal ideation (7, 8). Still, studies investigating PE in ASD are limited with an inconsistent pattern of results. For example, while two studies found significant associations between childhood autistic traits and PE in adolescence (9, 10), Taylor et al. (11) demonstrated weak or non-significant associations. Given that PE may lead to more severe psychopathology, it is essential to enhance knowledge about its (risk for) occurrence in ASD. Identifying sex differences may be necessary for understanding the underlying mechanisms of PE in ASD, which can lead to effective prevention and better-tailored treatment. Previous studies in general population samples demonstrated significantly higher levels of PE in females than in males (12, 13). However, we only found one study in children with ASD, which showed that 57% of girls with ASD experienced schizophrenia spectrum traits compared with 28% of boys (14).

Stress is a well-known risk factor in the emergence of psychosis. Individuals who have experienced childhood adversity, trauma, or adverse life events have an increased risk of developing subclinical PE (15–20) or a psychotic disorder (21–23). In the last two decades, there has been increased interest in studying the influence of minor daily stressors on momentary PE, also known as psychotic reactivity (24, 25). A widely used method to investigate psychotic reactivity is the Experience Sampling Method (ESM). The ESM is an ecological momentary assessment (EMA) tool to gather information from participants about their experiences in the context of the natural flow of daily life. Typically, multiple times a day, short questionnaires are presented to participants at semi-random moments in time over several consecutive days. This method is less susceptible to recall bias and has been applied to a wide range of psychiatric disorders (26). Although ESM research in ASD is still limited, the feasibility and usefulness of this method have been supported (27–29). Previous ESM studies observed an increased psychotic reactivity in patients at increased risk for psychosis compared with controls (30, 31). Currently, the interplay between stress and momentary PE in ASD has not yet been investigated. However, in another paper on this sample, we reported an increased negative affect (NA) in response to daily stressors in those with ASD relative to controls (submitted for publication). NA may also be directly associated with momentary PE (32–36). More specifically, a recent ESM study demonstrated that NA predicted paranoia, but, conversely, paranoia did not predict changes in NA in patients with a psychotic disorder (35). To date, no study has investigated the association between NA and momentary PE in adults with ASD.

Our first aim was to examine the frequency of experiences related to the extended psychosis phenotype and accompanying distress using the Community Assessment of Psychic Experiences (CAPE, a validated retrospective self-report questionnaire) (37, 38). That is, three individual dimensions (i.e., subclinical positive, negative, and depressive symptoms), as well as the total CAPE score, were investigated. The reason to examine beyond the positive symptom dimension is that the extended psychosis phenotype is multidimensional in nature and complements a general transdiagnostic psychosis factor (6). Our second aim was to investigate the presence and course of ESM momentary subclinical psychotic phenomena in daily life and their association with minor daily stressors and NA. Therefore, the main objectives of the current study were to examine group (ASD versus controls) and sex differences in i) levels of lifetime psychic experiences (positive, negative and depressive symptoms) and accompanying distress, ii) levels of momentary PE, iii) the impact of different types of daily stressors on momentary PE (psychotic reactivity), and iv) the impact of NA on momentary PE.

METHOD

Sample

The final sample included 50 participants with an ASD diagnosis (N= 26 males, N= 24 females) and 51 controls (N= 26 males, N= 25 females) between 18 and 65 years of age. Participants with ASD were recruited by contacting mental healthcare facilities in the South of the Netherlands, through patient associations, and *via* social media. The first author (KL) conducted the Autism Diagnostic Observation Schedule II (ADOS-2) (39) module 4 (fluent speech) in all participants of the ASD group to confirm their diagnoses. Only those participants with ASD who had i) a short-term psychological treatment history (maximum 2 years), and ii) no past psychiatric admission were included. Medication use and other psychiatric disorders were no cause for exclusion except in the case of acute psychotic symptoms, suicidal tendencies, or a bipolar disorder. The Mini-International Neuropsychiatric Interview (MINI) (40, 41) was used to assess the presence of psychiatric disorders in participants with ASD. Controls without a developmental or psychiatric disorder were recruited *via* social media. Participants were excluded if they had a first-degree family member diagnosed with, or suspected of

having, ASD. The Autism Spectrum Quotient (AQ) (42, 43) was used to identify the degree of ASD features in controls; a score above 26 led to exclusion (44). The MINI was also used to exclude any control participants with a current psychiatric disorder. General exclusion criteria were i) suffering from known genetic abnormalities, brain injury, epilepsy, or metabolic disorders, and ii) an intelligence quotient (IQ) below 70. The latter was screened with two subtests (matrix reasoning and vocabulary) of the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV) (45). Six participants were excluded during the screening procedure (due to an IQ below 70 or ADOS-2 scores under the threshold for an ASD diagnosis). The sample characteristics are summarized in **Table 1**.

Procedure

This study was approved by the medical ethics committee of Maastricht University (NL51997.068.15) and was carried out in accordance with the Declaration of Helsinki (46). All participants were well informed about the study and gave written informed consent before the first appointment. During the first appointment, participants were screened for meeting the inclusion criteria and they filled in the CAPE. The ESM protocol was explained in a following session.

Daily life assessments were done with the ESM, delivered via the PsyMate™ application. Participants received an iPod or downloaded the app on their smartphone. During 10 days, 10 times a day, the application sent an alert at random moments between 07:30 and 22:30 h. Participants then answered questions about mood, social context, and activities, completing their reports within an allotment of 10 min after the signal. The questionnaire consisted of 7-point Likert scales to capture momentary experiences and categorical questions to capture context (e.g., social context, activities). Participants were encouraged to follow their daily routines. All participants were contacted by telephone after 2 days of sampling to ask if they experienced any problems concerning the protocol. It was also possible for them to contact the researchers, if they had questions or experienced problems with the ESM data collection. Exclusion

TABLE 1 | Sociodemographic and clinical characteristics of the research sample.

	ASD (N = 50)	Controls (N = 51)	Group comparisons	
			Test statistic	P
Demographic Variable				
Age, mean (SD), range	41.1 (12.9), 18-64	35.5 (12.2), 18-63	F = 4.95	.028
Sex (m/f)	26/24	26/25	$X^2(1) = .01$	.918
Civil status, *n* (%)			$X^2(4) = 10.81$	.029
Never married	25 (50%)	14 (27%)		
Married	13 (26%)	16 (31%)		
Living together	3 (6%)	14 (27%)		
Divorced	8 (16%)	6 (12%)		
Widowed	1 (2%)	1 (2%)		
Work situation, *n* (%)			$X^2(6) = 27.39$	<.001
Household	1 (2%)	1 (2%)		
School/education	4 (8%)	11 (21.5%)		
Regular work full-time	6 (12%)	22 (43%)		
Regular work part-time	13 (26%)	11 (21.5%)		
Structured work	10 (20%)	4 (8%)		
Non-structured activities	15 (30%)	1 (2%)		
Other	1 (2%)	1 (2%)		
Educational level, *n* (%)			$X^2(2) = 3.77$	.152
Primary school	1 (2%)			
Secondary school	12 (24%)	6 (12%)		
Higher education	37 (74%)	45 (88%)		
Clinical variables				
ADOS-2 classification, *n*				
Autism	32			
Autism spectrum	18			
AQ score, mean (SD), range		9.4 (4.9), 0-25		
WAIS-IV subtests, mean (SD), range				
Matrix reasoning	11.0 (2.6), 6-18	10.9 (2.2), 5-15	F = .03	.874
Vocabulary	11.8 (2.9), 5-16	11.4 (3.0), 6-19	F = .40	.530
Estimated IQ, mean (SD), Range	110.1 (17.7), 79-147	108.5 (15.4), 73-141	F = .23	.636
DSM-IV axis I diagnosis *n*				
Depression current	3	0†	$X^2(1) = 3.15$	.076
Depression lifetime	23	6	$X^2(1) = 14.46$	<.001
Valid ESM beeps, mean (SD), range	79.8 (12.7), 49-103	75.8 (12.9), 32-97	F = 2.51	.116

†*Current depression was an exclusion criterion in the control group; ASD, Autism Spectrum Disorder; ADOS-2, Autism Diagnostic Observation Schedule II; AQ, Autism Spectrum Quotient; IQ, intelligence quotient; WAIS-IV, Wechsler Adult Intelligence Scale - Fourth Edition; ESM, Experience Sampling Method.*

from the analysis followed in case less than 30% valid reports were acquired (30 out of 100), as previous work has shown that these data are less reliable (47). However, none of the participants were excluded for this reason. After collecting the data, participants were invited for a debriefing session and their experiences were evaluated.

Measures

CAPE—Lifetime Psychic Experiences

The CAPE is a reliable and valid retrospective self-report questionnaire to assess the frequency and distress of a set of different symptom dimensions of the extended psychosis phenotype. The questionnaire consists of 42 items, and the frequency score is measured on a 4-point scale: never (1), sometimes (2), often (3), and nearly always (4). Distress is measured on a 4-point scale: not distressed (1), a bit distressed (2), quite distressed (3), and very distressed (4). For both the frequency scales as well as the distress scales, items are arranged around three dimensions, i.e., positive psychotic experiences (20 items), as well as subclinical negative (14 items), and depressive symptoms (8 items). The internal consistency for this sample was determined by calculating Cronbach's alpha. Excellent internal consistency was found for the frequency scale (.90) and good internal consistency for the distress scale (.80) in the ASD group. In the control group, a good internal consistency was found for the frequency scale (.83) and an excellent score for the distress scale (.93). The total CAPE scores as well as the three individual dimensions (i.e., positive, negative, and depressive symptoms) were used as outcome measures.

ESM—Momentary Psychotic Experiences

PE were operationalized with four questions ("I feel suspicious", "I can't get these thoughts out of my head", "My thoughts are influenced by others", and "I hear voices that others don't"). These questions were scored on 7-point Likert scales (1 = not, 7 = very) and were combined into a mean momentary PE measure.

ESM—Momentary Stress

Stress was conceptualized as subjectively appraised stress after regular daily life encounters or activities. Three different stress measures were obtained: activity-related, event-related, and social stress. Activity-related stress was operationalized, starting with the question "What are you doing?". Three items followed this question, i.e., "I would rather do something else"; "This is difficult for me", and "I can do this well", reverse coded. These questions were scored on 7-point Likert scales (1= not, 7 = very) and were combined into a mean activity-related stress variable. Event-related stress was based on the question "What was the most important event since the last beep?". Participants subsequently scored how pleasant/unpleasant the event was on a bipolar scale (-3 very unpleasant, 0 neutral, +3 very pleasant). Positive events (scores 1, 2, and 3) were recorded to zero, and negative scores were reverse coded (i.e., higher ratings reflect more stress). Lastly, social stress was operationalized by asking participants if they were in the company of others or alone. If in the company of others, they were asked to rate the item "I would prefer to be alone" (1–7).

ESM—Negative Affect

NA was assessed at each beep with five adjectives (down, insecure, lonely, anxious, irritated) rated on 7-point Likert scales (1 = not, 7 = very). However, detailed factor analyses based on the present ESM data showed that the item 'irritated' also had high negative cross-loadings on a positive affect measure (based on the items relaxed, enthusiastic, satisfied, and cheerful). Therefore, the mean of the items "down", "insecure", "lonely", and "anxious" was used as a measure of NA in the analyses.

Statistical Analysis

All analyses were carried out in Stata version 13.1 (48).

CAPE—Lifetime Psychic Experiences

Eight regression analyses were performed to test for differences in frequency of lifetime psychic experiences and degree of distress between adults with ASD and controls. First, two regression analyses were computed with the total CAPE sum scores (on both the frequency and the distress scale) as the dependent variables. Group, sex, and their interaction were added as the independent variables. Second, six regression analyses were performed with the individual CAPE dimensions (positive, negative, and depressive symptoms, again on both the frequency and distress scale) as the dependent variables. Again, group, sex, and their interaction were added as the independent variables. Moreover, previous research showed that young adults are more prone to develop PE than middle-aged and older adults (49), and individuals with depression and lower educational achievement are more vulnerable to develop PE (19, 50, 51). Therefore, we used age, lifetime depression, and education level as covariates, because these variables may partially explain variance in overall and dimensional CAPE scores. Lastly, the predicted marginal means were estimated from these models. In case of a significant two-way interaction, we computed the pairwise differences in simple slopes between the four groups (i.e., males with ASD, females with ASD, control females, and control males). When only a significant main effect for group was found, we estimated the marginal means between ASD and controls.

ESM—Momentary Psychotic Experiences

ESM data have a multilevel structure. Therefore, two-level mixed-effects regression models (using the "mixed" command in Stata) were used to analyze data, with observations (level 1) nested within subjects (level 2). The independent variables, their interactions, and the covariates were entered into the models as fixed effects. Random intercepts and random slopes were added at the subject level, using an unstructured covariance matrix for the random effects. Models were fitted using restricted maximum likelihood estimation (REML). Fixed effects were tested *via* Wald-type tests with α=.05 (two-sided). As a first step, five multilevel models were fitted to test whether momentary PE, NA, and the three stress variables (independent variables) differed between groups (dependent variable: 0 = controls, 1 = ASD). Next, four models were fitted for activity-related stress, event-related stress, social stress, or NA as a continuous predictor and momentary PE as the outcome variable. Age, lifetime depression,

and education level were added as covariates in all models as these might explain part of the variance in momentary PE, similar to the lifetime CAPE scores in the previous subsection. We added two-way (stress/NA x group, stress/NA x sex, group x sex) and three-way (stress/NA x group x sex) interactions to test whether associations between stress or NA and PE differed by group or sex. Based on each fitted model, we computed the slopes (of stress or NA on PE) for all four groups (i.e., males with ASD, females with ASD, control females, and control males) with corresponding 95% confidence intervals (CIs). Given that the current sample size was expected to yield limited power to investigate a three-way interaction, we collapsed these to appropriate marginal slopes if the three-way interaction was not significant. Thus, instead, the marginal slopes for the two-way interaction between stress or NA and group were reported. Lastly, we computed, only in case of a significant three-way interaction, the pairwise differences between the simple slopes to investigate the effects of group and sex on PE.

Sensitivity Analysis

To verify whether the results of the main analyses were robust, we performed a sensitivity analysis. First, we excluded the few participants diagnosed with depression (ASD N = 3, controls N = 0). Since depression is known to be associated with perceived stress (52), NA (53), and PE (54) it might explain some variance in the results. Second, the item "I can't get these thoughts out of my head" was excluded from the repeated analyses since one may argue that this item is related to persistent thinking, a known feature in ASD (55). Thus, for the sensitivity analysis, momentary PE were operationalized as the total sum of the items: "I feel suspicious", "My thoughts are influenced by others", and "I hear voices that others don't".

RESULTS

CAPE—Lifetime Psychic Experiences

CAPE—Overall Scores

There were no significant effects found in sex or group x sex interaction terms for the overall CAPE scores on frequency and distress (**Table 2**). Results showed significant group differences in overall CAPE scores. Moreover, the margins demonstrated distinctly higher levels of lifetime CAPE sum scores and accompanying distress in participants with ASD than controls. The estimated marginal means are summarized in **Table 3**.

CAPE—Symptom Dimensions

None of the individual CAPE symptom dimensions were significantly associated with the interaction between group and sex, and no significant effects were found for sex (all P >.05) (**Table 2**). The results showed significant group differences for all three symptom dimensions of frequency and distress (see **Tables 2** and **3**) except for the positive symptom frequency scale. Thus, adults with ASD reported higher levels of negative and depressive symptoms on the CAPE frequency scale and higher levels of accompanying distress on all three symptom dimensions.

TABLE 2 | Regression estimates of group, sex, and their interaction associated with CAPE overall score and subscale scores.

	Obs	B	SE	P	95% CI
Lifetime psychic experiences					
Total sum	101				
Group		.30	.07	<.001	[.15,.45]
Sex		.01	.07	.923	[-.13,.14]
Group x sex		.15	.10	.117	[-.04,.35]
Positive symptoms	101				
Group		.09	.07	.180	[-.04,.22]
Sex		-.02	.06	.726	[-.14,.10]
Group x sex		.13	.09	.130	[-.04,.30]
Negative symptoms	101				
Group		.48	.11	<.001	[.26,.70]
Sex		.00	.10	.970	[-.20,.21]
Group x sex		.16	.15	.259	[-.12,.45]
Depressive symptoms	101				
Group		.52	.12	<.001	[.27,.77]
Sex		.08	.11	.481	[-.15,.31]
Group x sex		.19	.16	.243	[-.13,.51]
Degree of distress					
Total sum	100				
Group		.55	.12	<.001	[.31,.80]
Sex		.06	.11	.568	[-.16,.29]
Group x sex		.22	.16	.168	[-.09,.54]
Positive symptoms	89				
Group		.45	.20	.023	[.06,.85]
Sex		.09	.19	.629	[-.28,.46]
Group x sex		.31	.25	.217	[-.19,.81]
Negative symptoms	99				
Group		.54	.12	<.001	[.30,.78]
Sex		.16	.11	.144	[-.06,.38]
Group x sex		.10	.16	.513	[-.21,.41]
Depressive symptoms	100				
Group		.72	.17	<.001	[.39, 1.06]
Sex		-.04	.16	.813	[-.35,.27]
Group x sex		.34	.22	.136	[-.11,.78]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval. All models control for age, lifetime depression (yes/no), and education level. CAPE, Community Assessment of Psychic Experiences.

ESM—Momentary Psychotic Experiences

Higher levels of momentary PE were found in adults with ASD relative to controls (**Table 4**).

ESM—Momentary Stress and Negative Affect

The ASD group reported significantly higher levels of NA, activity-related, event-related, and social stress than controls (**Table 4**). Note that the number of observations of the social stress variable was lower than for the other predictors because social stress was only measured in situations where participants reported being in the company of others.

ESM—the Impact of Daily Life Stressors on Momentary Psychotic Experiences

Activity-Related Stress

The interaction between activity-related stress, group, and sex in the model of momentary PE was not significant; neither was the two-way interaction between group and activity-related stress. There were significant main effects of both activity-related stress and group (**Table 5**).

TABLE 3 | Estimated marginal means for the CAPE overall score and subscale scores, per group.

	ASD (N = 50)				Controls (N = 51)			
	Margin	**SE**	**P**	**95% CI**	**Margin**	**SE**	**P**	**95% CI**
Frequency								
Total	1.73	.04	<.001	[1.66, 1.80]	1.36	.04	<.001	[1.29, 1.43]
Positive symptoms	1.29	.03	<.001	[1.23, 1.36]	1.14	.03	<.001	[1.08, 1.21]
Negative symptoms	2.11	.05	<.001	[2.00, 2.22]	1.55	.05	<.001	[1.45, 1.66]
Depressive symptoms	2.16	.06	<.001	[2.04, 2.28]	1.55	.06	<.001	[1.43, 1.67]
Distress								
Total	2.27	.06	<.001	[2.15, 2.38]	1.60	.06	<.001	[1.49, 1.72]
Positive symptoms	2.01	.09	<.001	[1.84, 2.18]	1.40	.10	<.001	[1.20, 1.59]
Negative symptoms	2.17	.06	<.001	[2.05, 2.28]	1.58	.06	<.001	[1.46, 1.69]
Depressive symptoms	2.72	.08	<.001	[2.56, 2.89]	1.83	.08	<.001	[1.67, 2.00]

SE, standard error; 95% CI, 95% confidence interval; ASD, Autism Spectrum Disorder; CAPE, Community Assessment of Psychic Experiences.

TABLE 4 | Multilevel regression estimates of the ESM variables between groups.

	Obs	B	SE	P	95% CI
Negative affect	7846	.83	.14	<.001	[.56,.1.10]
Activity-related stress	7844	.61	.14	<.001	[.34,.88]
Event-related stress	7836	.09	.04	.028	[.01,.17]
Social stress	4696	1.21	.20	<.001	[.82, 1.60]
Psychotic experiences	7845	.49	.11	<.001	[.28,.70]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval; ESM, Experience Sampling Method.

Event-Related Stress

The analyses showed no significant three-way interaction. As shown in **Table 5**, a significant two-way interaction was found between group and event-related stress in the model of momentary PE. The results of the simple slopes showed a stronger association between event-related stress and PE in the ASD group (B = .15, S.E. = .02, P <.001, 95% CI [.11,.19]) than in controls (B = .05, S.E. = .02, P = .016, 95% CI [.01/.09]) (see **Figure 1**).

Social Stress

No significant interaction was found between group, sex, and social stress nor between group and social stress in the model of momentary PE. Results demonstrated a trend-significant main effect for group.

ESM—the Impact of Negative Affect on Momentary Psychotic Experiences

The results showed a non-significant three-way interaction (group x sex x NA), and two-way interaction (group x NA) in the model of momentary PE. The analyses showed a significant effect of NA on momentary PE (**Table 5**).

Sensitivity Analysis

Additional analyses were carried out, excluding participants diagnosed with depression from the sample (ASD: N = 3, controls: N = 0), and with momentary PE as the total sum of three items instead of four (the item "I can't get these thoughts out of my head" was excluded). All analyses were repeated within the new sample (ASD N = 47, controls N = 51). The results remained similar for all analyses except one: a significant two-

TABLE 5 | Multilevel regression estimates of stress, group, sex, and their interactions in the model of momentary psychotic experiences.

	Obs	B	SE	P	95% CI
1. Activity-related stress	7843	.04	.02	.032	[.00,.08]
Group		.26	.13	.046	[.00,.51]
Group x activity-related stress		.05	.03	.063	[-.00,.10]
Sex		.12	.12	.320	[-.12,.35]
Sex x activity-related stress		-.01	.03	.773	[-.06,.05]
Sex x group		-.08	.17	.629	[-.42,.25]
Group x sex x activity-related Stress		.03	.04	.430	[-.04,.11]
2. Event-related stress	7835	.04	.03	.195	[-.02,.10]
Group		.32	.16	.041	[.01,.63]
Group x event-related stress		.11	.04	.006	[.03,.19]
Sex		.11	.15	.468	[-.18,.39]
Sex x event-related stress		.02	.04	.558	[-.06,.11]
Sex x group		.05	.21	.797	[-.35,.46]
Group x sex x event-related stress		-.03	.06	.599	[-.14,.08]
3. Social stress	4695	.02	.02	.298	[-.02,.07]
Group		.28	.14	.049	[.00,.56]
Group x social stress		.02	.03	.404	[-.03,.08]
Sex		.10	.13	.470	[-.16,.35]
Sex x social stress		.04	.03	.223	[-.02,.10]
Sex x group		.01	.19	.942	[-.36,.39]
Group x sex x social stress		-.02	.04	.711	[-.10,.06]
4. NA	7842	.21	.05	<.001	[.11,.31]
Group		.05	.11	.607	[-.15,.26]
Group x NA		.10	.07	.121	[-.03,.23]
Sex		.11	.10	.262	[-.08,.30]
Sex x NA		.01	.07	.914	[-.13,.14]
Sex x group		.03	.14	.840	[-.25,.30]
Group x sex x NA		.01	.09	.933	[-.17,.19]

Obs, number of observations; B, standardized regression coefficient; SE, standard error; CI 95%, 95% confidence interval; NA, negative affect. The dependent variable in all models is psychotic experiences. All models control for age, lifetime depression, and education level.

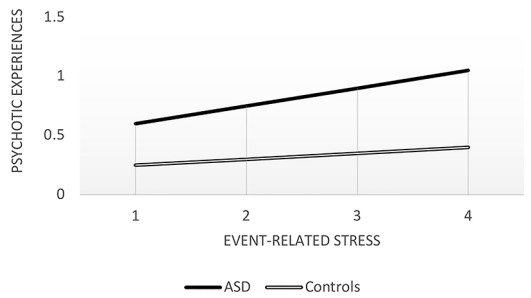

FIGURE 1 | Associations between event-related stress scores and psychotic experiences. ASD, Autism spectrum disorder.

way interaction was found between activity-related stress and group on momentary PE (B = .05, S.E. = .02, P = .019, 95% CI [.01,.08]). Marginal effects of the interaction term showed that activity-related stress was significantly associated with momentary PE in the ASD group (B = .07, S.E. = .01, P <.001, 95% CI [.05,.08]) but not in the control group (B = .02, S.E. = .01, P = .094, 95% CI [-.00,.04]). All results are presented in **Supplementary Tables S1** and **S2**.

DISCUSSION

The current study aimed at acquiring more insight into (subclinical) psychotic symptom expression and potential contributing risk factors in adults with ASD. Participants with ASD reported significantly higher lifetime CAPE sum scores (reflecting the extended psychosis phenotype), as well as higher lifetime subclinical negative and depressive symptom scores, all accompanied with higher levels of distress than controls. Although no significant group differences were found in lifetime CAPE PE scores, the ASD group reported more accompanying distress than controls. Adults with ASD reported more ESM momentary PE than controls and event-related stress was associated with increased momentary PE in adults with ASD. There was no moderating effect of group on the associations between either activity-related stress, social stress, or NA, and the outcome variable momentary PE. Overall, no significant differences between male and female outcomes were found.

CAPE—Lifetime Psychic Experiences

Adults with ASD reported significantly more lifetime experiences related to the extended psychosis phenotype, including higher levels of distress. Analyses of the sub-dimensions showed that adults with ASD reported higher levels of negative and depressive symptoms compared to controls, but not higher levels of PE. Although the latter finding differs from previous literature, current results are in line with studies that found a stronger association between autistic features and negative, rather than positive, symptoms (56, 57). Moreover, this is the first ASD study to investigate distress related to symptoms of the extended psychosis phenotype. Higher levels of distress were found in the ASD group compared with controls, for the total scale and all three sub-dimensions. Thus, even though no evidence was found that individuals with ASD have more lifetime PE, they experienced more distress from those experiences than controls. These findings are (clinically) informative since previous studies showed that distress related to PE, rather than frequency of PE, is associated with a higher risk of developing clinical need (58–61). The increased frequency and distress levels of negative and depressive symptoms also point out that clinicians and caregivers should be alerted for a transdiagnostic approach in the mental health care of individuals with ASD, encompassing support and treatment interventions for these extended psychosis phenotype features. Moreover, higher levels of distress related to lifetime experiences may suggest that stress sensitivity plays a role in the emergence of PE (62, 63) in adults with ASD. More specifically, previous research has demonstrated that early trauma and adverse life events can result in altered stress sensitivity, which in turn may lead to a higher frequency and intensity of PE later in life. This pathway has been described as the "affective pathway towards psychosis" (34, 62). An increased stress sensitivity in adults with ASD may be due to a higher vulnerability for childhood adversities, e.g., family and neighborhood adversities (64), and peer victimization (65, 66).

No sex differences were found with respect to lifetime psychic experiences. Given that there is no previous research available, it is not possible to make direct comparisons. However, our results seem to be in contrast with the replicated finding from general population studies that males experience more negative symptoms while females experience more positive symptoms (67, 68). Although there is one general population study that showed higher levels of the CAPE total frequency scale in females (69), this study did not provide data on the subscales. The current results suggest that negative and depressive symptoms are related to ASD in general instead of being sex-dependent. Still, since this is the first study investigating lifetime experiences in adult males and females with ASD, more studies are warranted to further examine this topic. Future studies should aim for larger sample sizes since the current sample was relatively small to investigate sex differences. Furthermore, previous studies examining sex differences in co-occurring symptoms (e.g., anxiety) found significant differences in children and adolescents with ASD (70–72), but not in adults (73–75). Therefore, the results of the present study may not be illustrative of the complete lifespan.

ESM—Momentary Psychotic Experiences

Levels of Momentary Psychotic Experiences

Despite the absence of group differences in frequency levels of CAPE PE, higher levels of ESM momentary PE were demonstrated in ASD. This may indicate that real-time, real-world, daily life monitoring can signal (small changes in) PE, whereas a retrospective instrument may lack the sensitivity to do so. This urges the need for the combination of well-validated (retrospective and EMA) instruments to investigate transdiagnostic

phenomenological features in ASD, as the different approaches may be (partly) complementary. Of note, concerning affect, the two instruments yielded overlapping results. As no questions on negative symptoms were included in the ESM questionnaire for this study, this may be a consideration for future research on ASD. In summary, the present study showed the feasibility and relevance of studying momentary PE in a naturalistic environment.

The Impact of Daily Stressors on Momentary Psychotic Experiences

The ASD group showed higher PE levels in association with event-related stress than the control group. Another paper on this sample demonstrated that adults with ASD report higher levels of NA associated with event-related stress, i.e., increased stress-reactivity (submitted for publication). Findings seem to concur with research reporting on unpleasant events as an important stressor in individuals with ASD (76, 77). The absence of a moderating effect of sex could be related to a lack of power. Still, it may also indicate that an increased psychotic reactivity associated with event-related stress is characteristic of ASD in general. Group and sex had no significant effect on the association between activity-related stress and momentary PE. Although, the interaction between group and activity-related stress did reach significance in the sensitivity analysis. No significant moderation effects of group and sex on social stress in the association with momentary PE were found. This was unexpected, especially since problems in social functioning and communication have been found in ASD as well as in individuals who are at clinical high risk for psychosis and individuals with a first psychotic episode (78). The results may comply with a longitudinal study of Bevan Jones et al. (10), which observed that maternal concerns about social interaction in childhood were not significantly associated with increased PE in adolescence. The present findings show that even though adults with ASD reported an increased desire to be alone when in the company of others, momentary PE levels associated with social stress were comparable in both groups. A possible explanation for these findings may be that adults with ASD do experience benefits of social contact (79, 80). It may be that the presence of social support provides a feeling of safety and improves quality of life (81). Thus social support may be a protective factor for momentary PE in ASD, in agreement with the results of a recent longitudinal cohort study in the general population (82).

The Impact of Negative Affect on Momentary Psychotic Experiences

Results showed a significant association between NA and momentary PE but no significant effect of sex and group. Despite the lack of significant group differences, these findings are in line with research that demonstrated an association between NA and momentary PE (34, 36). Moreover, although adults with ASD reported significantly higher levels of NA than controls, the current findings implicate that NA is not a specific risk factor for momentary PE. Nevertheless, in line with the affective pathway to psychosis as described in subsection *CAPE—Lifetime Psychic Experiences*, research has shown that increased NA in response to daily stress is associated with higher levels of lifetime CAPE scores in the general population (83). Therefore, it may be suggested that NA should not be viewed as a separate risk factor, but may lie on the causal pathway between stress and momentary PE.

Clinical Implications

Present findings highlight the critical role of stress with the emergence of PE in ASD. Results demonstrated that adults with ASD not only experience higher levels of distress in response to (lifetime) PE, but also that stressful events in daily life may increase momentary PE. This may lead to a vicious cycle where adults with ASD may feel distressed by their PE, which, in turn, increases the frequency and intensity of PE. Stress prevention may be one way to disrupt this cycle. Although research on treatment interventions in adults with ASD is limited, some studies demonstrated that cognitive-behavioral therapy (84), acceptance and commitment therapy (85), and dog-assisted therapy (86) led to a significant stress reduction in this population.

Strengths and Limitations

Previous research mainly investigated PE in the ASD population using standard clinical measures. We have tried to bridge the gap in the present literature by examining both self-reported lifetime experiences and momentary assessment of PE in a naturalistic environment. Another strength is that this study included an equal number of males and females, while most research in ASD is focused on male children and adolescents. Furthermore, an ASD group with minimal treatment history was included, and therefore it was possible to examine psychotic reactivity minimally influenced by prior treatment. Although we included a relatively large sample and a sufficient number of self-reports, a lack of power may have affected the three-way interactions. Furthermore, it may be questioned whether all the items used to investigate momentary PE were suitable for the ASD group. A previous study (87) from our department showed, however, that these momentary PE were strongly associated with the positive symptom items of the Positive and Negative Symptom Scale (PANSS) (88) in patients with a psychotic disorder. Lastly, a high functioning group was included, and therefore results may not be generalized to the whole ASD spectrum.

Conclusion

Current results underline that adults with ASD are more prone to encounter lifetime extended psychosis phenotype features, i.e., subclinical negative and depressive symptoms, accompanied with more distress. Even though no group differences were found in the frequency of lifetime PE, these symptoms were accompanied with greater distress in ASD. Results showed higher levels of momentary PE in adults with ASD compared to controls. Furthermore, event-related stress was associated with increased levels of momentary PE, indicating increased psychotic reactivity, in participants with ASD. No significant differences between males and females were found.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of patient confidentiality and participant privacy. Requests to access the datasets should be directed to MM (m.marcelis@maastrichtuniversity).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medisch-ethische toetsingscommissie azM/UM, Maastricht, the Netherlands. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to conception and design of the study. KL organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. CS, TA, and MM critically reviewed 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.2020.00766/full#supplementary-material

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The Attenuated Psychosis Syndrome and Facial Affect Processing in Adolescents With and Without Autism

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Background: Autism and schizophrenia spectrum disorders both represent severely disabling neurodevelopmental disorders with marked impairments in social functioning. Despite an increased incidence of psychosis in autism, and substantial overlap in symptoms and cognitive markers, it is unclear whether such phenotypes are specifically related to risk for psychosis or perhaps reflect more general, idiosyncratic autism traits. The attenuated psychosis syndrome (APS) is primarily defined by the presence of attenuated psychotic symptoms, which currently constitute the best and most-replicated clinical predictors of psychosis, and are common in clinical youth with and without autism. The aims of this study were to test the hypothesis that facial affect processing is impaired in adolescents with APS and to explore whether such deficits are more indicative of psychotic or autistic phenotypes on a categorical and dimensional level.

Materials and Method: Fifty-three adolescents with APS and 81 typically developing controls (aged 12–18) were included. The APS group consisted of adolescents with (n = 21) and without (n = 32) a diagnosis of autism spectrum disorder. Facial affect recognition was assessed with the Amsterdam Neuropsychological Tasks using a cascade model of cognitive processing, in which disturbances in "lower-level" cognitive abilities (pattern recognition), affect "higher-level" cognitive processes (face recognition and facial affect recognition). For associations with schizotypal and autistic-like traits the Schizotypal Personality Questionnaire and Social Communication Questionnaire were used in a confirmatory item factor analysis framework.

Results: Contrary to expectation, APS in adolescents was not associated with impairments in pattern, face, or facial affect recognition. However, the APS group with autism spectrum disorder showed a general latency in response time to social and non-social stimuli. Dimensionally assessed schizotypal and autistic-like traits did not predict the accuracy or the speed of face or facial affect recognition.

Conclusion: Facial affect processing performance was not associated with APS in adolescence and represents an unlikely early vulnerability marker for psychosis. APS

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individuals with a more autistic-like profile were characterized by slower responses to social- and non-social stimuli, suggesting that the combined effect of APS and autism spectrum disorder on cognition is larger than for APS alone.

Keywords: autism spectrum disorder, psychosis, schizophrenia, ultra-high risk, social cognition, emotion perception, attenuated positive symptoms

INTRODUCTION

Autism spectrum disorder (ASD) and schizophrenia spectrum disorders (SSD) both represent severely disabling neurodevelopmental disorders with marked impairments in social functioning. ASD and SSD co-occur more often than would be expected by chance (1, 2), and have been found to share both phenotypic similarities as well as multiple risk factors (3). Recently, more parallels between ASD and SSD have come to light, such as overlapping genetic mechanisms and brain developmental trajectories (4–6). Furthermore, studies are increasingly focussing on dimensional rather than categorical approaches, with the aim of testing the hypothesis that both conditions represent extremes on an extended continuum of symptomatic severity. These efforts provide evidence for elevated rates of autistic traits in individuals diagnosed with SSD, and also report that these traits negatively affect clinical outcome such as quality of life and global functioning (3, 7–10)

Of interest for the present study is the striking overlap of many cognitive traits between ASD and SSD (11), especially within the domain of social cognition (8, 12–15). For example, investigations of emotion recognition in both ASD and SSD reveal consistent impairments compared to healthy controls (13, 16). However, in a recent direct comparison of substantial clinical samples, adults with ASD seemed significantly more impaired than adults with SSD in emotion perception from faces (15). Although this difference may become less pronounced with increasing age due to progressive cognitive deterioration in SSD (12), cross-sectional studies show that clear social cognitive impairments are already present at first onset of psychosis (17, 18). In addition, numerous studies have reported social cognitive deficits in individuals at risk for psychosis, that is, in both first-degree relatives of schizophrenia patients (19), as well as in individuals with a clinical or "ultra" high risk (UHR) for psychosis (20). However, it remains unclear as to how and when these impairments develop (21) and whether they convey a similar risk for psychosis in UHR and ASD.

The UHR criteria were developed to help identify young help-seeking individuals at imminent risk for developing a psychotic disorder (22). In the past decades it has been established that approximately 20% of UHR positive individuals will develop a psychotic disorder within two years of identification (23), depending on the study population base rate and type of inclusion criteria (24). Also, transition rates have been slowly declining over time (25) and tend to be somewhat lower in young adolescent UHR populations (26, 27), though they remain staggeringly high compared to the general population. Of the different UHR inclusion criteria, attenuated positive symptoms are by far the most commonly represented and currently constitute the best and most-replicated clinical predictors of psychosis (28). Together with the proposal to include an attenuated psychosis syndrome (APS), which is almost exclusively defined by the presence of attenuated positive symptoms, into the DSM (29), this has led to a partial shift in research focus toward (presumably) more homogenous APS samples to improve replicability of factors associated with risk for psychosis.

Like APS, a childhood diagnosis of ASD is also characterized by much greater odds to develop psychosis compared to the general population (2, 30). Psychotic symptoms are not included in diagnostic ASD criteria, yet many individuals diagnosed with ASD report psychotic symptoms, even at a young age (31–34). Given the elevated risk for psychosis in young people with APS and ASD, as well as the shared phenomenology, direct comparisons between the two are notably absent from the literature. As an exception, a recent longitudinal study reported that UHR patients with and without premorbid ASD showed similar APS at baseline and conversion rates to full-blown psychosis for both groups (35). However, baseline social cognitive performance (i.e. social perception and theory of mind) was more affected in UHR with ASD. This suggests that social cognitive deficits contain a different level of risk for transition to psychosis in UHR individuals with and without ASD.

As highlighted above, social cognition deficits are commonly proposed as a potential early vulnerability marker for psychosis. However, actual associations with transition to psychosis are few and inconsistent in high-risk research (36). Regardless, some studies suggest a positive predictive value of specific impairments in facial affect processing for the transition to psychosis (37–39) and negative outcomes (40), which warrants further investigation. Facial affect processing is associated with non-affective facial processing and, in addition to involvement of the limbic regions, partially requires activation of the same cortical structures, such as the fusiform face area (41). In turn, non-affective facial processing involves similar brain regions as non-affective visuospatial processing, i.e. the processing of patterns or objects, but evokes differential activity patterns (42). In this view, more complex and "higher-level" social cognitive skills such as facial affect processing and non-affective facial identity recognition may partially rely on "lower-level", non-social visual processing skills for optimal functioning, which is often reported as being aberrant in schizophrenia (43–45). Simultaneous assessment of these three separate, yet interrelated, levels of visual processing can therefore further inform us on their associations with psychotic and/or autistic behavior.

The aims of this study were to test facial affect processing in help-seeking adolescents (12–18 years) suffering from APS with and without ASD and to explore whether any deficits are more indicative of psychotic or autistic phenotypes on a categorical and dimensional level. Furthermore, facial affect recognition was assessed within the context of a cascade model of cognitive processing, in which disturbances in "lower-level" cognitive abilities (pattern recognition), affect "higher-level" cognitive processes (facial identity and facial affect recognition). Previous studies using the same cognitive paradigms have indicated that facial affect recognition was most impaired in chronic schizophrenia compared to controls (46) and that disadvantages in facial recognition was a typical feature in children with ASD (47, 48). However, direct comparisons of APS adolescents with and without ASD have not been investigated previously. Based on findings described above, we hypothesized that: 1) facial affect processing would be affected in young adolescents with APS in general, but more strongly related to autism than psychosis on both a categorical and dimensional level; 2) a negative association exists between autistic features and face recognition; and 3) pattern recognition ability would have a stronger, negative impact on facial (affect) recognition in APS without ASD, compared to those with ASD and controls.

MATERIALS AND METHODS

Participants

The study was conducted at the Child and Adolescent Psychiatry Department of the University Medical Center Utrecht. This subsample of the Dutch Prediction of Psychosis Study recruited adolescents (aged 12–18 at intake; M = 15.26, SD = 1.73) putatively at UHR for psychosis. All patient participants were referred help-seekers. Having APS was defined as meeting the Attenuated Positive Symptom Psychosis-Risk Syndrome, as defined in the Criteria of Psychosis-risk Syndromes of the Structured Interview for Prodromal Syndromes (SIPS version 3.0; 49). To fulfil these criteria a patient must receive a rating of level "3", "4", or "5" on at least one of the P1-P5 positive symptom items. Having a prepubertal clinical diagnosis of ASD was obtained from information present in the medical records and was confirmed by expert clinical opinion after psychiatric examination including the Autism Diagnostic Interview—Revised (50). The APS groups without and with ASD are from here on referred to as APS/ASD – and APS/ASD+, respectively. Typically developing controls were recruited by distributing information brochures about the research project at several secondary schools in the region of Utrecht. They were excluded if they or a first degree relative had a history of any psychiatric illness, or if they had a second degree relative with a history of a psychotic disorder, as determined by using the Family Interview for Genetic Studies (51). The control group was also screened using the SIPS and individuals were excluded if they met APS criteria. All participants signed an informed consent, and for those younger than 16, the primary caretaker(s) co-signed. The study was approved by the Dutch Central Committee on Research Involving Human Subjects.

Schizotypal and Autistic Traits

The Schizotypal Personality Questionnaire [SPQ; (52)] is a self-report instrument for assessing trait levels of psychotic-like experiences. It consists of 74 "yes/no" statements addressing the Cognitive-Perceptual Deficits, Interpersonal Deficits, and Disorganization subtraits. This postulated structure of three highly correlated traits has been found to describe clinical data well (53).

The Social Communication Questionnaire (SCQ), previously known as the Autism Screening Questionnaire (54), is a parent-report instrument which addresses autistic traits over the lifetime. Of the 40 "yes/no" questions, all items except 3–8 are scored as reversed. Item 1 was deleted as it is the verbal ability screen for items 2–7, and items 2–7 were deleted for the two cases who responded "no" to item 1. The SCQ has recently been reported to measure three subdimensions of autistic behaviour, namely the Social, Rigidity, and Non-Verbal Communication subtraits, of which the former is moderately correlated with the two latter (55). Like Martin et al. (55), we found items 24 and 25 to have an extremely high tetrachoric sample correlation, but item 25 was retained and assigned to Non-Verbal Communication. Due to the low levels of autistic traits in healthy controls, the parents of that group of participants were not asked to fill in this questionnaire.

Cognitive Paradigms

Facial affect recognition, face recognition, as well as "lower-level" cognitive skills, namely pattern recognition, were assessed with the Amsterdam Neuropsychological Tasks (ANT), version 2.1 (56). The ANT is a computerized neuropsychological test battery and has proved to be a reliable and valid instrument. Three modules of the ANT were administered for the purpose of this study, namely 1) Feature Identification (FI); 2) Face Recognition (FR); and 3) Identification of Facial Emotions (IFE). The tasks will be described in detail below, for visual representations of the paradigms we refer to Barkhof et al. (46).

The Feature Identification (FI) task consists of 40 trials (20 each of easy and hard conditions) of recognizing a briefly seen target pattern of red and white squares in a subsequently presented 2-by-2 matrix of potential matches. Participants were asked to determine whether the target pattern was present in the 2-by-2 matrix by pressing either YES (target present) or NO (target not present). The target pattern was presented only at the beginning of the task, and had to be kept in mind during the whole task. There were an equal number of target and lure trials, presented in a standard pseudorandom order. Face Recognition (FR) was otherwise similar, but used face stimuli. Participants had to determine whether a target face was present in a set of four, subsequently shown faces. Again, there were 40 trials, half of which required a YES response, and half of which required a NO response, presented in a random order.

Identification of Facial Emotions (IFE) also used the same general setup, but the participant was required to determine whether a target emotion was expressed by a succession of faces that could express any of the following eight emotions: happiness, sadness, anger, fear, disgust, surprise, shame, and

contempt. The complete task has eight different parts, i.e., one for each emotion, but only the first four parts were used in the present study, namely happiness, sadness, anger and fear. Each part consisted of 40 trials, half of which were faces that expressed the target emotion (requiring a YES response), and half of which are faces that expressed a random selection of the other seven emotions (requiring a NO response). All trials were analysed jointly for both accuracy as well as speed as a single task.

Individual task results with an error rate of 40% or greater were discarded (one task of one participant in each group), as were those where the task administrator determined that the respondent was confused regarding the instructions (all tasks of one participant in the ASD group). To correct for individual response bias tendencies, the signal detection theory (SDT) discriminability index *d'* was used as the measure of accuracy. To make error-free accuracy possible to score as *d'*, the loglinear transformation rule was applied throughout, as recommended by Hautus (57). In addition to accuracy, response times for correct responses were recorded as a measure of performance. Since response times had skewed distributions, these were converted to response speed (responses per second), which normalized distributions in each group.

Performance in the non-social FI task was used primarily as a baseline for separating the face-specific component of the FR and IFE tasks from its more general visual memory and task performance.

Statistical Analyses

To assess whether questionnaire responses were sufficiently one-dimensional to use as indicators of single underlying constructs, the included items of the clinical scales were used as categorical indicators of their respective latent variables in separate confirmatory item factor analyses (IFA) using the WLSMV estimator in Mplus 8.3 (58); each item was assigned to a single factor, but all threshold, loading, and factor correlation parameters were freely estimated. Model fit was assessed with the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA), and explained common variance (ECV). Further analyses used the *maximum a posteriori* factor scores derived from these factor analyses. Confirmatory IFA analyses of the published three-dimensional structures were done in a similar manner.

As cognitive task performance was somewhat dependent on age and gender in the control group, all accuracy and speed analyses used standardized regression residuals of *d'* or response speed, that is, the difference between the individual's observed score and the expected score in the control group for that age and gender. In analyses additionally controlling for FI, the performance on that task was entered as a covariate in the regressions along with age and gender. All analyses additionally controlling for FI use the same data (accuracy/accuracy, and speed/speed).

For group comparisons on the trait and cognitive measures we used *U* tests (as most data was non-normally distributed, and at a conservative $p < 0.01$ due to the number of tests) and reported the corresponding non-parametric effect size *A* (59), which is equivalent to the Area Under the Curve of SDT, and can be estimated with the formula $(n_1n_2 - U)/n_1n_2$ (60). In Cohen's (61) terminology an effect size $A = 0.57$ (~ d = 0.2) can be considered small, an effect size $A = 0.64$ (~ d = 0.5) can be considered medium and an effect size $A = 0.71$(~ d = 0.8) can be considered large. All analyses except the IFAs were done in IBM SPSS Statistics 26.0. In the primary linear dependence regression analyses, accuracy and response speed were predicted in separate forward-stepping linear regressions by the latent factor scores of the two trait dimensions (SPQ and SCQ). In the similar secondary and exploratory analyses, the predictors were the SPQ and SCQ subdimension factor scores.

RESULTS

Subgroup Characteristics

A total of 66 patient participants and 81 healthy controls contributed partial or complete data. Of the patients, 53 had both clinical and cognitive data available, and fulfilled APS criteria, forming the patient subsample for the main analyses. In addition to meeting APS criteria, six patients also met brief, limited, or intermittent psychotic symptoms (BLIPS) criteria as assessed by the SIPS, and three patients also met criteria for genetic risk of psychosis and deterioration (GRD). The patient subsample consisted of adolescents with (n = 21; APS/ASD+ group) and without (n = 32; APS/ASD− group) a diagnosis of ASD. Group characteristics are reported in **Table 1**. APS/ASD− patients were significantly older than APS/ASD+ patients and healthy controls. Both patient groups had somewhat lower IQs than healthy controls. Both APS/ASD− and APS/ASD+ patients showed higher SPQ scores than healthy controls, with no significant difference in SPQ scores between the two patient groups. As expected, the APS/ASD+ group had higher scores on SCQ than the APS/ASD− group.

Data Quality

Age, cognitive variables, and latent psychopathological factors were approximately multivariate normal, and linear regression between them was thus appropriate. The few missing values were treated as being missing at random and all analyses were performed with all available values. The fit of the SPQ and SCQ in unidimensional factor analyses was acceptable (CFI.90/.89, RMSEA.04/.05, with 44%/41% mean explained variance, respectively), and the fit of the three-dimensional models was good (CFI.96/.94, RMSEA.03/.04, with 54%/52% explained variance).

Latent factor scores on the two clinical SPQ and SCQ measures were weakly negatively associated with each other among the patients, Pearson $r = -0.17$ ($p = 0.25$), only the SCQ was predicted by age, $r = -0.37$ ($p = 0.01$), and there was a trend towards girls having higher SPQ factor scores, $A = 0.67$ ($U = 204$).

Cognitive Group Comparisons

The cognitive group comparisons are described in **Table 1** and summarized below. Firstly, there was no significant difference between the three groups (APS/ASD− vs. APS/ASD+ vs.

TABLE 1 | Demographic and clinical characteristics with group comparisons.

	Group statistics						Group comparisons (Mann-Whitney *U* test)††								
	APS/ASD− (*n* = 32)		APS/ASD+ (*n* = 21)		Controls (*n* = 81)		APS/ASD− vs. APS/ASD+			APS/ASD− vs. Controls			APS/ASD+ vs. Controls		
	% or Mean (SD)		% or Mean (SD)		% or Mean (SD)		*A*	*U*	*p*	*A*	*U*	*p*	*A*	*U*	*p*
Female	41	%	29	%	51	%	0.56	296.5	0.40	0.55	1166.5	0.41	0.61	663	0.09
Age	16.4	(1.7)	14.0	(1.7)	15.2	(1.5)	0.83	114	<0.001**	0.69	796	0.001**	0.70	510	0.004*
IQ	100.3	(14.7)	98.7	(13.3)	107.7	(12.83)	0.51	329	0.90	0.67	861.5	0.005	0.69	530.5	0.01*
GAF	54.0	(14.3)	58.7	(12.2)	94.0	(7.53)	0.63	249.5	0.12	0.99	35	<0.001**	0.99	21.5	<0.001**
Current psychotropic medication	37	%	62	%	0	%	0.62	254	0.10	–	–	–	–	–	–
SPQ score†	32.5	(13.8)	30.9	(14.0)	9.3	(7.3)	0.54	297.5	0.68	0.92	196.5	<0.001**	0.94	104	<0.001**
SCQ score†	6.3	(4.8)	16.6	(6.8)	–		0.88	72.5	<0.001**	–	–	–	–	–	–
SPQ factor score	0.84	(0.64)	0.76	(0.58)	−0.59	(0.70)	0.55	290	0.58	0.94	164	<0.001**	0.95	80	<0.001**
SCQ factor score	−0.53	(0.67)	0.66	(0.56)	–		0.92	50	<0.001**	–	–	–	–	–	–
Feature Identification (FI) Discriminability *d'*	3.04	(0.62)	3.22	(0.71)	3.15	(0.59)	0.63	217	0.12	0.56	1106	0.33	0.59	629	0.22
Feature Identification (FI) Speed**	0.72	(0.11)	0.59	(0.15)	0.71	(0.14)	0.68	191	0.01*	0.53	1190	0.50	0.69	476	0.002*
Face Recognition (FR) Discriminability *d'*	2.83	(0.61)	2.56	(0.85)	2.89	(0.65)	0.53	298	0.69	0.55	1149	0.40	0.58	665	0.25
Controlling for FI†††	−0.10	(0.63)	−0.23	(0.84)	0.00	(0.64)	0.57	276	0.72	0.57	1104	0.38	0.59	655	0.36
Face Recognition (FR) Speed**	0.68	(0.16)	0.54	(0.14)	0.72	(0.18)	0.65	221	0.04	0.60	1015	0.07	0.73	432	<0.001**
Controlling for FI†††	−0.05	(0.13)	−0.05	(0.09)	0.00	(0.14)	0.49	325	0.85	0.60	1026	0.09	0.61	627	0.06
Identify Facial Emotion (IFE) Discriminability *d'*	3.02	(0.59)	2.74	(0.64)	2.90	(0.55)	0.64	231	0.10	0.57	1108	0.23	0.58	684	0.29
Controlling for FI†††	0.18	(0.63)	−0.14	(0.63)	0.00	(0.54)	0.68	202	0.07	0.65	918	0.03	0.57	694	0.51
Identify Facial Emotion (IFE) Speed**	1.09	(0.18)	0.95	(0.21)	1.10	(0.22)	0.61	249	0.12	0.55	1155	0.37	0.64	577	0.02
Controlling for FI†††	−0.01	(0.15)	0.00	(0.18)	0.00	(0.16)	0.51	316	0.73	0.53	1223	0.65	0.49	832	0.88

*Significant at $p<.01$.
**Significant at $p<.001$.
†Estimated with mean substitution.
††All statistical tests on cognitive performance used residuals taking into account age and gender (using control group parameters).
†††Residuals after taking into account age and gender (using control group parameters), as well as corresponding Feature Identification performance (accuracy/accuracy and speed/speed).

Controls) with respect to accuracy on the FI task. However, APS/ASD+ patients were slower in their responses on the FI task than the APS/ASD− and the control groups (**Figure 1**). Secondly, there was no significant difference between the three groups (APS/ASD− vs. APS/ASD+ vs. Controls) in accuracy on the FR task. Again, the APS/ASD+ patients were slower than the other groups (**Figure 1**). However, this difference did not remain significant after controlling for response speed on the "lower-level" FI task. Lastly, no significant group differences were found for the IFE task with respect to either accuracy or response speed. The APS/ASD+ group was again slower in responding than the APS/ASD− group and controls with medium effect sizes, but this difference was not statistically significant.

Linear Prediction of Social Cognition With Clinical Features

The only cognitive variable which was predicted by SCQ or SPQ factor scores was Feature Identification (FI) accuracy, which was predicted by the SPQ ($\beta = 0.37$). Secondary analysis revealed that the subfactor Disorganization sufficed to account for this effect ($\beta = 0.37$).

DISCUSSION

The aim of this study was to test the hypothesis that facial affect processing is impaired in young adolescents with APS, and whether visual processing at different cognitive levels could help differentiate between those with and without a prepubertal diagnosis of ASD. Neither of the APS groups displayed generalized impairments in the accuracy of facial affect recognition, nor in face or pattern recognition, indicating that these cognitive skills may have limited use as early psychosis vulnerability markers in APS. However, the APS group with ASD generally showed slower responses for affective and non-affective face stimuli than APS participants without ASD and healthy controls, which was fully explained by a slower response time on "lower-level" feature identification.

Contrasting previous findings in UHR samples (62–65), we did not find general emotion processing deficits in the APS groups compared to healthy controls. Given that most individuals with UHR would also qualify for APS, it is unlikely that this stark contrast is due to the inclusion of a more homogenous subset of individuals putatively at-risk. Furthermore, it is undisputed that psychotic conditions are characterized by deficits in facial affect processing (41, 66), but the questions of how and when these deficits manifest remain unresolved so far. A possible explanation of why deviations were not detected in our sample, could be that the number of "false positives" (APS individuals who never convert to psychosis) was too high to be able to discriminate between the APS groups and healthy controls, or perhaps cognitive deterioration only occurs closer to the onset of frank psychosis. Alternatively, facial affect processing difficulties may not emerge until a later age, provided that the involvement of crucial brain structures, such as the amygdala, are still undergoing developmental changes during adolescence (67, 68) that may obfuscate meaningful associations.

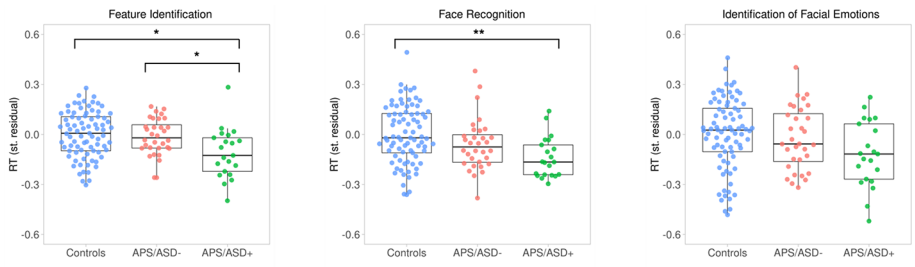

FIGURE 1 | Response times (RT; standardized residuals of responses per second, corrected for sex and age) plotted by group for all three cognitive tasks. Dots represent individual averages with higher scores reflecting faster response times. The summary of the data is shown as a boxplot, with the box indicating the interquartile range (IQR), the whiskers showing the range of values that are within 1.5*IQR and the horizontal line indicating the median. *p <.01; **p <.001.

Finally, due to limited clinical sample sizes, we applied a conservative statistical approach and did not test for emotion-specific variables. There is evidence that facial affect deficits may be more specific in at-risk individuals, e.g. the mislabelling of positive/neutral expressions (37, 40, 69)

Surprisingly, we did not find categorical or dimensional associations with facial emotion or face recognition accuracy in APS with and without ASD. The largest meta-analysis to date directly comparing emotion perception from faces between ASD and SSD subjects reported that both patient groups are impaired and that ASD subjects are significantly more impaired than SSD patients. However, this difference disappears with increasing age (12). The authors suggest that this may reflect a deterioration of social cognitive skills in SSD patients with increasing age, or an age-dependent improvement of emotion perception skills in ASD as a result of social learning. The fact that the APS group without ASD was significantly older in our study could therefore partially explain the negative findings for facial affect recognition. However, we did account for age in our analyses by using standardized regression residuals. Equally striking is the lack of a hypothesized negative relation between face recognition and autistic traits, which has previously been described for this task in ASD populations (47, 48). Together these findings are more in line with the general notion that social cognitive performance in psychosis and ASD are perhaps more similar than dissimilar (15, 70) and teasing this apart may require more refined paradigms, for example by using more ecologically valid stimuli, such as dynamic faces, and by combining them with methods with high temporal resolution, such as EEG or eye-tracking. These commonly available approaches are only just starting to be utilized for direct group comparisons between individuals with ASD and SSD (71–73).

Regarding our third and final hypothesis, no evidence was detected that could indicate basic visual processing may have a stronger, negative impact on facial (affect) recognition in APS without ASD. We did observe a trend towards a significant difference in accuracy, but results were pointing in the opposite direction, i.e. relatively better performance in APS without ASD, and even more so when corrected for pattern recognition. This finding appears to be at odds with common notions of early visual processing difficulties in schizophrenia research (43, 44) and recently also in UHR individuals (39). In contrast to APS individuals without ASD, those with ASD showed slower speed of processing on all cognitive tasks in lieu of typical accuracy. This in line with the notion that it may take more time to process faces in autism, except evidence for this has been inconsistent in ASD (74, 75) and here it appeared to be explained by a more general delay in processing speed, and not by the increased complexity of social stimuli. However, together these findings do suggest that studying the relative impact of psychotic or autistic traits on facial affect processing may benefit from taking into account the individual trade-off between speed and accuracy. Future studies are encouraged to also include a group of ASD individuals without APS to address this issue more thoroughly.

An important limitation of this study is that the use of psychotropic medication was not an exclusion criterion for the psychosis-risk groups, and that the effects of different types of medication on neurocognitive performance are still poorly understood. Secondly, it is possible that the group differences in the present study did not reach statistical significance, because the sample sizes were relatively small. Thirdly, the number of psychotic transitions in this particular APS sample are reportedly low (data available for 10 or less transitions) (27, 76, 77) and could suggest our sample was not highly representative of UHR/APS samples with higher transition rates.

To conclude, this study demonstrated that traditional computerized assessment of facial affect processing is unlikely to detect early vulnerability markers for psychosis in adolescents with APS. A more autistic-like APS profile may be characterized by a generalized increase in response latencies, suggesting that the combined presence of autistic and psychotic traits may disproportionately affect cognitive performance. However, this needs to be replicated with more realistic and dynamic social cognitive stimuli, and supplemented by taking into account speed-accuracy trade-offs. The majority of intervention studies in patients at risk for psychosis focus on a variety of cognitive behavioural therapies for treatment of APS, but until now no specific intervention has been designed for the ASD group (78). Given the elevated risk for psychosis in ASD and our current inability to sufficiently discern between cognitive features in both conditions, there is dire need for more comparative studies to help inform personal treatment guidelines.

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 Dutch Central Committee on Research Involving Human Subjects (CCMO). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

TZ, HS, and ST planned and designed the study. TZ and HS were involved in subject recruitment and assessment. AM conducted the literature searches. ST undertook the statistical analysis. AM was responsible for drafting the manuscript. All authors contributed to the article and approved the submitted version

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Categorical and Dimensional Approaches to Examining the Joint Effect of Autism and Schizotypal Personality Disorder on Sustained Attention

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Introduction: Accumulating evidence for the co-occurrence autism spectrum disorder (ASD) and schizotypal personality disorder (SPD) at both the diagnostic and symptom levels raises important questions about the nature of their association and the effect of their co-occurrence on the individual's phenotype and functional outcome. Research comparing adults with ASD and SPD, as well as the impact of their co-occurrence on outcomes is extremely limited. We investigated executive functioning in terms of response inhibition and sustained attention, candidate endophenotypes of both conditions, in adults with ASD, SPD, comorbid ASD and SPD, and neurotypical adults using both categorical and dimensional approaches.

Methods: A total of 88 adults (Mean Age = 37.54; SD = 10.17): ASD (n = 26; M/F = 20/6); SPD (n = 20; M/F = 14/6); comorbid ASD and SPD (n=9; M/F=6/3) and neurotypicals (n=33; M/F=23/10) completed the Sustained Attention to Response Task (SART) in both its fixed and random forms. Positive and autistic symptom severity was assessed with the positive subscale of the Positive and Negative Syndrome Scale (PANSSpos) and the PANSS Autism Severity Score (PAUSS), respectively.

Results: Controlling for full scale IQ, working memory and medication dosage, group analyses revealed that the comorbid group committed fewer omission errors than the ASD group on the fixed SART, and fewer omission errors than the ASD and SPD groups on the random SART. The individual difference analyses of the entire sample revealed that the PANSSpos and PAUSS interactively reduced omission errors in both the fixed and random SARTs, as well as increased d' scores, indicative of improved overall performance. We observed no significant results for commission errors or reaction time.

Conclusions: Concurrent elevated levels of autistic and positive psychotic symptoms seem to be associated with improved sustained attention abilities (reduced omission errors) but not inhibition (commission errors). Our findings highlight the importance of

investigating the concurrent effect of ASD and SPD at both the symptom and diagnostic levels, and raise important questions for future research regarding the clinical and behavioral phenotypes of adults with dual diagnosis and, more generally, about the nature of the relationship between ASD and SPD.

Keywords: attention, comorbidity, executive function, inhibition, schizotypy, The Sustained Attention Response to Task (SART), vigilance

INTRODUCTION

Autism spectrum disorder (ASD) and schizotypal personality disorder (SPD) are considered diagnostically independent (1). ASD is a neurodevelopmental disorder typically associated with impairments in social development, language, and repetitive, circumscribed behaviours/interests. SPD is a nonpsychotic schizophrenia spectrum disorder (SSD) involving milder symptoms of schizophrenia, and can be diagnosed in children as young as 6 years of age (2–4). However, the nosologic separation between them is not clear (5), particularly in light of accumulating evidence suggesting that ASD and SPD share etiological and risk factors, and that they can co-occur at both the diagnostic and symptom/trait levels (6–8). For example, reports show that 41% of adolescents with ASD met the DSM-IV-TR diagnostic criteria for SPD (9). Moreover, schizotypal symptoms are found at significant levels in children with ASD (2), and vice versa (10). This raises important questions about the nature of their association and the effect of their co-occurrence on the individual's phenotype and functional outcome. It has been recommended that informing etiological and phenotypic overlaps between ASD and SSD would require the utilization of a dual-diagnosis cohort compared with two control groups, each singly diagnosed with ASD or SSD (11), and that the development of a multidimensional model for understanding the relationship between these two spectra would require cohorts to be described not solely by diagnosis, but also by using dimensional measures that cut across diagnostic boundaries (11–14). To fill in this gap, the current study investigated executive functioning in terms of response inhibition and sustained attention in adults with ASD, SPD, comorbid ASD and SPD (CM), and neurotypical adults using both categorical and dimensional approaches.

Dysfunction associated with sustained attention and inhibition has been proposed as endophenotypes for both conditions (15–17), and thus they represent common features wherein the relationship between the two disorders can be evaluated. Since we examine sustained attention and inhibition with The Sustained Attention to Response Task (SART) (18), our survey of the literature has primarily focused on studies that have utilized this task in particular in both its random and fixed versions (see Materials and Methods). Research in SSD, both at the diagnostic and dimensional levels, reports performance difficulties on the SART (19–21). For example, O'Gráda et al. (19) showed that the schizophrenic group was more impaired than controls on sustained attention (measured through omission errors), but not inhibition (measured through commission errors), and that severity of negative symptoms correlated with difficulties in sustaining attention. Another study (20) found no statistically significant differences in commission errors between healthy controls, individuals with schizotypal features, and schizophrenic patients, nor an association between schizotypal features or schizophrenia symptoms with any of the SART's performance indices. However, it reported differences in overall task performance, with the schizotypy group intermediately positioned. With respect to ASD, one study (22) showed that while the ASD children did not show sustained attention deficits (measured through omission errors), it showed dissociation in response inhibition performance (measured through commission errors), but only on the random version of the SART. Similar results were reported in elderly with ASD while performing the fixed SART (23); compared to controls, they made more commission errors and a similar number of omission errors. A later study (24) also reported the absence of sustained attention deficits in ASD children, but not for those with comorbid ADHD.

Research directly comparing ASD and SSD on executive function in adults is extremely limited. In one study, Demetriou et al. (25) compared executive function in young adults with ASD, Early Psychosis, and Social Anxiety Disorder, using a battery of neuropsychological and self-report assessments. Relative to the typically developing group, the ASD group was impaired on mental flexibility, sustained attention and fluency, while the early psychosis group was impaired on sustained attention and attentional shifting. Notably, the early psychosis group was significantly more impaired than the ASD group on sustained attention. To our knowledge, only one study (26)—albeit in male children—compared response inhibition in ASD and SSD using the fixed version of the SART. They found that both the ASD and SSD groups had significantly lower correct responses than the typically developing group, and that the SSD group had slower reaction time and lower efficiency than the ASD group. With respect to response inhibition, the commission error rate in the ASD group was higher than the typical developing group, and non-significantly different from the SSD group.

Taken together, results from previous SART studies in ASD and SSD suggest that while ASD appears to be primarily associated with response inhibition problems, SSD appears to be associated with sustained attention deficits.

We are only aware of one study, performed in children, that has directly compared executive functioning in ASD, SPD, and CM groups (3). Results showed that while the overall performance of the ASD and SPD groups on the intra-/extra-dimensional set-shifting (IED) task was worse than the typically developing group, the overall performance of the CM group was significantly better than the ASD and SPD groups, and not significantly different from the

typically developing group. Interestingly, relative to the typically developing group, clear distinctions between the ASD and SPD groups were present. Specifically, the ASD group had difficulties with extra-dimensional shifts, and the SPD group with intra-dimensional shifts. The study found no differences between the groups in non-verbal short-term or working memory, or response inhibition.

Given previous findings from studies using the SART, it was hypothesized that the frank clinical groups would demonstrate performance deficits on the SART relative to the neurotypical group. Specifically, relative to the neurotypical group, we predicted worse performance on response inhibition for the ASD group, and worse performance on sustained attention for the SPD group. In addition, based on evidence for improved performance in children with comorbid ASD and SPD on the IED task (3), and the fact that performance on the SART requires the recruitment of both sustained attention and response inhibition (22), we hypothesized that the CM group might perform better than the ASD and SPD groups, and that it would show no or attenuated impairment relative to the neurotypical group. This hypothesis is conceivable if we assume that response inhibition and sustained attention represent two poles of irregularities across the autism and schizotypal spectra that converge in a compensatory manner in the CM group. From a dimensional perspective, a corollary hypothesis would be to expect performance benefits in individuals jointly expressing elevated levels of autistic and positive psychotic symptoms.

MATERIALS AND METHODS

Participants

A total of 88 individuals participated in the study (Mean age (SD) = 37.54(10.17); Male/Female = 63/25). The sample, which has been previously used in another study (27), consisted of an ASD, SPD, comorbid (CM), and neurotypical (NT) control groups (see **Table 1** for demographic and clinical details). As previously described (27), individuals with ASD were recruited from clinical and support services in Southeast Scotland. All had a DSM-IV diagnosis of either autism or Asperger Syndrome and met ASD cut-offs on the Autism Diagnostic Observational Schedule-Generic (ADOS-G) (28). Individuals with SPD were recruited from nonpsychotic people who had previously participated in the Edinburgh High Risk Study of schizophrenia (EHRS) (29), and from clinical services in Southeast Scotland. All met DSM-IV criteria for SPD using the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) (30). Individuals in the comorbid group met criteria for both ASD (determined by DSM-IV and the ADOS) and SPD (determined by the SCID-II). Finally, controls were recruited from participant and investigator acquaintances and the Scottish Mental Health Network research register. Individuals with a history of, or first degree relative with ASD, SPD, or a psychotic illness were excluded. General exclusion criteria were IQ < 70, substance dependence or history of schizophreniform disorder, schizophrenia or bipolar affective disorder. Full Scale Intelligence Quotients (FSIQ) was assessed with the Wechsler Abbreviated Intelligence Scale (31). The study was approved by the NHS Lothian Research Ethics Committee. Written informed consent was obtained from all participants.

Assessments

In addition to the ADOS-G, the SCID-II, and FSIQ, all participants were assessed with the Positive and Negative Syndrome Scale (PANSS) (32). From the PANSS, both the positive and the PANSS autism severity score (PAUSS) subscale were calculated. The PAUSS (33) is a validated dimensional measure of autism symptom severity in individuals with schizophrenia, and consists of PANSS items indicative of autistic behavior: difficulties in social interaction (Items N1, N3, N4), difficulties in communication (Items N5, N6), and limited, repetitive, and stereotypic patterns of behavior (Items N7, G5, G15). The PAUSS has been shown to be a sensitive measure of autism symptom severity in young people with first-episode psychosis (34), and in individuals with schizophrenia (35–38). The internal consistency of the PAUSS in this study was fair (Cronbach's $\alpha = 0.75$). For the PANSS positive, Cronbach's α was 0.62. However, the average inter-item correlation was good ($r_{IICorAvg} = 0.164$), which is a more suitable measure of internal consistency for scales less than 10 items (39).

For those on antipsychotic medication, doses were converted to chlorpromazine (CPZ) equivalents (40, 41).

Working Memory

Following O'Gráda et al. (19), we included working memory to index higher 'executive' functioning, which was assessed using the letter-number sequencing (LNS) task from the Wechsler Adult Intelligence Scale, 3rd edition [WAIS-III, (42)]. In this task, individuals were presented with a pseudorandom series of numbers and letters. They were then asked to respond with the numbers first in numerical order, followed by the letters in alphabetical order. The task consisted of 7 levels with gradually increasing number of components (ranging from level 1 with two components – one letter and one number, to level 7 with 8 components). Each level contained 3 items. For the current study, performance on the LNS was considered for the level reached and the total number of correctly recalled sequences (Maximum score = 21).

The Sustained Attention Response to Task (SART)

The SART (18) was employed in both its fixed and random forms (22). **Figure 1** provides a summary of the random version of the task. In both forms, numbers between 1 and 9 were presented on a laptop screen 225 times over 4 min and 19 s. The numbers were in one of 5 different font sizes and no font size occurred more than twice in a row. Each number appeared on the screen for 250 ms and was followed by a mask (a cross in a circle) for 900 ms. Participants were asked to press the space bar for every number (Go trials) except for the number 3 (No-go trials). In order to minimize impulsive responses, they were asked to not press the space bar until the appearance of the mask.

TABLE 1 | Demographics and clinical characteristics of the study groups.

Variables*	NT (N = 33)	ASD (N = 26)	SPD (N = 20)	CM (N = 9)	Stat F/χ^2/H	p-value
Gender (M:F)	23:10	20:6	14:6	6:3	0.72[b]	0.88
Age	36.53	39.65	37.26	35.80	0.56[a]	0.64
	(9.33)	(11.89)	(9.42)	(10.03)		
FSIQ	118.06	114.81	106.40	102.44	4.68[a]	**0.005**
	(9.86)	(16.75)	(10.69)	(23.61)		SPD, CM < NT[d]
LNS Level	5.64	4.62	5.00	3.89	14.35[c]	**0.002**
	(1.19)	(1.13)	(1.38)	(1.54)		ASD, CM < NT[d]
LNS Total	13.39	11.54	11.60	10.7	7.67[c]	0.053
	(2.65)	(3.09)	(3.47)	(4.30)		
PANSS positive	7.52	9.92	12.95	14.11	48.05[c]	**<0.001**
	(1.16)	(2.67)	(2.37)	(2.42)		SPD, CM > ASD > NT[d]
PAUSS	8.00	12.88	11.63	14.89	33.12[c]	**<0.001**
	(0.00)	(4.29)	(3.18)	(5.21)		ASD, SPD, CM > NT[d]
PAUSS Social	3.00	4.66	4.47	5.44	19.11[c]	**<0.001**
	(0.00)	(2.21)	(2.09)	(2.24)		ASD, SPD, CM > NT[d]
PAUSS Communication	2.00	3.46	3.00	4.67	22.90[c]	**<0.001**
	(0.00)	(1.77)	(1.25)	(2.29)		ASD, SPD, CM > NT[d]
PAUSS Stereotypies	3.00	4.77	4.16	4.78	18.48[c]	**<0.001**
	(0.00)	(1.53)	(1.50)	(1.64)		ASD, CM > NT[d]
CPZ	0.00	3.85	23.75	63.89	12.73[c]	**0.005**
	(0.00)	(13.56)	(52.24)	(135.27)		SPD, CM > NT[d]

**Continuous variables are presented in means with standard deviations.*

M, Male; F, Female; FSIQ, Full Scale Intelligence Quotients; LNS, Letter Number Sequencing; PANSS positive, Positive Subscale of the Positive and Negative Syndrome Scale; PAUSS, PANSS Autism Severity Scale; CPZ, Chlorpromazine equivalents;

[a]F statistics; [b]Fisher's exact test; [c]Kruskal-Wallis Test (H); [d]Bonferroni corrected.

The p-values are indicated under the p-value column (right most column), and significant values are in bold.

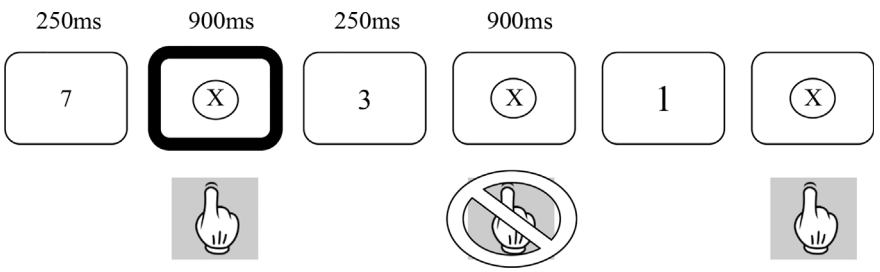

FIGURE 1 | Schematic diagram of the Random Sustained Attention to Response Task.

In the fixed form of the SART, the numbers are presented in repeated cycles of a fixed ascending order (i.e., 1, 2, 3, 5, 6, 7, 8, 9, 1, 2,…). In the random form, the numbers are presented in a pseudorandom order. In both versions, each number appears 25 times. All participants completed the Fixed SART followed by the Random SART.

The SART differs from traditional continuous performance tasks in that it requires the inhibition of response to an infrequent target as opposed to requiring a response to an infrequent target. Withholding of the primed response is suggested to place greater load on sustained attention networks (18). Clearly, in addition to sustained attention, individuals must also show intact response inhibition to perform the SART. To the extent that response inhibition and sustained attention can be dissociable, the use of the fixed and random forms of the SART allows these two aspects of performance to be dissociated. The Random SART places greater load on inhibitory functions than the Fixed SART due to the random presentation of either Go or No-go trials, whereas the Fixed SART places relatively greater demand on attentional compared to inhibitory functions due to the predictable nature of the Go and No-go trials (22).

Performance on the SART is measured through the number of omission (failed Go trials) and commission (failed No-go trials) errors. Omission errors on both versions of the SART are related to lapses in sustained attention. Commission errors on the random SART are related to difficulties in both sustained attention and response inhibition, whereas commission errors on the Fixed SART are primarily related to lapses in sustained attention with a much smaller load being placed upon response inhibition. In addition, overall performance, d-prime (d'), was calculated as the standardized difference between hits and false alarms as follows: d' = z(H) - z(F). A correction was applied when the rate of false alarms was zero [$1/(2N_{lures})$], and when the rate of hits was one [$1-1/(2N_{targets})$].

We also recorded response reaction time (RT) of correct responses for both tasks.

Statistical Analyses

Differences in demographics and clinical variables of the groups were analyzed using F, χ^2, and H statistics, as appropriate. Group analyses of the omission and commission errors of the fixed and random SART tasks were performed using Generalized Linear Models (GLMs) with negative binomial distribution, using Wald chi-square statistics. A negative binomial distribution is appropriate for the analysis of count data and when the expected variance is greater than the mean (43, 44). The shape parameter k of the negative binomial distribution of each of the omission/commission errors was calculated as follows: $k = \frac{m^2}{v-m}$, where m is the mean and v is the variance (43). *d'* scores, indicative of overall performance on the SART tasks, were analyzed with GLMs, using the *identity* link function. Mean reaction time to correct responses was analyzed with GLMs, using the *log* link function. All group analyses were conducted while controlling for FSIQ, LNS level, and CPZ on which the groups differed (see **Table 1**).

Individual difference analyses of SART outcome measures were also analyzed as a function of PANSSpos, PAUSS and their interaction using GLMs as above, while controlling for FSIQ, LNS level, CPZ, and diagnosis. Analyses were performed using SPSS Version 24. Significant interactions were probed with the Johnson-Neyman method in R Studio (45). The Johnson-Neyman method provides a "high-resolution picture" of the interaction by estimating the value(s) of one predictor at which the other predictor has a significant effect on the outcome measure. This is established by identifying the precise value(s) along the continuum of one predictor for which the regression slopes of the other predictor are estimated to be significantly different from zero.

Unless it is otherwise noted, all p-values are FDR adjusted (q-value = 0.05) for multiple testing (46). Effect sizes are reported in terms of Pseudo-R^2 and Cohen's d.

RESULTS

Preliminary analyses are presented in **Tables 1** and **2**. **Table 1** presents the demographics and clinical characteristics of the study groups. Group comparisons did not reveal differences in age, gender distribution, or the total number of correctly recalled sequences of the LNS task. However, significant group differences were observed in FSIQ, LNS level, and CPZ dosage.

Table 2 presents the correlations between the study variables. We note that neither the PAUSS nor the PANSS positive significantly correlated with either the Fixed or Random SART outcome measures.

Group Differences in Fixed and Random SART

Figure 2 depicts the results of the group analyses on omission and commission errors and overall performance (d') of the fixed and random SART tasks. **Figure 3** depicts the results of the group analyses on mean reaction time of correct responses of the fixed and random SART tasks.

Fixed SART Omission Errors

The overall model was significant (χ^2 = 63.71, df = 6, p_{corr} < 0.001, Pseudo R^2 = 0.12). As can be seen in **Figure 2A**, there was a significant main effect for group (Waldχ^2 = 13.94, df = 3; p = 0.003) such that the CM group made fewer errors than the ASD group (MD(se) = -2.59(0.77), p_{corr} = 0.005, Cohen's d = 0.79). The ASD group made more errors than the NT group at a trend level (MD(se) = 2.20(0.89); p_{corr} = 0.065, Cohen's d = 0.68). This was independent of the significant effect of FSIQ, where increasing FSIQ scores were associated with fewer errors (β(se) = - 0.009(0.002), Waldχ^2 = 33.64, df = 1; p_{corr} < 0.001).

TABLE 2 | Spearman's correlations between the study variables in the entire sample*.

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Age		0.02	-0.02	-0.07	-0.04	0.18	0.22	-0.09	0.00	-0.02	-0.08	0.05	0.08	0.02	0.03
2. FSIQ	0.02		**0.42**	**0.47**	-0.18	-0.25	**-0.29**	**-0.42**	**-0.36**	**-0.28**	**-0.29**	**0.39**	**0.34**	-0.10	-0.01
3. LNS Level	-0.01	**0.42**		**0.89**	**-0.30**	-0.18	**-0.35**	**-0.32**	**-0.38**	**-0.29**	-0.23	**0.37**	**0.29**	-0.19	-0.06
4. LNS Total	-0.07	**0.47**	**0.89**		-0.18	-0.11	-0.24	**-0.35**	**-0.42**	**-0.28**	**-0.30**	**0.42**	**0.33**	-0.13	0.03
5. CPZeq	-0.04	-0.18	**-0.30**	-0.18		**0.41**	0.24	0.08	0.13	0.05	-0.07	-0.11	0.02	**0.25**	0.20
6. PANSS Pos.	0.18	**-0.25**	-0.18	-0.11	**0.41**		**0.51**	0.15	0.09	0.01	0.08	-0.14	-0.08	0.05	0.05
7. PAUSS	0.22	**-0.29**	**-0.35**	**-0.24**	0.24	**0.51**		0.17	0.08	0.02	0.05	-0.14	-0.07	0.13	0.08
8. F SART OE	-0.09	**-0.42**	**-0.32**	**-0.35**	0.08	0.15	0.17		**0.66**	**0.56**	**0.60**	**-0.89**	**-0.68**	-0.21	**-0.26**
9. F SART CE	0.00	**-0.36**	**-0.38**	**-0.42**	0.13	0.09	0.08	**0.66**		**0.47**	**0.58**	**-0.91**	**-0.62**	-0.11	**-0.26**
10. R SART OE	-0.02	**-0.28**	**-0.29**	**-0.28**	0.05	0.01	0.03	**0.56**	**0.47**		**0.47**	**-0.56**	**-0.68**	-0.04	-0.06
11. R SART CE	-0.08	**-0.29**	**-0.23**	**-0.30**	-0.07	0.08	0.05	**0.60**	**0.58**	**0.47**		**-0.66**	**-0.95**	**-0.50**	**-0.71**
12. F SART d'	0.05	**0.39**	**0.37**	**0.42**	-0.11	-0.14	-0.14	**-0.89**	**-0.91**	**-0.56**	**-0.66**		**0.72**	0.19	**0.31**
13. R SART d'	0.08	**0.34**	**0.29**	**0.33**	0.02	-0.08	-0.07	**-0.68**	**-0.62**	**-0.68**	**-0.95**	**0.72**		**0.42**	**0.58**
14. F CR RT	0.02	-0.10	-0.19	-0.13	**0.25**	0.04	0.13	-0.21	-0.11	-0.04	**-0.50**	0.19	**0.42**		**0.66**
15. R CR RT	0.03	-0.01	-0.06	0.03	0.20	0.05	0.08	**-0.26**	**-0.26**	-0.06	**-0.71**	**0.31**	**0.58**	**0.66**	

FSIQ, Full Scale Intelligence Quotients; LNS, Letter Number Sequencing; PANSS pos, Positive Subscale of the Positive and Negative Syndrome Scale; PAUSS, PANSS Autism Severity Scale; CPZ, Chlorpromazine equivalents; F SART, Fixed SART; R SART, Random SART; OE, Omission errors; CE, Commission errors; d', d prime; F CR RT, Fixed SART Correct Responses Mean Reaction Time; R CR RT, Random SART Correct Responses Mean Reaction Time;

** Coefficients in bold are significant (p < 0.05). Coefficients above the diagonal are FDR adjusted for multiple tests.*

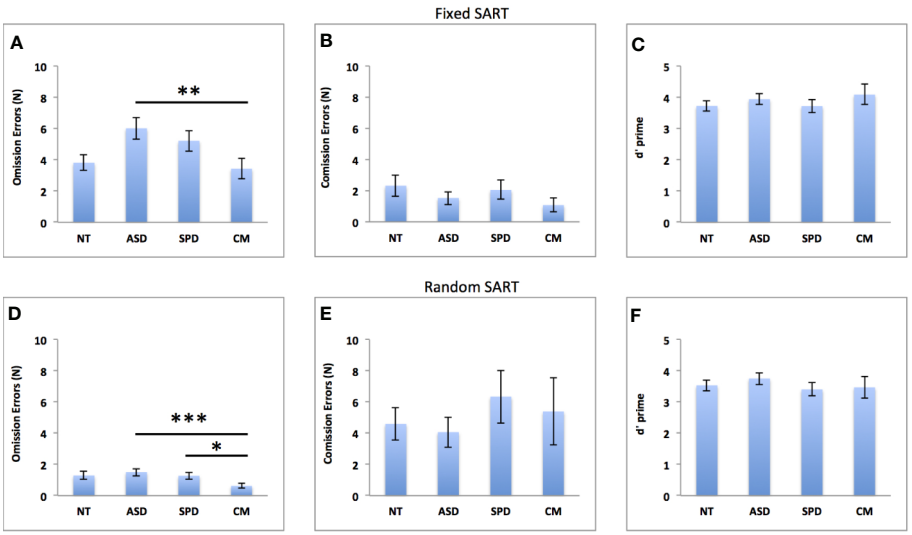

FIGURE 2 | Groups comparisons on omission errors, commission errors and overall performance (d') in the fixed **(A–C)** and random **(D–F)** SART tasks. NT, Neurotypical Controls; ASD, Autism Spectrum Disorder; SPD, Schizotypal Personality Disorder; CM, Comorbid group. Error bars represent standard error of the mean (SEM). *p < 0.05, **p < 0.01, ***p < 0.001.

Fixed SART Commission Errors

The overall model was non-significant (χ^2 = 7.61, df = 6, p_{corr} = 0.357). See **Figure 2B**.

Fixed SART d Prime

The overall model was significant (χ^2 = 18.58, df = 6, p_{corr} = 0.013, Pseudo R^2 = 0.19). Better task performance was significantly associated with FSIQ (β(se) = 0.018(0.008), Waldχ^2 = 5.45, df = 1; p = 0.020), and higher LNS levels (β(se) = 0.181(0.087), Waldχ^2 = 4.30, df = 1; p = 0.038). However, as can be seen from **Figure 2C**, the difference between the groups was non-significant (Waldχ^2 = 1.64, df = 3; p = 0.644).

Fixed SART Mean Reaction Time of Correct Responses

The overall model was non-significant (χ^2 = 9.10, df = 6, p_{corr} = 0.269). See **Figure 3A**.

Random SART Omission Errors

The overall model was significant (χ^2 = 143.55, df = 6, p_{corr} < 0.001, Pseudo R^2 = 0.37). There was a significant main effect of group (Waldχ^2 = 31.72, df = 3; p < 0.001) such that the CM group made fewer errors than the ASD (MD(se) = -0.88(0.18); p_{corr} < 0.001, Cohen's *d* = 0.80) and SPD (MD(se) = -0.64 (0.21); p_{corr} = 0.012, Cohen's *d* = 0.74) groups (see **Figure 2D**). This was independent of the significant effects of FSIQ, LNS levels and CPZ dosage, where increasing FSIQ (β(se) = - 0.031(0.004), Waldχ^2 = 66.80, df = 1; p < 0.001), and LNS level (β(se) = - 0.173 (0.057), Waldχ^2 = 9.11, df = 1; p = 0.003) were associated with fewer errors, while higher CPZ dosage was associated with more errors (β(se) = 0.003(0.001), Waldχ^2 = 5.37, df = 1; p = 0.021).

Random SART Commission Errors

The overall model was non-significant (χ^2 = 4.91, df = 6, p_{corr} = 0.635). See **Figure 2E**.

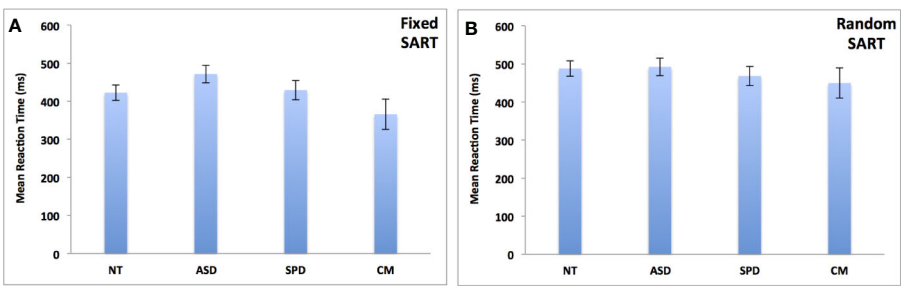

FIGURE 3 | Groups comparisons on mean response time (in milliseconds) of appropriate responses in the fixed **(A)** and random **(B)** SART tasks. NT, Neurotypical Controls; ASD, Autism Spectrum Disorder; SPD, Schizotypal Personality Disorder; CM, Comorbid group. Error bars represent standard error of the mean (SEM).

Random SART d Prime

The overall model was significant (χ^2 = 15.24, df = 6, p_{corr} = 0.037, Pseudo R^2 = 0.16). Task performance was marginally associated with FSIQ (β(se) = 0.015(0.008), Waldχ^2 = 3.48, df = 1; p = 0.062) and LNS level (β(se) = 0.161(0.093), Waldχ^2 = 3.02, df = 1; p = 0.082). The difference between the groups was non-significant (Waldχ^2 = 1.52, df = 3; p = 0.678). See **Figure 2F**.

Random SART Mean Reaction Time of Correct Responses

The overall model was non-significant (χ^2 = 1.83, df = 6, p_{corr} = 0.935). See **Figure 3B**.

Individual Difference Analyses: Fixed SART

Fixed SART Omission Errors

The overall model was significant (χ^2 = 65.85, df = 9, p_{corr} < 0.001, Pseudo R^2 = 0.33). Parameter estimates revealed a significant negative PAUSS x PANSSp interaction on omission errors (β(se) = - 0.067(0.027), Waldχ^2 = 6.21, df = 1; p = 0.013).

Fixed SART Commission Errors

The overall model was non-significant (χ^2 = 8.64, df = 9, p_{corr} = 0.539).

Fixed SART d Prime

The overall model was significant (χ^2 = 24.23, df = 9, p_{corr} = 0.011, Pseudo R^2 = 0.30). Parameter estimates revealed a significant positive PAUSS x PANSSp interaction on d' prime (β(se) = 0.302(0.101), Waldχ^2 = 8.94, df = 1; p = 0.003).

The results of the interaction probes for the omission errors and overall performance (d') of the fixed SART task are summarized in **Figure 4**. **Figures 4A, B** depict the results for the omission errors. **Figure 4A** shows that the PAUSS is associated with a significant increase in omission errors when PANSS positive is ≤ - 0.76 SD from the mean, but with a significant decrease in errors when PANSS positive is ≥ 0.69 SD from the mean. Conversely, **Figure 4B** shows that PANSS positive is significantly associated with an increase in errors when PAUSS is ≤ 1.08 SD from the mean, but with a significant decrease in errors when PAUSS is ≥ 3.23 SD from the mean.

Figures 4C, D depict the results for d'. **Figure 4C** shows that PAUSS is significantly associated with better performance when PANSS positive is ≥ 1.47 SD from the mean. Conversely, **Figure 4D** shows that PANSS positive is significantly associated with worse performance when PAUSS is ≤ - 0.04 SD from the mean, but with significantly better performance when PAUSS is ≥ 3.46 SD from the mean, albeit this is outside the range of the PAUSS scores in our data [PAUSS range = -0.89, 3.40].

Fixed SART Reaction Time

The overall model was non-significant (χ^2 = 11.71, df = 9, p_{corr} = 0.368).

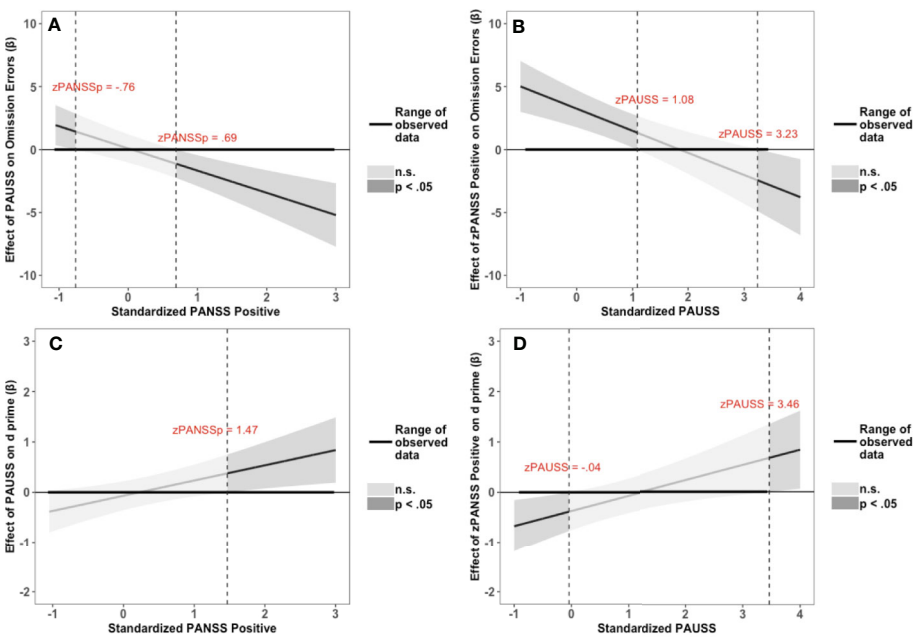

FIGURE 4 | Results of the Johnson-Neyman interaction probes for omission errors (OE) and d prime scores (d') of the Fixed Sustained Attention to Response Task (SART) task. **(A, C)** depict the association (β weights) of the Positive and Negative Syndrome Scale (PANSS) Autism Severity (PAUSS) scores with OE and d', respectively, along the range of the standardized values of the PANSS positive scores. **(B, D)** depict the association (β weights) of the PANSS positive scores with OE and d', respectively, along the range of the standardized values of the PAUSS scores. Areas shaded in dark grey represent the zone of significant effects (p < 0.05), and areas shaded in light gray represent the zone of non-significant effects (p > 0.05). Slopes are bounded by 95% confidence intervals.

Individual Difference Analyses: Random SART

Random SART Omission Errors

The overall model was significant (χ^2 = 37.80, df = 9, p_{corr} < 0.001, Pseudo R^2 = 0.41). Parameter estimates revealed a significant and negative PAUSS x PANSS positive interaction on omission errors (β(se) = - 0.24(0.102), Waldχ^2 = 5.60, df = 1; p = 0.018).

Random SART Commission Errors

The overall model was non-significant (χ^2 = 7.44, df = 9, p_{corr} = 0.591).

Random SART D' Prime

The overall model was significant (χ^2 = 23.35, df = 9, p_{corr} = 0.011, Pseudo R^2 = 0.291). Parameter estimates revealed a significant and positive PAUSS x PANSS interaction on errors (β(se) = 0.253(0.110), Waldχ^2 = 5.24, df = 1; p = 0.022).

The results of the interaction probes for the omission errors and overall performance (d') of the random SART task are summarized in **Figure 5**. **Figures 5A, B** depict the results for the omission errors. **Figure 5A** shows that PAUSS is associated with an increase in omission errors when PANSS positive is ≤ -0.74 SD from the mean, but with a significant decrease in errors when PANSS positive is ≥ 0.58 SD from the mean. Conversely, **Figure 5B** shows that PANSS positive is associated with an increase in omission errors when PAUSS is ≤ 0.11 SD from the mean, but with a significant decrease in errors when PAUSS is ≥ 1.67 SD from the mean. **Figures 5C, D** depict the results for d'. **Figure 4C** shows that PAUSS is significantly associated with better overall performance when PANSS positive is ≥ 0.44 SD from the mean. Conversely, **Figure 4D** shows that PANSS positive is significantly associated with better overall performance when PAUSS is ≥ 2.30 SD from the mean.

Random SART Reaction Time

The overall model was non-significant (χ^2 = 10.69, df = 9, p_{corr} = 0.397).

Exploratory Analyses

To gain further insight into the association of the interaction of PANSS positive x PAUSS scores with reduced omission errors, we performed a serious of exploratory analyses in the entire sample as well as in each of the ASD and SPD groups, separately. First, for the entire sample, we examined the association of PANSS positive with each of the three subdomains of the PAUSS (i.e., social difficulties, communication difficulties, and stereotypies/narrowed interests) with omission errors in both the fixed and random SART tasks to see if the interactions we observed in the main analyses were driven by a specific subdomain of autistic features. For each model, we examined the association of PANSS positive and its interaction with each of the PAUSS subdomains while controlling for the other two subdomains as well as for FSIQ, LNS level, CPZ, and diagnosis. In the fixed SART, omission errors were associated with a negative PANSS positive x PAUSS stereotypic behavior interaction (β(se) = -0.112(0.037), Waldχ^2 = 9.11, df = 1; p = 0.003). The interactions of

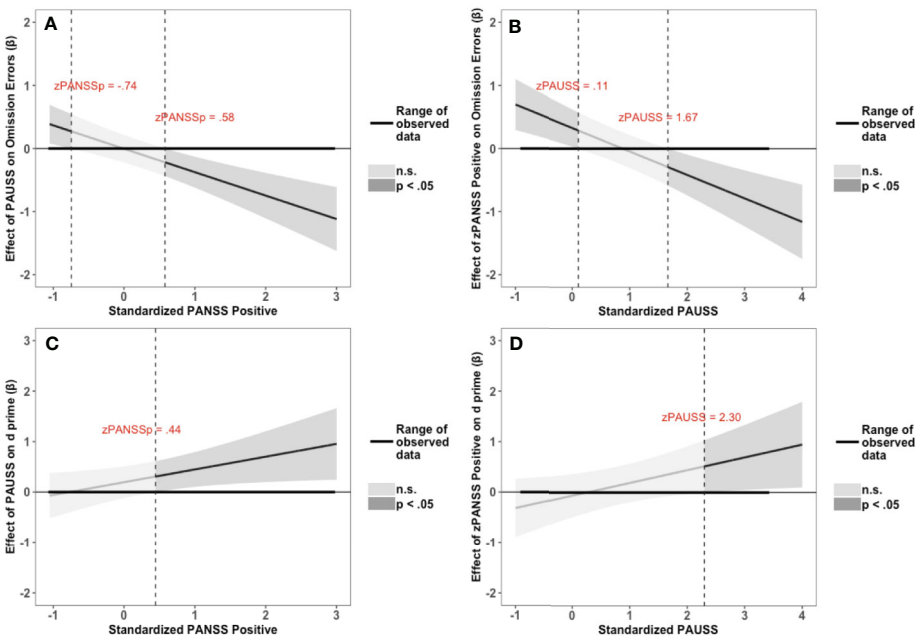

FIGURE 5 | Results of the Johnson-Neyman interaction probes for omission errors (OE) and d prime scores (d') of the Random Sustained Attention to Response Task (SART) task. **(A, C)** depict the association (β weights) of the Positive and Negative Syndrome Scale (PANSS) Autism Severity (PAUSS) scores with OE and d', respectively, along the range of the standardized values of the PANSS positive scores. **(B, D)** depict the association (β weights) of the PANSS positive scores with OE and d', respectively, along the range of the standardized values of the PAUSS scores. Areas shaded in dark grey represent the zone of significant effects ($p < 0.05$), and areas shaded in light grey represent the zone of non-significant effects ($p > 0.05$). Slopes are bounded by 95% confidence intervals.

PANSS positive with the PAUSS social (p = 0.131) and PAUSS communication (p = 0.955) subdomains were non-significant. For the Random SART, omission errors were associated with a negative PANSS positive x PAUSS stereotypic behavior interaction (β(se) = -0.547(0.133), Waldχ^2 = 16.94, df = 1; p < 0.001), as well as with a negative PANSS positive x PAUSS communication interaction (β(se) = -0.323(0.129), Waldχ^2 = 6.24, df = 1; p = 0.013). The interaction of PANSS positive with the PAUSS social subdomain was non-significant (p = 0.076).

Following the same analyses we performed for the entire sample, we explored the association of the PANSS positive x PAUSS interaction with omission errors in the ASD only group, and in the SPD only group. The results revealed significant models only for the random SART in both the ASD (χ^2 = 17.10, df = 6, p_{corr} = 0.018, Pseudo R^2 = 0.52) and SPD (χ^2 = 21.49, df = 6, p_{corr} = 0.004, Pseudo R^2 = 0.70) groups. In the ASD group, the PANSS positive x PAUSS interaction was associated with reduced omission errors (β(se) = -0.736(0.318), Waldχ^2 = 5.37, df = 1; p = 0.021). In the SPD group, while the interaction was not significant (p = 0.281), the main effects of the PANSS positive and PAUSS were significant, such that increasing PANSS positive scores were associated with increased omission errors (β(se) = 2.595(0.731), Waldχ^2 = 12.60, df = 1; p < 0.001), and increasing PAUSS scores were associated with reduced omission errors (β(se) = -2.736(0.976), Waldχ^2 = 8.63, df = 1; p = 0.003). As can be seen from **Figures 6A, B**, the pattern of associations of PAUSS and PANSS positive with omission errors in the ASD group was reversed in the SPD group.

DISCUSSION

Using the SART task, we examined executive functioning in terms of response inhibition and sustained attention, two candidate endophenotypes in both ASD and SPD. Overall, we found that while the clinical groups did not differ from healthy controls, there were clear differences between the single diagnosis groups and the CM group in sustained attention (as measured with omission errors) but not response inhibition (as measured with commission errors). The group analyses revealed that the CM group committed fewer omission errors than the ASD group in both the fixed and random SART, as well as fewer errors than the SPD group in the random SART. The individual difference analyses confirmed and extended these results to show that autism and positive symptom severity interactively reduced omission errors. In addition, the individual difference analyses also revealed that the interaction was associated with better overall performance (as indexed by higher d' values). The individual difference analyses suggest that dimensional measures are more sensitive than group level analyses, and that performance might be more aptly characterized by examining the relative severity of autistic and positive symptoms in the individual rather than the absence or presence of an ASD or SPD.

Our predictions of increased omission errors in the SPD group, and increased commission errors in the ASD group relative to the neurotypical group were not supported by our findings in either the fixed or random version of the SART. We also found no statistically significant differences between the four groups on commission errors, nor between the ASD, SPD, and NT groups on omission errors. While the lack of differences may be due to the SART being relatively an easy task to perform, these results partially overlap with findings from previous research, although caution is warranted since we are comparing our results to findings from populations with different diagnoses (schizophrenia) and at different developmental stages (children, elderly). With respect to commission errors on the fixed SART, O'Gráda et al. (19), Chan et al. (20), and Ho et al. (21) found no differences between healthy controls and schizophrenic patients, Shi et al. (26) found no differences between ASD and SSD children, and Johnson et al. (22) found no differences between ASD and typically developing children. In contrast, however, Johnson et al. (22) reported higher number of

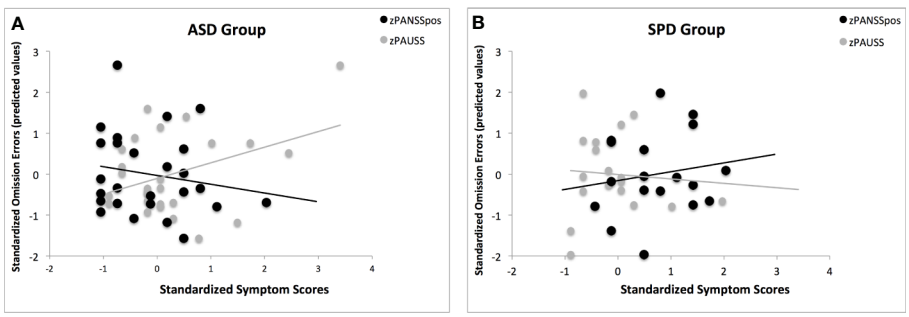

FIGURE 6 | The association of the PANSS Autism Severity (PAUSS) and PANSS Positive (PANSSpos) scores with omission errors on the Random SART task in the ASD and SPD groups. **(A)** shows the association of the standardized PAUSS and PANSSpos scores with the standardized predicted values of the omission errors in the ASD group, where PAUSS scores are associated with increased omission errors and the PANSSpos scores are associated with reduced omission errors. Here, the interaction of PAUSS x PANSSpos is significant ASD (β(se) = -0.736(0.318), Waldχ^2 = 5.37, df = 1; p = 0.021)**. (B)** shows the association of the standardized PAUSS and PANSSpos scores with the standardized predicted values of the omission errors in the SPD group, where PANSSpos scores are associated with increased omission errors (β(se) = 2.595(0.731), Waldχ^2 = 12.60, df = 1; p < 0.001) and the PAUSS scores are associated with reduced omission errors (β(se) = -2.736(0.976), Waldχ^2 = 8.63, df = 1; p = 0.003). Here, the PAUSS x PANSSpos interaction is not significant (p = 0.281).

commission errors in ASD relative to typically children while performing the random SART, and Geurts et al. (23) reported similar results in elderly with ASD while performing the fixed SART. Moreover, unlike our results, O'Gráda et al. (19) found that the schizophrenic group made more omission errors than the controls while performing the fixed SART.

However, we observed differences between the clinical groups on sustained attention, with the CM group out-performing the ASD group in the fixed SART and both the ASD and SPD groups in the random SART. Cognizant of the different tasks and methodologies employed in other studies, these results are consistent with the few available studies that compared individuals with comorbid ASD-SSD to individuals with ASD or SSD. In children, the performance of those with a dual diagnosis of ASD and SPD were similar to typically developing children, and largely better than the children with the frank conditions on both attentional set shifting and socio-pragmatic skills (3). In adults, brain activations in the ASD-SPD comorbid group during a social judgment task were generally indistinguishable from the typically developing group and fell intermediately between the ASD and SPD groups (27). More recently, Sunwoo et al. (47) reported that young people with comorbid first episode psychosis (FEP) and ASD were: (1) less likely than young people with FEP only to have comorbid substance use issues, (2) more likely to be engaged in employment or education at the time of discharge, but also (3) more likely to experience impairments in interpersonal skills.

From a dimensional perspective, the results regarding the association of the interaction of PANSS autistic and positive symptoms with performance benefits on the SART resonate with those obtained for social cognition and functioning in patients with schizophrenia (38) and bipolar I disorder (48). This tentatively suggests that benefits can be observed in both the social and attentional domains in comorbid individuals at both the diagnostic and symptom level. We note, however, no such benefit was observed for social cognition and functioning in a sample of individuals with various psychotic disorders that self-reported autistic traits and positive psychotic experiences (49).

Moreover, O'Gráda et al. (19) found that severity of negative symptoms correlated with difficulties in sustaining attention. Intriguingly, this effect was reported for patients in whom the positive symptoms were low (Mean= 2.02; SD= 2.25). This appears to parallel our finding where the PAUSS scores were associated with more omission errors when positive symptoms were low (see **Figures 4A** and **5A**).

What might explain the benefit we observed in the CM group and in individual with elevated autistic and positive symptoms? As stated above, performance on the SART requires the recruitment of both sustained attention and response inhibition. However, the hypothesized dissociation between SPD and ASD in terms of these respective abilities was not supported by our results, and as such our pattern of results do not support the hypothesis that these two abilities converge in a compensatory manner in the CM group. Perhaps this is inherent in the inability of the SART task to truly dissociate inhibition from sustained attention. In this regard, Robertson et al. (18) point out that "arbitrating between the relative contributions of an inefficiency in response inhibition *per se* and a failure to inhibit responses due to a lack of continuous attention to response is of course difficult and indeed somewhat circular within this task" (p. 749).

However, the exploratory analyses provide some important leads that might be leveraged in future research to understand the mechanisms underlying benefits conferred by the co-presence of autistic and positive symptoms. First, the analyses pertaining to the subdomains of the PAUSS suggest that autistic features associated with stereotypies and narrowed interests appear to largely drive the interaction of the PAUSS total scores with PANSS positive symptoms on omission errors. This dovetails with the findings of a study on probabilistic reasoning showing that relative to individuals with delusional disorder (DD) only and individuals with obsessive-compulsive disorder (OCD) only—who respectively were reliant on less and more evidence to make their decision—probabilistic reasoning was normalized in individuals with comorbid DD and OCD (50). Stereotypic behavior is a main feature that is common to both OCD and ASD (51), and so it might be of particular importance to understanding how autistic and positive symptoms become adaptive when co-present.

Moreover, the independent analyses in the ASD and SPD groups show that the pattern of associations of PAUSS and PANSS positive symptoms with omission errors in the ASD group is reversed in the SPD (see **Figures 6A, B**). This suggests that the PAUSS and PANSS positive symptoms are associated with diametric influences on sustained attention independent of the disorder. This is consistent with (i) the diametric model (52, 53)—which posits that ASD and SSD are characterized by opposing phenotypic patterns—, (ii) evidence suggesting that ASD and SSD can be characterized by opposing patterns of attentional abilities (3, 54), and (iii) existing evidence suggesting that the presence of both disorders may be associated with attenuated impairments (3, 27, 38). Importantly, this pattern of association also suggests that the omission errors in ASD and SPD might be precipitated by different mechanisms, which is consistent with the notion that apparent overlaps between autism and schizophrenia spectrum disorders might be precipitated by different cognitive styles or biases (55, 56). Altogether, this pattern of association gives credence to the idea and that some compensatory mechanism might nonetheless be at play in the comorbid group. If so, future research (behavioral, cognitive, and neural) is necessary in order to test the prediction that these mechanisms are highly interactive and possibly of contrasting nature. Hence, assessments that require the recruitment of dissociable contrasting abilities, such as global-local processing (57, 58) and zoom-in and zoom-out attentional mechanism (59) might be particularly beneficial in discriminating between the groups and thus potentially mechanistically more informative. Within the neural domain, future research might consider the default mode and task-positive networks in search for a potential mechanism. Lapses in attention have been associated with reduced task-induced deactivation of the default mode network (60) and its anticorrelation with the task-positive network has been related to consistent behavioral performance (61). Examining disorder-specific resting state

activity of these networks in ASD and SPD might provide a mechanistic account of how autism and positive symptom severity converge adaptively in sustaining attention.

We acknowledge a number of limitations of our study. First, findings of our study may be limited by the small sample size of the CM group. Thus, future work with a larger sample of CM individuals is needed in order to have a better understanding of their clinical phenotypes. Second, controls were mainly recruited through acquaintances. This recruitment strategy may have biased our sample. Third, as pointed above, the SART offered limited insight into the mechanisms that might explain the performance benefits we observed in the comorbid group. Therefore, it would be profitable for future research to implement a Research Domain Criteria (RDoC) strategy (62) for a more comprehensive assessment of the participants' clinical and functional phenotypes that may help interpret the current results.

Fourth, while the PAUSS allows for a dimensional cross-disorder analysis (33), it has been validated against the ADOS that measures current autistic traits. As such, it may be argued, and particularly for the SPD group, that the PAUSS merely reflects the severity of later-onset, autistic-like symptoms rather than actual childhood-onset autistic traits. While, to our knowledge, the PAUSS is yet to be validated against instruments that assess childhood-onset autistic traits, nascent results suggest that PAUSS levels in schizophrenia patients with ASD, assessed with the Autism Diagnostic Interview-Revised [ADI-R, (63)]—a measure that is based on the patients' early developmental history through a parent/caregiver interview—are similar to those of schizophrenia patients with ASD, assessed with the ADOS (35). In addition, negative symptoms in schizophrenia spectrum disorders (from which the PAUSS is largely derived) have been suggested to be of neurodevelopmental origin and predate the onset of the disorder (64, 65). Taken together, the PAUSS may be capturing childhood-onset autistic traits rather than current autistic-like features. Yet, the current lack of a unified classification instrument for cross-disorder analysis represents a general challenge to this young field, and so the development and refinement of such instruments is crucial to advance research into underlying cross-disorder mechanisms.

In conclusion, comorbid ASD-SPD or concurrent elevated levels of autistic and positive psychotic symptoms counterintuitively appear to confer greater functional advantages than simply having an ASD or SPD alone. These findings raise intriguing questions about possible mechanisms underlying the observed performance benefits. While we found no direct support for the hypothesis that sustaining attention and response inhibition converge in a compensatory manner in the comorbid group, our findings suggest that autistic and positive symptoms exert diametric influences on sustained attention abilities. More broadly, our findings highlight the importance of investigating the concurrent effect of ASD and SPD at both the symptom and diagnostic levels, and it raises important questions and directions for future research regarding the clinical and behavioral phenotypes of adults with dual diagnosis.

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 NHS Lothian Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AS, SL, EJ, and RP designed the study and wrote the protocol. AA-A conducted statistical analysis and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Social Cognition in a Research Domain Criteria Perspective: A Bridge Between Schizophrenia and Autism Spectra Disorders

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Schizophrenia and autism spectra disorders are currently conceptualized as distinct clinical categories. However, the relationship between these two nosological entities has been revisited in recent years due to the evidence that they share some important clinical and neurobiological features, putting into question the nature and the extent of their commonalities and differences. In this respect, some core symptoms that are present in both disorders, such as social cognitive deficits, could be a primary target of investigation. This review briefly summarizes the commonalities and overlapping features between schizophrenia and autism spectra disorders in social cognitive functions, considering this construct in a Research Domain Criteria perspective. The clinical manifestation of deficits in social cognition are similar in schizophrenia spectrum disorders and autism spectrum disorders, and brain areas that appear to be altered in relation to these impairments are largely shared; however, the results of various studies suggest that, in some cases, the qualitative nature of these alterations may be different in the two spectra. Moreover, relevant differences could be present at the level of brain networks and connections. More research is required in this field, regarding molecular and genetic aspects of both spectra, to better define the neurobiological mechanisms involved in social cognition deficits, with the objective of developing specific and targeted treatments.

Keywords: schizophrenia spectrum disorder, autism spectrum disorder, neurodevelopmental disorders, social cognition, research domain criteria (RDoC) neuroimaging, genetic

INTRODUCTION

Social cognition (SC) can be broadly defined as a domain encompassing all the cognitive processes related to interpersonal contacts and to the perception of oneself and others in the social environment (1, 2). It includes a wide range of abilities, from basic ones such as recognition and processing of emotions in facial expressions and tones of voice, to more complex skills involving the attribution of

mental states or the perception and understanding of social cues and contexts. These processes regulate and determine social behaviors and are closely linked to interpersonal relationships and social functioning (3).

SC currently represents a prominent field of study in Schizophrenia Spectrum Disorders (SSD), as deficits in socio-cognitive performance are related to poorer functional capacity and community-living skills, worse real-world functioning and lower quality of life (4–9). The socio-cognitive processes that appear to be most commonly impaired in patients diagnosed with SSD are emotional processing, social perception, attributional style, and Theory of Mind (ToM) (7, 10–12); these deficits may predate the clinical onset of the disorder and appear to be present since the early phases of illness, remaining substantially stable afterward (13–16).

Autism Spectrum Disorders (ASD) also represent a category of conditions characterized by significant impairments in interpersonal understanding and behaviors, with atypical social interactions and communication (17, 18). Social isolation and community-living impairment resulting from these socio-cognitive deficits are common features in individuals with ASD (19–21), often leading to lower quality of life (22–24). These SC deficits appear to have an impact on functional and social skills in subjects with ASD also in the presence of a normal Intelligence Quotient (IQ) (25).

The aim of the present narrative and critical review is to provide an overview of clinical, neuroanatomical-neurofunctional and molecular features involved in socio-cognitive deficits across the SSD and ASD spectra, highlighting how implementing knowledge in these fields in a Research Domain Criteria (RDoC) perspective could represent a valid step in improving the management and the treatment of these disorders. In fact, the issue of overlaps between SSD and ASD has not yet been explored in a RDoC perspective: filling this current gap could improve the understanding of interactions between neurobiological and clinical observations and further the integration of recent scientific knowledge into daily clinical practice.

Schizophrenia and Autism Spectra Disorders: Areas of Clinical Overlap

SSD and ASD are currently conceptualized as separate nosological entities, emerging at different developmental periods and characterized by specific and distinctive features (26). However, this dichotomic separation has been recently called into question, and the areas of overlap between the two spectra have become the focus of a growing body of literature (27–32).

ASD symptoms are more frequent in subjects diagnosed with SSD than in healthy controls (33, 34), and appear to play a relevant role in the clinical situation of patients with SSD, as more severe ASD symptoms represent an individual predictor of worse SC performance (35, 36) and poorer real-world social functioning (37), and are correlated with greater impairments in the ability to judge the quality of everyday functioning (38). Individuals diagnosed with SSD and showing prominent ASD features could represent a particular sub-population with specific clinical characteristics, including lower IQ and poorer cognitive performance (39, 40) and worse response to antipsychotic treatment (41).

On the other hand, psychotic features are frequent in subjects diagnosed with ASD (42, 43). Childhood ASD features and ASD diagnosis are associated with psychotic experiences (44) and with substantially increased risk of SSD (45, 46). Moreover, individuals with ASD and prominent psychotic features appear to represent a peculiar sub-population, characterized by fewer stereotyped interests and behaviors and lower IQ (47).

A recent meta-analysis comparing non-social cognitive profiles of subjects diagnosed with SSD and ASD reported important differences between the disorders regarding deficits in visuospatial perception and reasoning and problem solving domains; however, differences in working memory and language performance were small, and a substantial overlap was observed in processing speed and verbal comprehension domains (48).

Social Cognition: A Bridge Between Schizophrenia and Autism Spectra Disorders

Deficits in SC in particular represent a key feature of both spectra (13, 49, 50). A systematic review and meta-analysis, including 19 different studies comparing socio-cognitive performance between individuals diagnosed with SSD and those diagnosed with ASD, reported that the level of SC impairment was similar across the disorders: no significant differences emerged in ToM tasks, emotional intelligence and social skills, and, although patients with SSD had a better performance in emotion perception, only a modest effect size was observed (51). These results were however limited by a significant heterogeneity in the tasks employed in the individual studies and by the small sample sizes. A more recent study has therefore performed a comprehensive evaluation of SC performance in large samples of adult subjects with schizophrenia, ASD and typical development, confirming that the level of impairment is very similar between the two disorders, with small differences that become non-significant when the analyses are controlled for symptoms severity (52). These results could suggest that interventions which have shown effectiveness in improving SC performance in one condition could lead to positive results if adopted in the other.

However, as much as the clinical observation and measurement of this overlap between the spectra is important and interesting, a deeper understanding of the neurobiological and molecular mechanisms underlying SC deficits of both disorders, with particular attention to which aspects are shared and which are divergent in the two conditions, could represent a relevant improvement in the perspective of developing and implementing dedicated treatment strategies. In fact, deficits in social interactions and in SC performance observed in SSD and ASD could result either from similar, partially overlapping, independent or even completely opposite neurobiological causes: the latter case has been observed in different independent studies, leading to the

hypothesis that SSD and ASD may represent diametrically divergent disorders of the social brain (53, 54). Moreover, as SSD and ASD share a number predisposing neurodevelopmental features and risk factors, it has been theorized that the co-occurrence of the two disorders, or of different neurobiological alterations belonging to the two spectra, could be frequent, explaining the association and similarities often observed on a clinical level (43).

Social Cognition as a Research Domain Criteria

The RDoC project represents a framework for research that conceptualizes mental illnesses as brain disorders and assumes that the dysfunctions in neural circuits can be identified with the tools of clinical neuroscience and genetics. Data obtained in this perspective could yield specific biosignatures, possibly leading to an improvement in the clinical management of psychiatric disorders (55).

Disassembling the traditional diagnostic categories established in psychiatry on the basis of clinical observation does not represent the aim of the RDoC approach; rather, among its primary goals features a deeper understanding of neural circuits' functioning that could result in better knowledge of the causal relationships beyond symptoms and behaviors occurring in different disorders (56).

This might also represent a step forward in meeting the need of a more personalized medicine in psychiatry by improving the characterization of individual cases, an objective that is somehow currently difficult with the information conveyed by the diagnosis alone (57); this approach, including direct comparisons of clinical disorders, is recently attracting more scientific attention (58).

In particular, the RDoC perspective could be interesting in the study of neurodevelopmental disorders, as the developmental trajectory of different conditions currently represents an important object on neuroanatomical, neurobiological, molecular and behavioral research (59).

SC has been proposed as a major RDoC domain on the basis of the neurobiological evidences defining the brains systems involved in socio-cognitive processes and for its relevance as a transdiagnostic clinical construct (60).

Several studies have been performed to date to elucidate the roles played in SC by specific neural structures, genes, and neurotransmitter systems (61–64).

Neuroanatomical and Neurofunctional Brain Markers of Social Cognition

SC involves a broad range of neural regions and networks in stimulus processing in the central nervous system. Neuroimaging studies represent an important tool for the comprehension of the neural bases that explain the mechanisms of SC, since they can provide not only an assessment of brain anatomy but also of neural activity in specific regions as well as its relations (65–69). In this sense, the use of structural Magnetic Resonance Imaging (sMRI) and functional Magnetic Resonance Imaging (fMRI) has become a fundamental strategy for understanding these neural bases, as well as for studying psychiatric diseases that classically present alterations in SC, such as ASD and SSD (70–73). Several neuroimaging studies have identified specific brain areas most frequently involved in SC, but also networks formed by the connections between these focal brain areas (70, 74). This group of brain regions may also be collectively referred to as the "social brain" (75, 76). It comprises the following areas, all relevant in SC processes: the prefrontal cortex (PFC) and its subdivisions, that are dorsomedial, dorsolateral, ventromedial, ventrolateral and orbitofrontal, the amygdala, the thalamus, the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC), the temporal cortex more specifically the surroundings of the superior temporal sulcus (STS) and temporo-parietal junction (TPJ), and occipitotemporal regions, encompassing the fusiform gyrus (70, 75). Other regions that are also involved in the SC phenotype are the somatosensory areas and motor cortex (71, 72). Although many studies of SC impairments in ASD and SSD show alterations in most of the aforementioned brain regions (77–79), there is an increasing consensus that the abnormalities are usually not focal, but are rather distributed in functional brain networks important to support social functions (71, 74, 75, 80).

Prefrontal Cortex

Classically, research studies have focused in structural and functional changes in specific brain areas related to the SC process to describe the neural bases of ASD and SSD (77–79). Indeed, focal alterations in the PFC are largely described in ASD and SSD. Specifically, the medial PFC is recruited in tasks that need conscious attribution or judgment of mental states, traits or dispositional intentions of the individual or others. This region is also involved in the interpretation of non-verbal social information and in the contextual interpretation of complex social information, such as inferring the beliefs of others (81). Activation of the medial PFC is also involved in emotion generation, especially when assessing self-relevant characteristics or emotional awareness (82, 83). The ventrolateral PFC is involved in adaptive responses to social situations, modulating the influence of emotional stimuli on cognition in relation to socially appropriate behaviors (84, 85). A meta-analysis of studies using fMRI in SC tasks, directly comparing patients with SSD and ASD, pointed to important results (79). In this study both groups showed hypoactivation in the medial PFC during ToM related tasks, more pronounced in ASD patients. On the other hand, ventrolateral PFC disruption in facial emotion recognition (FER) tasks was associated mostly with SSD. The finding of reduced ventrolateral PFC, implying connection to social appropriateness of behavior, may be more relevant to SSD patients, while in both disorders, reduced medial PFC activation may contribute to alterations in conscious awareness of others' emotional states (79). Further studies using fMRI in social tasks have demonstrated heterogeneous results, with either hypoactivation in the medial PFC in patients with ASD (86) and SSD (87) and a hyperactivation of the PFC in patients with SSD (88) and ASD (89). The involvement of the PFC in SC impairment has also been demonstrated in morphometric studies, suggesting a reduction in the PFC gray matter volume in patients with ASD (78, 89) and in those with SSD (90).

Amygdala

Besides frontal regions, the amygdala structure also contributes to SC by mediating arousal or biological salience associated with different stimuli (91). This structure is also involved in recognizing facial emotional expressions and in evaluating stimuli (72). Both SSD and ASD patients present amygdala hypoactivation when processing social stimuli and this may occur in a stimulus type dependent manner, with SSD patients presenting alteration in tasks related to the attribution of affective states (FER) and ASD individuals showing impairment in tasks related to epistemic and intentional attributions (ToM) (79). These findings seem to be particularly related to the known deficits in emotion perception among persons with ASD (92). Corroborating the involvement of the amygdala in the social cognitive dysfunctions in these two disorders, other studies have demonstrated that this structure present both volumetric changes in ASD and SSD (78, 93, 94) as well as functional alterations in ASD (76, 89). The amygdala of toddlers and children with ASD was reported to be significantly enlarged relative to controls and this increase in amygdala volume was accompanied by more severe impairments in the social and communication aspects (94). On the other hand, patients with ASD showed smaller gray matter volume in the amygdala compared to controls (78) and the amygdala volume was also found to be smaller in SSD patients, compared to controls (93). As for functional alterations, a meta-analysis revealed differences in activation in the amygdala between ASD and typically developing individuals,with ASD showing reduced activity in amygdala in face processing tasks (89). Lower level of amygdala activation has been also found to play a important role in social and emotional processing in ASD (95, 96). Also, the amygdala showed reduced activity in ASD group compared with the typically developing group in the processing of emotional facial expressions (76).

Thalamus

Another structure also involved in SC is the thalamus, which plays a role in coordinating the information flow in various cognitive and sensory processes (97). The thalamus is directly involved in visual perception (directing attention towards salient stimuli) and its dorsomedial portion is associated with executive functions through its connections with the PFC. Atrophy and impaired function were observed in the thalamus of ASD subjects from late childhood to adulthood (98). In ASD individuals, a decrease in the right thalamus volume after a developmental period of two years was reported, and it was correlated with social deficits, while typically developing controls did not show volume change in this structure (99). Also, abnormalities of verbal and nonverbal communication in ASD individuals are probably due to thalamic hyperactivation and subsequent dysfunction of other areas such as visual cortex and frontal regions (98). In SSD patients, there exist consistent evidence for structural changes (both reduced volume and cell numbers) in the pulvinar located in the posterior thalamus and also evidence that the thalamo-cortical dysfunction in this disorder might be attributable to structural alterations in the thalamus (100). In SSD patients a decreased engagement of the thalamus during SC tasks in comparison to controls was observed (79). Another study suggested that changes in thalamic activation appear to play a fundamental role in the development of both ASD and SSD (98).

Cingulate Cortex

The regions surrounding the cingulate cortex are also referred to as important areas in the evaluation of SC (76, 79, 93, 94). The ACC is associated with processing positive and negative judgments of social situations and integrating such judgments with emotional information to motivate behavior patterns (72). The PCC is associated with mentalizing or inferring others' mental states (70). ASD subjects showed more engagement of the ACC and PCC in comparison to SSD in FER tests. SSD patients showed greater engagement in PCC in comparison to ASD individuals in ToM tasks (79). Another previous meta-analysis comparing grey matter deficits in ASD and SSD had reported common deficits in right PCC (93). A meta-analysis showed a positive relationship between ACC gray matter thinning and high risk for SSD, which may be associated with increasing social withdrawal (101), while for ASD individuals the alterations in the regions of the cingulate cortex appears to be more functional than structural (102). The findings of altered recruitment of cingulate cortex in ASD was also reported by other authors (76, 89, 94).

Somatosensory Cortices

Social interactions also involve the somatosensory cortices, as these brain areas play a role in internal representations of affective states. Engagement of somatosensory cortices is related to invoking mirror bodily states associated with relevant emotions or other internal states and facilitates their recognition in oneself or in others (103). In ASD patients, there was a hypoactivation in somatosensory cortices, in comparison to controls and to SSD patients, during both FER and ToM tasks, which corroborates the dysfunction in invoking mirroring mechanisms when processing social stimuli observed in ASD. On the other hand, the increased engagement of somatosensory regions in SSD individuals may explain hyper-mentalization states that can be found in these patients (79). Subsequent findings also pointed to changes in the somatosensory cortex of patients with SSD and ASD, with both groups presenting weaker cortical responses to visual, somatosensory and auditory stimuli in sensory fMRI, compared to controls. However, in ASD individuals there were greater cortical variabilities, whereas in SSD patients there were smaller response amplitudes (104). All these findings might help differentiate between the two groups and aid in the elucidation of neural diverse mechanisms underlying each disorder.

Temporal Lobe Regions

Finally, temporal lobe regions, including the STS and TPJ, are also key components of the social brain. The regions around STS play a major role in social perception by analyzing biological motion cues, including gaze direction, body movements and

facial expressions. This is important in inferring or formulating attributions about others' intentional or affective states (105). The involvement of the STS in the SC of patients with ASD and SSD are demonstrated by numerous studies, often reporting heterogeneous results (79, 87, 89, 106). For example, similar hypoactivation in these regions during ToM tasks were found in SSD and ASD. On the other hand, ASD patients showed increased engagement in these regions in comparison to controls and to SSD patients during FER tasks (79). Both ASD and SSD showed hypoactivation in the STS, compared to controls, for the contrast intentional versus physical information processing. Relative increased activation for physical information processing in SSD and relative decreased activation for intentional information processing in ASD patients were observed, endorsing differences between the groups (87). The TPJ have been linked with SC tasks requiring individuals to "think about other people's thoughts" or to take another perspective about affective or cognitive states of others (107, 108). The TPJ was hypoactivated in ToM tasks in ASD patients, in comparison to controls. The TPJ was more activated in FER tasks in SSD patients, in comparison to ASD individuals (79). The involvement of TPJ in the SC process has also been demonstrated in more recent studies in patients with SSD (88, 109) and ASD (89).

Neural Networks

More recently, there has been a major interest in broadening the study of structural alterations underlying the neural basis of these two disorders to include the relationship between the functionality of different brain regions, combined in more complex and connected neural networks. In this sense, when expanding the scope from changes in focal brain areas to include broader alterations in neural functional networks, a new range of possibilities is found, opening the door to wider explanations for the common neural bases among ASD and SSD, as well as for their differences (71, 74, 75, 80, 110).

The connection between areas belonging to the frontal lobe and the temporal lobe are commonly described in studies assessing SC in ASD and SSD. Changes in connectivity patterns between the STS and frontal regions in SC processes have been demonstrated in patients with ASD and SSD (87, 106, 111), as well as in patients diagnosed with early psychosis (112). Still regarding frontotemporal connections, Eack and collaborators found increased frontotemporal and orbito-frontal connectivity in ASD patients and decreased connectivity between the same areas in SSD patients (71). A recent study also described connections between frontotemporal areas through fMRI evaluation of the ToM network (which is composed of connections between medial PFC, STS, TPJ and precuneus) in patients with SSD, revealing a raise in these connectivities during emotional peaks in comparison to controls (113).

Networks involving connections in fronto-parietal areas also seem to play an important role in the SC of patients with ASD and SSD. A study using a connectivity approach (74) found that, although both groups present significant enrichment in the frontoparietal and limbic networks regarding the cortical thickness of structures involved in these networks, this occurs in opposite directions, with SSD patients showing increased cortical thickness and those with ASD presenting decreased cortical thickness.

Regarding the surface area, patients with ASD present increased surface values of structures involved in the ventral attention network, while those with SSD present decreased values (74). The ventral attention network involves the TPJ and the ventral frontal cortex and is usually recruited when behaviorally relevant stimuli occur unexpectedly (for instance, when they appear outside the focus of spatial attention) (114).

Other neural networks described as possible protagonists in the SC process in ASD and SSD are the Default Mode Network (DMN) and the Salience Network (SN). The DMN is a major network encompassing the medial PFC, PCC, precuneus and bilateral inferior parietal lobules, which is activated when there is no engagement in any specific task and deactivated in the context of effortful cognitive tasks and SC tasks (115–118). The SN is a task activated brain network and comprises the anterior insula, dorsal ACC, the anterior PFC and the thalamus (119). This network is related to redirecting attention to unexpected but salient stimuli and is involved in SC, non-SC and emotional processes (120). A recent study showed distinct atypical connections in the DMN and SN in ASD and SSD patients, with ASD individuals showing altered intra-SN connections and SSD participants showing inter-DMN-SN atypical connections (80). These findings may suggest that, although ASD and SSD have common neural networks with regard to changes in SC, these two conditions may differ in the way in which these networks are involved.

All the aforementioned findings suggest that the assessment of the neural bases involved in these psychiatric diseases should also be analyzed through coordinated and diffuse changes in networks responsible for the processing of complex human traits and not just through focal structural changes.

Molecular Biomarkers of Social Cognition

To date, most studies carried out on molecular mechanisms of SC have been focused on neuropeptides oxytocin and arginine vasopressin receptors (*OXTR* and *AVPR*, respectively) genes, since the OXT and AVP neuropeptides have been largely involved in a wide range of social behaviors (121). OXT is a key modulator of the most intuitive and yet most complex socioemotional behaviors. OXT affects social cognition by enhancing the salience of social cues and reward sensitivity to these cues (122). OXT is associated to various forms of social attachments and affects the activity and the connectivity of a social brain network that includes the areas described above.

In humans, the *OXTR* gene is located on chromosome 3p25.3, and one of the most studied single nucleotide polymorphism (SNP) is the rs53576, which consists of a guanine (G) to adenine (A) change within the third intron of *OXTR*. This SNP has been associated with SC phenotypes, such as empathy (123–127), prosocial behaviors (128, 129), and social abilities (130). Although some contrasting results exist, evidence for the

different phenotypes related to SC converge in demonstrating a deficit of A allele carriers that showed less dispositional empathy (124) and lower trust behavior (128). Moreover, several studies have been shown that the rs53576 A allele represents a genetic risk for SC, because social dysfunctions of A allele subjects was reflected in morphometric alterations of the hypothalamus and amygdala, as well as on the structural connectivity of the system limbic structures involved in social behaviors (123, 129). *OXTR* SNPs rs7632287 and rs2254298, are yet other interesting polymorphisms whose associations with SC phenotypes were reported (126, 131–134). Although all these studies indicate that there is an association between *OXTR* gene and SC dysfunctions, previous studies neither specify the nature of associations found in an unequivocal way nor select genotypes that are the basis for this association. Moreover, contrasting results have been published about correlation of peripheral plasma concentrations of oxytocin with *OXTR* SNPs as well as central nervous system level of this peptide (135, 136).

Interestingly, variability in *OXTR* methylation has been associated with differences in SC and brain response during social tasks (137, 138). In particular, DNA methylation of *OXTR* has been shown to negatively correlate with *OXTR* transcription across tissues indicating that increased levels of methylation correspond to greater deficits in social responsiveness (139, 140) in ASD subjects.

Finally, few studies with contrasting results are performed to date concerning correlation between oxytocin plasma levels and social cognition (141, 142). In the case of AVP, the genes encoding the 3 receptors (*AVPR1a*, *AVPR1b*, and *AVPR2*) and are located on chromosomes 12q14, 1q32, and Xq28, respectively. Concerning the relationship with SC, the most studied SNPs are SSRs, such as RS3 and RS1 located in the *AVPR1* gene, that along with others, were investigated in association to SC phenotypes with sparse and contrasting results (126, 130, 134, 143). In the same way, in literature few studies with conflicting data are present regarding correlations between blood AVP concentrations (141, 144) and SC phenotypes. Indeed, literature on SNPs in the *AVPR* genes is extremely poor, and therefore, further research is required to confirm or reject the hypothesis of their association with SC dysfunctions, in ASD as well as in SSD.

To date, in addition to *OXTR* and *AVPR* SNPs, sparse results on other systems were reported in correlation with SC in humans. Emotional behaviors are accompanied by biochemical changes *via* dopamine catabolism. The catechol-O-methyltransferase (*COMT*) is the major enzyme responsible for degrading amines like dopamine, norepinephrine, and epinephrine. The most studied polymorphism is the Val158Met *COMT* functional SNP that has been associated with differential response to affect in prefrontal brain areas and limbic structures and for this reason widely investigated in association with SC. In healthy volunteers, carriers of the Val allele that have an enhanced *COMT* enzyme activity compared to Met/Met-allele carriers, showed an increase in social cooperative behavior and a stronger response to social interactions (145). Moreover, Val homozygotes were more altruistic, empathetic, and cooperative than Met homozygotes (146). On the other hand, regarding SC, it has been suggested that Met allele confers more intensive emotional processing, with more anxiety and sensitive behavior in response to aversive stimuli, as well as habitually experienced more negative affect and negative attentional bias (146–149). However, to date the effect of the *COMT* gene on SC has not been sufficiently investigated in SSD and in ASD. Indeed, to date few, spare and contrasting results are available since *COMT* gene was investigated primarily in SSD and negative associations often has been provided (150, 151).

Some other candidate genes as well as immune markers were investigated in association to SC mainly in SSD, such as anti-inflammatory cytokine IL-10 that was associated with ToM, but no further strong replication occurred (152–155).

Finally, several studies reported associations between genetics and SC also in subjects with the 22q11.2 Deletion Syndrome (22q11.2 DS) that has a robust representation of genetic proneness to SSD (156–161). There is a strong agreement in all the results reported showing that compared to healthy controls, 22q11.2 CNV subjects showed significantly poorer SC such as emotion differentiation, emotion recognition, lie detection, sarcasm detection.

DISCUSSION

In a neuroanatomical and neurofunctional perspective, the regions interested in SC have recently been the focus of a growing body of evidence. The brain areas that appear to be altered in relation to deficits of SC are largely shared in SSD and ASD; however, the results of various studies suggest that, in some cases, the qualitative nature of these alterations may be different in the two spectra. In particular, some relevant differences could be present at the level of brain networks and connections (71, 80) (**Table 1**).

Although on a clinical level SC deficits in SSD and ASD appear to largely superimposable, suggesting that interventions that are effective in one spectrum could also be adopted in the other (52), further exploring the commonalities and the potential differences on a neurobiological level could provide additional confirmations to this hypothesis, but also lead to the development of specific and targeted treatments. Moreover, investigating with neuroimaging tools subjects diagnosed with SSD and showing prominent ASD features (39), and those diagnosed with ASD with relevant psychotic symptoms (42, 43), and evaluating if the neuroanatomical and neurofunctional profile of these individuals represents an intermediate phenotype or not, could provide further insight and represent an interesting perspective for future studies.

The neuroimaging findings related to SC in SSD and ASD, if considered in an RDoC context, confirm the importance of developing a framework based on neurobiological phenotypes and malfunctions, as the diagnostic categories currently employed in psychiatric practice do not appear to properly represent distinct nosological entities. This could be especially true when considering disorders as clinically heterogeneous and

TABLE 1 | Neurobiological features involving social cognition in SSD and ASD.

	Neuroanatomical and Neurofunctional Features	Neural Connections and Networks
Similar Alterations	Amygdala: hypoactivation when processing social stimuli. Thalamus: reduced volume and dysfunctions in SC tasks.	None
Different Alterations	SSC: hypoactivation in ASD and hyperactivation in SSD in SC tasks.	OF connections: increased in ASD and decreased in SSD. FP connections: decreased CT in the connected areas in ASD and increased CT in SSD. VAN: increased surface values in the involved structures in ASD and decreased surface values in SSD. DMN-SN: altered intra SN connections in ASD and altered inter DMN-SN connections in SSD.
Inconclusive or Conflicting Literature	ACC; PCC; PFC; STS; TPJ.	FT connections

ACC, anterior cingulate cortex; ASD, autism spectrum disorder; CT, cortical thickness; DMN, Default Mode Network; FP, frontoparietal; FT, frontotemporal; OF, orbitofrontal; PCC, posterior cingulate cortex; PFC, prefrontal cortex; SC, social cognition; SN, Salience Network; SSC, somatosensory cortex; SSD, schizophrenia spectrum disorder; STS, superior temporal sulcus; TPJ, Temporo-Parietal Junction; VAN, Ventral Attentive Networks.

complex as SSD and ASD, which may present important areas of overlap, but may also present relevant interindividual differences even within each of the two spectra.

On the contrary, literature concerning molecular markers related to SC is scarce and mainly focused on candidate gene studies, and potential commonalities and divergences between SSD and ASD on a molecular level still have to be further investigated. SC is a highly complex process requiring a vast regulatory network involving genetic, epigenetic, and environmental factors, consequently the use of powerful tools, such as genome-wide association studies (GWAS) is needed. Moreover, functional and structural brain imaging studies could also help in understanding the role of genetic variants in the development of SC phenotypes (159, 162). This link between genetics and neuroimaging changes can be explained, among other factors, by the role that genes have in regulating both synaptogenesis, synaptic function and the formation of neuronal circuits (75). Indeed, the combination of genetics and neuroimaging in a study of the association between variants of genetic loci linked to SSD and SC in healthy individuals found that those with an increased risk score (taking into account the combined risk of such genetic loci) presented changes in the ACC when evaluating episodic memory and changes in the PCC when the ToM was evaluated (162).

Some inconsistencies across studies were observed both in neuroimaging correlates and behavioral performance of SC in SSD and ASD, which can partly be the results of differences in task design: task characteristics have been shown to have an influence on outcomes and interpretation of social cognition performance assessment, and the choice of appropriate measures, balancing task sensitivity and ecological validity, represents an important factor that should be consistently taken account in the design of future studies (163). Moreover, it is possible that isolating SC in different components, such as emotion processing and ToM, might not be ideal, as in the real-world context of interpersonal relationships all these separate domains are likely to be involved in determining social behaviors (164).

The selection of evidences presented and discussed in the present review was not based on a systematic literature research, therefore the possibility that some study of potential interest may not have been included represents a limitation. However, the aim of this work was to provide a narrative and critical overview of current evidences highlighting the interest of implementing a RDoC approach in the study of SC in SSD and ASD, and the development of a systematic and comprehensive review investigating this topic represents a valid perspective for future research.

Research on neurobiological and molecular mechanisms underlying socio-cognitive functioning is an expanding field of notable scientific interest and is providing valuable insight in understanding the overlaps between SSD and ASD. However, more research is currently needed to define specific endophenotypes that could benefit from targeted treatments and interventions, concretely fulfilling the objectives that the RDoC project proposes as essential goals (55, 60). Indeed, there is some evidence of oxytocin's modulation of SC brain functions with intranasal oxytocin (165), however, contrasting results have been published about this issue, and although intranasal oxytocin seems to have potential therapeutic value, there are key questions that remain unanswered as to decide the optimal target groups and treatment course (166).

CONCLUSIONS

Current studies on neuroanatomical and neurofunctional bases of SC deficits are providing valuable insights in the overlaps and differences between SSD and ASD. However, more research is required in this field, in particular regarding molecular and genetic aspects. Applying the RDoC approach to further the study of SC in SSD and ASD could lead to a considerable improvement in the understanding of both spectra, with potential positive repercussion in the perspective of implementing these findings in clinical practice.

AUTHOR CONTRIBUTIONS

GN, SB, AM, and RCS participated in the writing process of the first draft of the manuscript. AC and GD made literature search and independently reviewed electronic databases. AV, CT, SB, and AM revised the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Visual-Tactile Spatial Multisensory Interaction in Adults With Autism and Schizophrenia

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Background: Individuals with autism spectrum disorder (ASD) and schizophrenia (SZ) exhibit multisensory processing difficulties and social impairments, with growing evidence that the former contributes to the latter. However, this work has largely reported on separate cohorts, introducing method variance as a barrier to drawing broad conclusions across studies. Further, very few studies have addressed touch, resulting in sparse knowledge about how these two clinical groups may integrate somatic information with other senses.

Methods: In this study, we compared adults with ASD (n = 29), SZ (n = 24), and typical developmental histories (TD, n = 37) on two tasks requiring visual-tactile spatial multisensory processing. In the first task (crossmodal congruency), participants judged the location of a tactile stimulus in the presence or absence of simultaneous visual input that was either spatially congruent or incongruent, with poorer performance for incongruence an index of spatial multisensory interaction. In the second task, participants reacted to touch in the presence or absence of dynamic visual stimuli that appeared to approach or recede from the body. Within a certain radius around the body, defined as *peripersonal space (PPS)*, an approaching visual or auditory stimulus reliably speeds reaction times (RT) to touch; outside of this radius, in *extrapersonal space (EPS),* there is no multisensory effect. PPS can be defined both by its size (radius) and slope (sharpness of the PPS-EPS boundary). Clinical measures were administered to explore relations with visual-tactile processing.

Results: Neither clinical group differed from controls on the crossmodal congruency task. The ASD group had significantly smaller and more sharply-defined PPSs compared to the other two groups. Small PPS size was related to social symptom severity across groups, but was largely driven by the TD group, without significant effects in either clinical group.

Conclusions: These results suggest that: (1) spatially static visual-tactile facilitation is intact in adults with ASD and SZ, (2) spatially dynamic visual-tactile facilitation impacting perception of the body boundary is affected in ASD but not SZ, and (3) body boundary perception is related to social-emotional function, but not in a way that maps on to clinical status.

Keywords: cross-modal congruency effect, peripersonal space, depth, logistic regression, psychopathology, somatic, developmental disorders, tactile perception

INTRODUCTION

Autism spectrum disorder (ASD) and schizophrenia (SZ) are clearly distinct clinical groups, but individuals on both the autism and schizophrenia spectra share some common categories of symptoms, including social and executive function deficits. There is evidence of considerable convergence in the nature and extent of these deficits (1–4), and common neural alterations in networks supporting social cognition (5–7). However, the phenotypic overlap in these high level social and cognitive domains is not complete (4, 8, 9), and more remains to be learned about points of divergence and convergence at multiple levels of function in these clinical groups (10). Given the dependence of higher level social cognitive functions on more basic component processes such as low-level perceptual integration, better characterization of sensory and perceptual function and their interrelationships in both groups could contribute to more complete understanding of both phenotypes.

In both ASD and SZ, sensory processing abnormalities are core to the phenotype, and difficulties in integrating and processing information across the different senses have been described [for a review, see (11)]. For example, individuals with ASD and individuals with SZ exhibit enlarged temporal multisensory binding windows, which reflect the temporal duration over which paired auditory and visual stimuli are bound together as a single percept (12–18). Among individuals with autism, this diminished temporal acuity for low-level multisensory stimuli is related to severity of social communication deficits (17, 19), and among patients with schizophrenia reduced temporal acuity is related to symptom severity with positive symptoms [i.e., hallucinations, delusions (15)]. These relationships prompt the idea that low-level multisensory processing may be a critical precursor to more complex, higher-order function. Indeed, aberrant temporal binding of audiovisual stimuli can have a profound impact on various aspects of language and social cognition, particularly speech comprehension (20), prosodic processing (21), and recognition of emotions in face/voice stimuli (22), all of which are impaired across both ASD and SZ (4, 23). While studies of multisensory binding have shown associations with social symptoms in ASD [e.g., socio-communicative abilities (17)], the association between multisensory processing and social function is less clear in SZ [e.g., (24)]. More vexingly, prior studies have been largely limited to the temporal domain (vs. spatial, for instance) and the pairing of audio and visual multisensory stimuli [(11) but see (2015) for a recent report indexing visuo-tactile interactions across both time and space in ASD].

Spatial multisensory integration is an inherent component in what is referred to as embodied cognition: the ability to separate oneself perceptually from the surrounding environment and to use that knowledge to plan and execute interactions within the environment. Recent work from our group and others has proposed that embodied cognition and its multisensory underpinnings may be a useful framework for comparing and contrasting the clinical profiles of autism and schizophrenia (25–27). For example, altered embodiment in ASD may cascade to influence deficits in non-verbal communication such as gesture (28) or violations of personal space (29). In SZ, altered embodiment could contribute to certain kinds of hallucinations (30). Converging inputs from touch, vision, and proprioception specify the location and boundary of the body within its environment, and the relative spatial properties of those inputs provide information about the potential for spatial interaction of the body with the social and physical environment. This spatial multisensory information is important in evaluating both how and when to enact motor programs in response to environmental events transpiring near or approaching one's body, and also the potential for threat or reward consequent to those interactions.

A commonly used paradigm to probe this spatial multisensory processing entails presentation of tactile stimulation together with auditory or visual stimuli manipulated to convey a sense of their approaching toward, or retreating away from, the body. By quantifying speeded reaction times (RTs) to approaching stimuli, one can define the individual's *peripersonal space (PPS)*, which is the radius immediately surrounding the body within which stimuli are perceived as physically relevant (31), whether for action or for self-defense (32). The boundary between PPS and extrapersonal space (EPS) is measured in terms of its size or radius and its sharpness or shallowness—the clarity of the delineation between peripersonal and extrapersonal space. PPS is highly malleable and can be modified by manual motor experience (31, 33), threat (34, 35), or social interaction. The interplay between social function and PPS is particularly noteworthy here, given our focus on individuals with ASD and SZ. In this regard, Teneggi et al. (36) demonstrated that in healthy controls PPS first shrinks upon encountering another individual, as to "give space," and following a cooperative social interaction, it expands again, as if "sharing space." Pellencin et al. (37) similarly demonstrated that the encoding of PPS is sensitive to the perceived morality of others. A prior study found evidence for smaller PPS in adults with autism using a audio-tactile

paradigm (38), suggesting altered bodily self-consciousness in autism driven by differences in multisensory integration. In the present study, we used a similar, visuo-tactile paradigm in an effort to replicate and extend this finding of constricted PPS to adults with autism and compare to those with schizophrenia.

Previous research points to potentially opposite PPS profiles across ASD and SZ that may correspond to distinct elements of the clinical phenotype associated with each disorder. Specifically, individuals with ASD are less susceptible to the rubber hand illusion (39–41), a visual-tactile paradigm that manipulates the sense of body ownership, suggesting decreased influence of visual-tactile input on perceived body ownership, whereas individuals with schizophrenia are *more* susceptible (42, 43), suggesting *increased* visual-tactile influence on perception of body ownership. These divergent findings have been theorized to reflect the degree to which the two groups rely on external stimuli to update their body representation, with under-reliance on external input characterizing autism and over-reliance on external input characterizing schizophrenia (42). Based on these findings, we hypothesized similarly divergent peripersonal space profiles across groups, with individuals with ASD showing smaller PPSs with sharper borders and individuals with SZ showing larger PPSs with shallower borders (26). In an attempt to determine whether putative differences in PPS between ASD and SZ are specific, or may reflect more general effects of visual-tactile integration, we also administered the cross modal congruency task [CCE; (44)], where visual cues may facilitate or impaired tactile processing, but cues are always presented in the same location, near the body [see (45), for modulation of the CCE in the presence of others]. We did not have an a priori hypothesis for group differences in this task, given that there is reasonable grounds to predict both generalized and embodiment-specific differences in multisensory processing. In light of previous findings, we additionally hypothesized that differences in peripersonal space profiles would correlate with the severity of social deficits both within and across diagnostic groups.

METHODS

Participants

A total of 84 participants took part in the current experiments. Participants were recruited into three groups: (1) adults with typical developmental histories (TD, $n = 36$), adults with autism (ASD, $n = 26$), and adults with schizophrenia (SZ, $n = 22$). Participants in all groups were between 18 and 60 years old (mean = 34.59, SD = 12.29). This age range is large and the average age across groups differed (the ASD cohort being younger; see **Table 1**). However, we considered this appropriate given difference in age of onset between autism and schizophrenia and our goal of assessing stabilized rather than first episode SZ patients. Importantly, age was incorporated as a covariate in analyses. Participants had no history of organic brain disease, lesions, head trauma, or neurological disorders, and were free from nerve damage, illnesses, or injuries that might influence sensation or perception in the tactile, visual, and auditory systems. All participants self-reported normal hearing and normal or corrected-to-normal vision (i.e., wore their prescription glasses). Recruitment was conducted through Vanderbilt University Medical Center clinical and research entities, including the Vanderbilt Kennedy Center, the Vanderbilt Early Psychosis Program, and community mental health providers and partners in the middle Tennessee area. Cognitive ability was measured using the 4-subtest Wechsler Abbreviated Scales of Intelligence—Second Edition [WASI-II (47)] and a full-scale estimated intelligence quotient (IQ) score of 70 or higher was required for inclusion in the study in all groups in order to assure that participants understood task demands. Further, similarly to age, cognitive ability was included as a covariate in all analyses.

Participants in the ASD and TD groups were free from any substance or alcohol abuse or dependence for at least 2 years prior to the study. The SZ group was also free from any substance or alcohol abuse or dependence, but this criterion was relaxed to the 3 months prior to the study and did not include nicotine, given the high rates of comorbidity between SZ and substance use disorders (48). Participants in the ASD and TD groups were free from antipsychotic medications and mood stabilizers, and medications with sedative effects, with the exception of one participant with ASD who reported taking a benzodiazepine. Participants in the TD group were additionally excluded for first degree relatives with either an ASD or SZ diagnosis, and personal history of any other psychiatric diagnosis (anxiety, mood disorders), ADHD, or learning disorders. Details of the entire sample, and the subsamples included in both psychophysical paradigms, are given in **Table 1.**

Diagnosis of autism was confirmed using research-reliable administration of the Autism Diagnostic Observation Schedule [ADOS-2 (49)], under the supervision of a licensed clinical psychologist. Diagnosis of schizophrenia was confirmed using diagnostic criteria in the Structured Clinical Interview-DSM-IV (SCID-IV); administered by a trained research assistant. Positive and negative SZ symptoms were assessed in the SZ group, either with the Scale for the Assessment of Positive Symptoms [SAPS (50)]/Scale for the Assessment of Negative Symptoms (SANS; 49, $n = 8$) or with the Positive and Negative Symptoms Scale [PANSS; (51), $n = 14$]. SAPS/SANS composite and global scores were converted to PANSS using linear regression as described in 51. Social symptom severity was quantified with the Social Responsiveness Scale adult self-report [SRS-2 (52)], which was administered to participants in all three groups. The SRS-2 is a 65 item measures that quantifies global traits relevant for ASD with a normalized total score as well as five clinical subscales (social awareness, social cognition, social communication, social motivation, and restricted/repetitive behavior). Higher total scores on the SRS-2 indicate greater social impairment. It has been validated in adults with ASD (53).

All participants gave their written informed consent prior to taking part in this study, which was approved by the Behavioral Sciences Committee at Vanderbilt University.

Cross-Modal Congruency Effect (CCE)

Participants held in their right hand a purpose-made square block ($8 \times 8 \times 6$ cm) housing a pair of motors (Adafruit, New York,

TABLE 1 | Sample and psychophysics paradigm subsample descriptive statistics.

	ASD	SZ	TD
Gender (M/F)	14/12	13/8 (1 unknown)	23/13
Mean Age (SD)	25.65 (6.05)	45.09 (9.94)	33.56 (11.19)
Handedness (%R, L, Other)	83%, 14%, 3%	87%, 13%, 0%	89%, 11%, 0%
Mean FSIQ (SD)	105.09 (17.54)	93.15 (17.07)	112.97 (13.31)
Mean SRS Total T-score (SD)	67.91 (12.63)	61.00 (11.74)	47.31 (7.67)
Mean ADOS calibrated severity score (SD)	7.59	N/A	N/A
Mean PANSS[a] (positive)	N/A	15.21	N/A
Mean PANSS[a] (negative)	N/A	15.54	N/A
Medication			
Antipsychotic	–	$N = 17$	–
SSRI or SNRI	$N = 3$	$N = 12$	–
Mood stabilizer	–	$N = 4$	–
Benzodiazepine	$N = 1$	$N = 2$	–
Other	$N = 2$	$N = 7$	–
Psychophysics			
Completed CCE task (% total sample)	23 (88.46%)	18 (81.81%)	33 (91.67%)
CCE excluded for $<$ 10 trials/condition (% of those completing task)	3 (13%)	4 (22%)	3 (9%)
Completed PPS task (% total sample)	20 (76.92%)	22 (68.18%)	20 (50%)
PPS excluded for poor sigmoid fit (% of those completing task)	6 (30%)	7 (31%)	2 (10%)

[a]*From PANSS (n = 14) or converted from SAPS/SANS to PANSS (n = 8) using method of van Erp et al. (46).*

NY, 5V, 11,000 RPM, 0.9 g, 10 mm diameter, 2.7 mm thick) and LEDs (Adafruit, New York, NY, 4 mm × 9 mm, white). The block was held horizontally, the thumb and index fingers placed on top of the motors (**Figure 1A**). LEDs were immediately adjacent to their closest motor (congruent motor-LED pair), and 8 cm away from their incongruent motor. Motors and LEDs were all controlled via a micro-controller (Arduino Uno, Arduino, Somerville, MA, USA; 16 MHz). Visual stimuli had a duration of 10 ms, and vibrotactile stimulation lasted 100 ms. In line with prior studies, LED onset preceded tactile stimulation by 30 ms to counteract the instrinsic tendency for touch to be experienced as preceding visual stimulation when the two events occur simultaneously [see (44), for the original report using a similar setup and further see (54), for a characterization of the "principles of multisensory behavior" suggesting that the driver of multisensory RT facilitation is matching unisensory RTs, and not their physical simultaneity].

Participants made speeded discrimination responses regarding the position (thumb vs. index finger) to which the vibrotactile targets were presented, using a button press with the non-stimulated (left) hand. The vibrotactile stimulation was preceded by either no visual stimulation (a tactile-only baseline condition), a visual cue matching the location of the subsequent tactile target (congruent condition), or matching the location of the opposite finger (incongruent condition). In total 6 different trial types were possible (baseline, congruent, and incongruent for the two digits), and each unique condition was repeated 15 times, for a grand total of 90 trials. The inter-trial interval between tactile targets was between 1.5 and 2.5 s (uniform distribution), and trials timed out if there was no response within 10 s. This portion of the experiment took ∼10 min, and was controlled via purpose-made MATLAB scripts (MathWorks, MA) communicating with the micro-controller via serial port.

RTs were calculated from the onset of vibrotactile stimulation. Responses slower than 2.0 s were discarded (<3% of all trials, no group difference). Data from participants with fewer than 10 trials per condition were excluded ($n = 10$; 3 ASD, 4 SZ, 3 TD). Responses that indicated tactile stimulation to the erroneous finger were marked as incorrect. Following the methods of Spence et al. (44), we subtracted values of RT and accuracy for congruent visuo-tactile stimulation from the incongruent condition in order to derive a measure of the impact of spatially congruency on low-level visuo-tactile RTs (44). Here we use these cross-modal congruency metrics (median RT and accuracy in percent) as outcome variables in separate ordinal logistic regression models (see *Analyses and Statistical Modeling* section below), with RTs and accuracy during the tactile-only (baseline) condition included as regressors in the corresponding models.

Peri-Personal Space (PPS)

Participants comfortably rested their right hand on a custom-made box with a strip of LEDs (5 cm wide by 110 cm long) affixed to the top surface. LEDs were spaced in increments of 10 cm, starting at a distance of 5 cm from the edge of the box closest to the participant. In total there were 11 LEDs, one at each of the following distances: 5, 15, 25, 35, 45, 55, 65, 75, 85, 95, and 105 cm (**Figure 1B**). The visual component on each trial comprised sequential presentation of the LEDs, with presentation lasting 50 ms with an inter-stimulus interval of 200 ms between successive LEDs; this series of visual events conveyed the appearance of a single visual stimulus moving either toward the subject's hand (i.e., from D1 to D11; receding

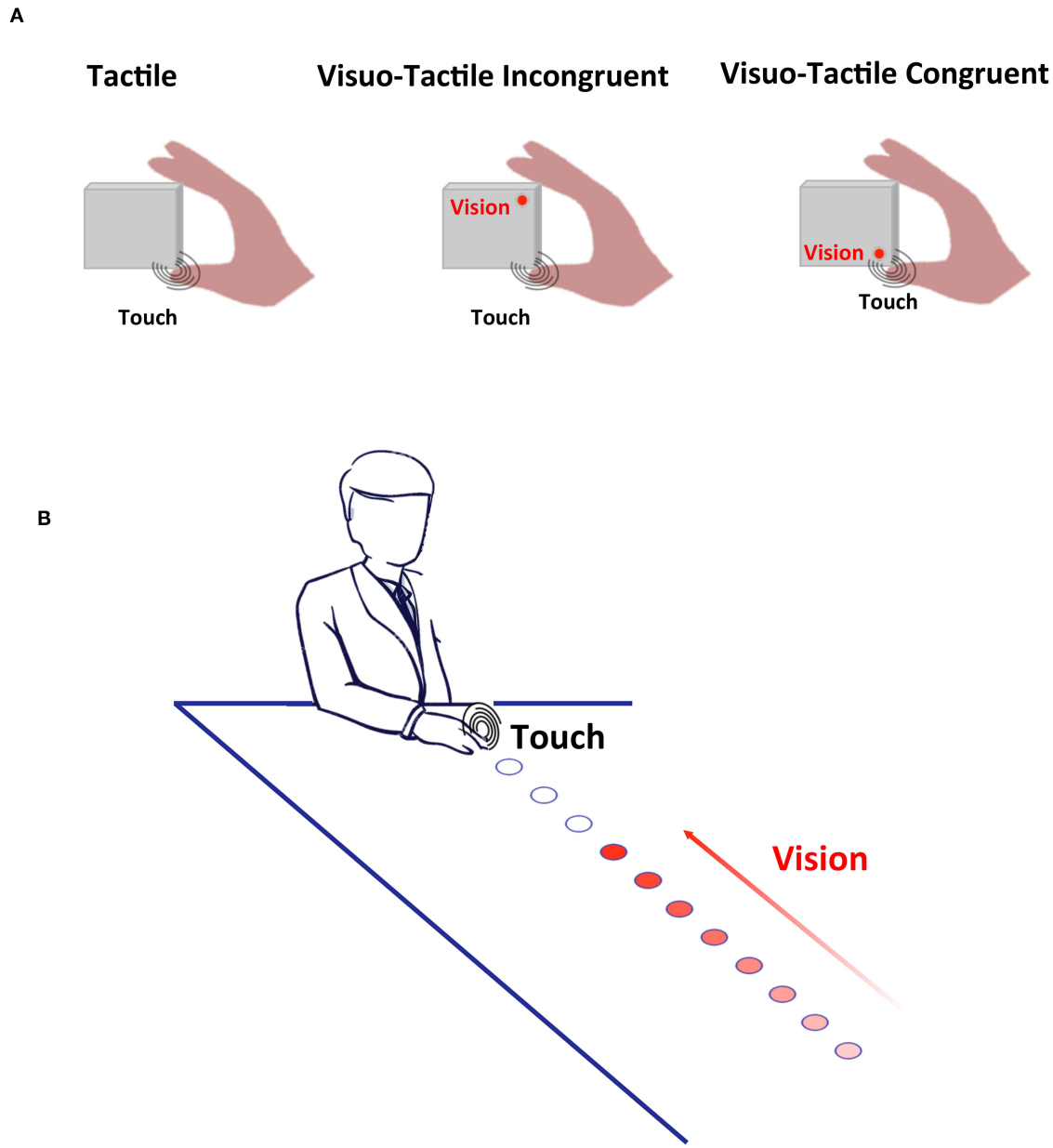

FIGURE 1 | Experimental Methods. **(A)** Cross-Modal Congruency. Participants responded as fast as possible to touch being applied either to the thumb (depicted) or the index finger. On a fraction of trials, a visual stimulus was also presented, either incongruently with the location of touch (middle panel) or congruently with the location of touch (rightmost panel). **(B)** Peri-personal Space. On catch trials visual stimuli were presented alone, and on baseline trials, tactile stimuli were presented alone. On the experimental trials (depicted), touch was given when the train of visual stimuli terminated at different distances from the body, and either looming or receding from the participants. In this case looming stimuli is shown, with increasing intensity conveying the direction of movement of the light source.

condition). A vibrotactile motor (Adafruit, New York, NY, 5V, 11,000 RPM, 0.9 g, 10 mm diameter, 2.7 mm thick) was attached to the participant's hand. Vibrotactile stimulation had a duration of 50 ms and could be activated in synchrony with one of the 11 different LEDs being turned on, or could be activated in isolation.

Participants were instructed to maintain gaze on a fixation point near the midpoint of the array of LEDs. They were informed that they would feel vibrotactile stimulation, and their task was to respond via button-press (with their non-stimulated, left hand) as fast as possible to this tactile stimulation. Additionally, they were informed that visual stimuli would be presented, but this visual input was task-irrelevant. The experiment comprised three type of trials; (1) experimental trials where tactile stimulation was given simultaneously with the onset of visual stimuli at a given distance and during a given movement direction (approaching or receding), (2) baseline trials

were tactile stimuli was given in isolation at a timing that would have been equivalent to the visual stimuli being either at the closest or furthest location, and (3) catch trials wherein visual stimuli were presented either approaching or receding, but no tactile stimuli was given. In line with previous studies (55, 56), the rationale is that visual stimuli should enhance tactile processing when within but not when outside PPS. The facilitation ought to be most prominent when stimuli appear to be approaching the individual compared to when they appear to be receding (57). Baseline trials were measured in order to determine whether a multisensory effect is truly observed (visual-tactile RT < tactile-alone RT), and catch trials were introduced in order to limit an expectancy effect where tactile stimulation is more and more likely the longer it has been absent during visual stimulation (58). In this case, each of the 22 different experimental conditions (2 directions × 11 distances) were presented 16 times, each of the two baseline conditions (at temporal onset equivalent to D1 and D11) was presented 16 times, and each of the two catch conditions (approaching and receding) were presented 39 times [the report introducing this method to measure PPS, 54, counted with half the number of repetitions per experimental conditions (8), and 55, being the report with the largest number of individual subjects−164 subjects across 7 studies—similarly used 16 repetitions per experimental condition]. In total the experiment consisted of 462 repetitions (∼17% catch), was divided in 3 blocks of equal length, and took ∼40 min to complete. Inter-trial interval was set to 2.5 s.

Overall, participants were accurate at withholding responses during catch trials [<0.5% of trials, see e.g., (59)], and thus analysis was centered on RTs. Contrast between visuo-tactile RTs during approaching and receding motion (regardless of group) indicated that despite the inclusion of a number of catch trials, putative speeding in RT as a function of visuo-tactile proximity were contaminated by an expectancy effect; the longer the duration between trial onset and tactile stimulation, the faster the RTs (**Supplementary Figure 1**). To compensate for this effect and truly examine the impact of distance (and not time) on visuo-tactile RTs, we inverted the spatial dimension for the receding condition, and performed a subtraction equating time but differentiating distances. That is, D1 during approaching visual motion matches in time D11 during receding visual motion, D2 during approaching matches D10 during receding, and so forth. Hence, by performing this subtraction (e.g., approaching D1—receding D11) we eliminate the effect of time, and study exclusively the impact of distance (near vs. far), and direction (approaching vs. receding); the two aspects for which PPS neurons are selective (60). After performing the subtraction, in line with previous studies [e.g., (13)], we fit RTs to a sigmoidal function,

$$y(x) = \frac{y_{\min} + y_{\max} * e^{(x-x_c)/b}}{1 + e^{(x-x_c)/b}} \quad (1)$$

where x represents the distance between visual and tactile stimuli, y(x) is the RT to touch at a given visual distance x, $y_{\min}$ and $y_{\max}$ are the saturation points of the sigmoidal which are fixed to the slowest and fastest mean RT in the experimental trials (i.e., not a free parameter), and x_c and b are, respectively, the central point and a parameter (negatively) proportional the slope of the sigmoidal at x_c. These last two parameters are free parameters we fit to concisely describe PPS and represent its size (x_c) and gradient (b)—how strongly are the near and far space separated. The parameters of subjects showing a good fit (a priori set to R^2 >0.5; TD = 18/20; ASD = 20/26; SZ = 15/22) were kept and contrasted across participants groups.

Analyses and Statistical Modeling

We used a proportional odds logistic ordinal regression model for continuous data [i.e., a cumulative probability model with logit link (61, 62)] to assess the impact of distinct regressors on multisensory spatial processing. For the CCE task, we regressed the mean difference in RT during congruent and incongruent visuo-tactile stimulation, as well as the change in accuracy, on gender, age, full-scale IQ, baseline tactile performance, and diagnostic group. For the PPS task, we first summarized the pattern of RTs by an estimate of the size and gradient of PPS. These latter values were then submitted to a regression with age, gender, full-scale IQ, and diagnostic group as predictors. One individual in the schizophrenia group did not report their gender, and five individuals (3 ASD, 2 SZ) were missing full scale IQ scores; these missing values were handled using 40-fold multiple imputation as implemented by the *aregImpute* function in the R package *Hmisc* (63).

While SRS-2 scores indexing social symptoms were available for all participants, positive and negative symptom scales (SAPS and PANSS) were only available for the schizophrenia group. Thus, we examined Spearman correlations between these scales and the multisensory variables of interest separately from the regression models.

RESULTS

Intact Cross-Modal Spatial Congruency Effect in ASD and SZ

As illustrated in **Figure 2**, all three groups of participants showed a cross-modal congruency effect, expressed both as a facilitation in RTs (**Figure 2A**, contrast to y = 0; all $p < 0.0013$) and enhanced response accuracy (**Figure 2B**, contrast to y = 0, all $p < 3.5e\text{-}05$) to tactile localization when a visual cue was spatially congruent as opposed to incongruent. The regression model assessing the influences on the cross-modal congruency effect as defined by RT suggested that none of the five predictors (diagnostic group, age, gender, IQ, and tactile-only RTs) predicted the multisensory congruency effect. The regression model assessing the impact of different predictors on the cross-modal congruency effect as defined by tactile localization accuracy suggested that baseline tactile accuracy in the absence of visual cues significantly predicted performance during the cross-modal congruency test ($aOR = 0.87$, CI_{95} [0.82, 0.91], $p < 0.001$), such that more accurate baseline tactile localization predicted less multisensory benefit regardless of age, gender, or diagnostic group.

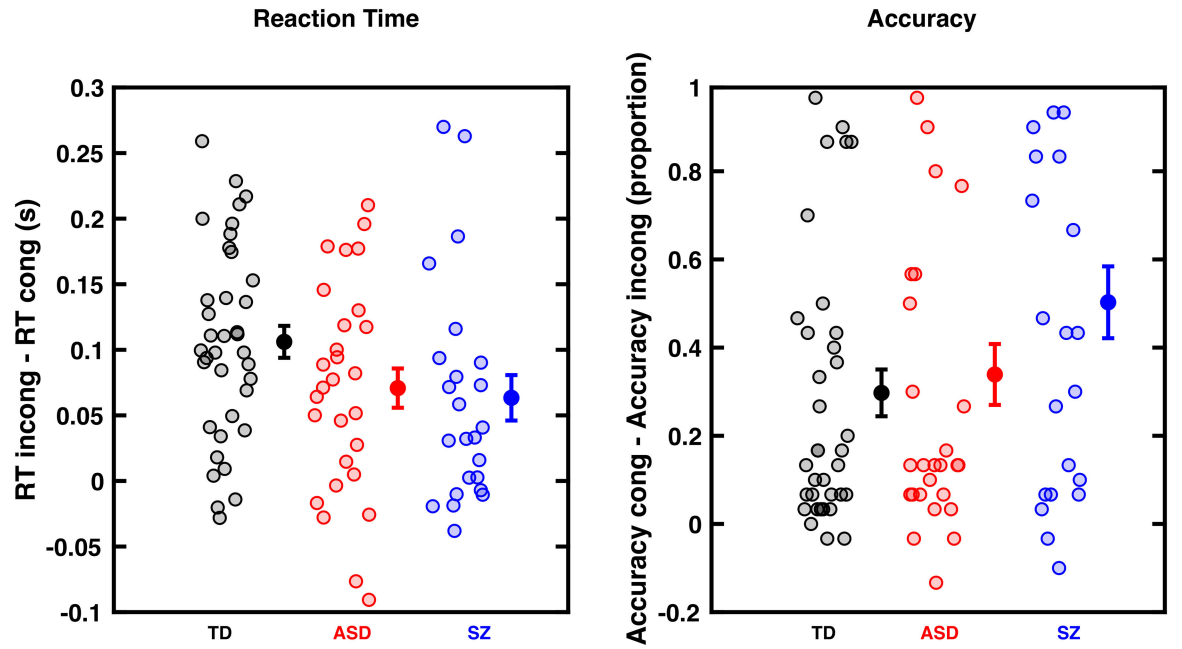

FIGURE 2 | Cross-Modal Congruency Effect (CCE) for RTs (left) and accuracy (right) in typically developing (TD) individuals, as well as Autism Spectrum Disorder (ASD), and Schizophrenic (SZ) patients. **(A)** CCE is the difference between tactile RTs when preceded by an incongruent or congruent visual cue (measured in seconds). Controls (black) individuals show numerically a larger cross-modal congruency effect than ASD (red) and SZ (blue) individuals, but this difference is not statistically significant. **(B)** Similar format but subtracting accuracy in incongruent trials from accuracy in congruent trials. Groups did not statistically differ. Dots are individual participants, error bars show the mean and ±1 S.E.M.

Peri-Personal Space Is Small and Its Boundary Sharp in ASD

After matching the temporal components of the PPS task and contrasting looming vs. receding visual stimuli in regard to enhancement of tactile RTs (see Methods section), all groups showed a profile of RTs suggesting tactile processing facilitation during multisensory trials at the nearest distance (**Figure 3**; expectancy-corrected multisensory RTs vs. unisensory tactile, all $ps < 0.005$). In line with prior studies [e.g., (55)] to succintly summarize the PPS data, we fit RTs to a sigmoidal function describing the size and sharpness (i.e., slope of the gradient) of the PPS boundary. These parameters were then submitted to statistical modeling, as described in the Methods section.

The model attempting to regress the size of PPS on diagnostic group, age, IQ, and gender suggested that only ASD as a diagnostic group significantly predicted PPS size such that a diagnosis of ASD was predictive of a smaller PPS ($aOR = 0.09$, $CI_{95}[0.02, 0.41]$, $p = 0.002$; see **Figure 3**). Schizophrenia as a diagnostic group was not a significant predictor of PPS size ($aOR = 0.84$, $CI_{95}[0.21, 3.45]$; $p = 0.814$). A similar model assessing the gradient of boundary between PPS and EPS suggested that ASD as a diagnostic group significantly predicted a sharper PPS gradient ($a\text{OR} = 0.18$, $CI_{95}[0.04, 0.74]$, $p = .0175$). In contrast, a diagnosis of SZ did not hold significant predictive power as a determinant of PPS gradient ($a\text{OR} = 1.4$, $CI_{95}[0.35, 5.67]$, p=0.6344). Neither age, IQ, nor gender significantly predicted PPS size or gradient.

Social Impairment Associated With Smaller PPS Across Groups, but Not Within Clinical Groups

In a secondary analysis, we used Spearman's correlation to determine the association between peripersonal space size and gradient with a measure of social-communication dysfunction, the total T score of the SRS-2. Although smaller PPS size was significantly associated with more severe social impairment in the whole sample ($r = -0.36$, $p = 0.009$), this association remained significant after Bonferroni correction and appeared driven by a non-significant trend in the TD group, and there were no significant associations in either clinical group (TD: $r = -0.38$, $p = 0.12$; ASD: $r = 0.18$, $p = 0.45$; SZ: $r = -0.17$, $p = 0.56$). PPS gradient was not associated with SRS scores either across or within groups. This secondary analysis is summarized in **Figure 4**.

Schizophrenia Symptoms Do Not Significantly Correlate With PPS Size or Slope

Despite the lack of group effects for our SZ sample, based on findings from previous studies (64, 65), we conducted an exploratory analysis testing for an association between PPS size or gradient and symptoms of schizophrenia. We hypothesized that PPS size and/or its slope may relate to schizophrenia

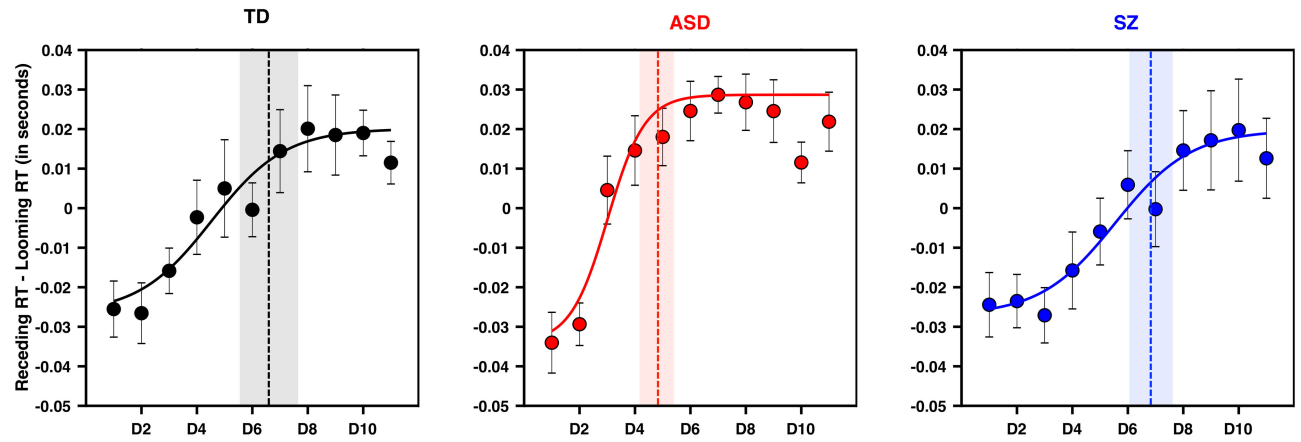

FIGURE 3 | PPS is smaller and sharper in ASD than TD and SZ. Y-axis is the difference between tactile RTs during approaching and receding visual stimuli when matched for time. X-axis is distance, in the frame of reference of the approaching stimuli. Namely, D1 corresponds to D1 for approaching, and D11 for receding (which are matched in time). Negative values along the y-axis indicate a further facilitation as a function of distance for approaching than for receding visual stimuli, as would be expected of a PPS effect. Error bars are ±1 S.E.M., the vertical line in each panel (TD = black, ASD = red, SZ = blue) is the average central point of the sigmoidal fit (the fit shown is for the average subject). Shaded area is ±1 S.E.M.

symptoms since positive symptoms have been linked with disturbances in the sense of self (66). However, we found no such association between PPS variables and positive (all $rs < |0.35|$, all $ps > 0.17$) or negative symptoms of SZ (all $rs < |0.23|$, all $ps > 0.37$).

DISCUSSION

A growing literature has emphasized deficits in sensory processing in ASD and SZ. Much of the work in characterizing these anomalies has been focused on multisensory processing, specifically examining the tolerance of these groups to temporal asynchronies between disparate signals arising within different sensory modalities. In addition to their temporal offset, however, another key feature ultimately leading to either the integration or segregation of sensory signals is their spatial disparity. This spatial factor has been less thoroughly explored within ASD and SZ. The present findings provide a start toward redressing this gap in knowledge by suggesting that that the spatial range over which visual stimuli facilitate tactile processing is diminished and has a more abrupt boundary relative to controls in ASD but not in SZ (peri-personal space experiment). However, visual-tactile integration in a more spatially constrained paradigm (cross-modal congruency experiment) was unaffected in both clinical groups, for whom spatially congruent visual stimuli facilitated tactile RTs similarly to that in the TD group. Broadly, these findings are consistent with recent observations from Poole et al. (67), in that they imply that the basic principles governing multisensory integration in ASD and controls is similar, but the exact spatial range over which interactions occur likely differ. While previous studies have reported associations between multisensory processing in the temporal domain and clinical symptoms in both groups (11, 19), we were unable to detect these associations for social symptoms, at least as indexed by the SRS-2. One consideration is that our sample was only assessed using the self-report version of the SRS-2, which depends on insight that may be diminished in both clinical groups.

The finding suggesting a sharper, more constricted PPS within the ASD group is in line with our predictions (26) derived from the observation that individuals with ASD are less susceptible to the rubber hand (39–41) and full-body (38) illusions than controls. Further, they corroborate and extend recent results from Mul et al. (38) by showing that whether PPS is mapped via an audio-tactile (38) or visuo-tactile (current study) pairing, PPS is more constricted and sharper in ASD. On the other hand, the data in SZ patients do not support our prediction (26), based on their heightened susceptibility to bodily illusions, of a larger PPS with a shallower border. Similarly, our results do not intuitively align with the replicated observation that patients with SZ need a relatively larger personal space (68, 69), nor do they replicate results from Di Cosmo et al. (70) that suggested individuals with SZ have a smaller PPS than controls when mapped via an audio-tactile pairing. Speculatively, it is possible that the sensory modality employed to index PPS—vision here and auditory in Di Cosmo et al. (70)— may explain the contradiction between the two studies, particularly given the much higher prevalence of auditory than visual hallucinations in SZ (71). Together, the findings highlight that while there are clear relations between aspects of embodiment [e.g., PPS (72)] and social aspects of personal space (35, 73), these relations are complex as they relate to clinical disorders with social deficits at their core.

The lack of an effect on the PPS task for our SZ group does not lend support to the theory advanced by Crespi and Dinsdale (25) that autism and schizophrenia represent diametrically opposed

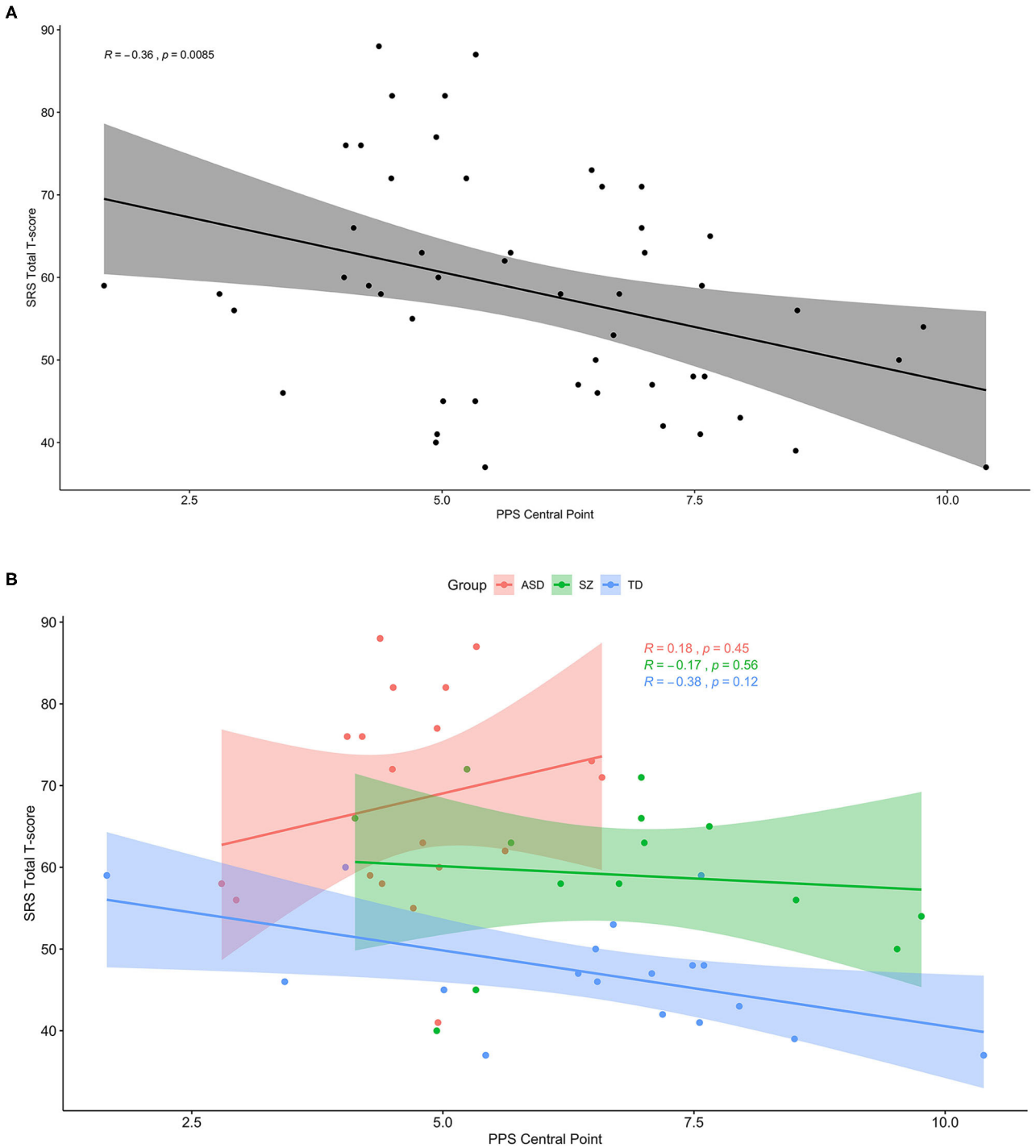

FIGURE 4 | Smaller PPS is associated with more social-communication deficit, but only in the subclinical range. **(A)** Across the whole sample, greater social-communication deficits as measured by the total T score of the SRS-2 was associated with smaller peripersonal space (PPS). **(B)** The same plot with groups separated by color (ASD: red, SZ: green, TD: blue), showing a trendline similar to that for the whole sample only within the TD group.

disorders of embodiment. However, the version of the task we used is non-social in nature (using only LEDs and vibrotactile stimuli); it is possible that with more social context in the stimuli (e.g., a ball being thrown), stronger group effects may have emerged. The theory of opposing embodiment was predicated on evidence from the rubber hand illusion, for which ASD and SZ

patients, respectively, show reduced and enhanced susceptibility (39, 41, 43, 74). The rubber hand illusion is arguably a more interpersonal paradigm, for which the peak effect transfers the sense of one's bodily ownership to the representation of another body, or part of a body. With the PPS paradigm, on the other hand, this kind of exchange is not measured. Rather, what is measured is the radius surrounding the body in which external sensory events are perceived to have physical relevance, a much broader and less inherently social construct. The presence of a difference in PPS representation for ASD but not SZ may be consistent with a broader base of evidence for generalized multisensory integration differences in ASD relative to SZ (75–77). It would also be interesting to explore these questions in unmedicated, first-episode SZ patients who would presumably have more active positive symptoms than our cohort.

Despite the more constricted, more sharply defined PPS in adults with ASD, we did not find clear associations with clinical symptoms—either core autism or core schizophrenia symptoms in our ASD or SZ groups. However, in the whole sample, smaller PPS size was significantly associated with more social-communication impairment as measured by the SRS-2 total score. The SRS measure is considered a continuous trait index that can meaningfully span the general population and clinical groups (78, 79); however, in our sample, there was a clear difference across groups in how this index mapped onto PPS size. The global finding was influenced heavily by the association in the TD group, while those adults with ASD or SZ, particularly those with higher SRS-2 scores approaching the clinically significant range (above 60) did not show a clear relationship between PPS size and social-communication impairment. This raises the possibility of non-linear relations between social function and PPS across the full range of social-communicative function, in which milder symptoms align with predictions based on previous experiments in TD individuals, but more severe symptoms have a different, or possibly absent relation to PPS. It is also worth considering that self-reported symptoms in the clinical groups may suffer from low validity given limited insight, which would obscure potential correlations. The malleability of PPS in the presence of social (36) and threatening (34) external stimuli highlights the fact that PPS can be construed as a "state" measure, which may not correspond to more stable "traits" of social deficits [see (80), for evidence that PPS remaps even on the time-scale of seconds]. Supporting the idea that PPS and the rubber hand illusion are measuring more generalized and more socially-specific aspects of embodiment, respectively, most studies have reported clear associations between altered rubber hand illusion effects and clinical symptoms (39, 43, 74). Thus, future studies may opt for more socially-relevant visual stimuli in PPS paradigms (e.g., a ball being thrown toward the participant) to determine whether the expected relationships emerge in more social contexts.

All experimental groups—control, ASD, and SZ—showed a cross-modal congruency effect (44) of equal magnitude. Additionally, all three groups showed a PPS representation: reaction times to touch were modified by the spatial location of the visual stimulus. As such, the commonalities in multisensory processing between these groups outweighs their differences, despite the smaller size and sharper gradient of PPS in ASD. This complement of multisensory similarities and differences across groups may be interrogated in future work alongside previously-developed neural network models for PPS (80, 81). This is recommended as an approach that may help bridge from behavioral sensory deficits to putative neural circuitry anomalies relevant for multisensory integration.

The current study has a number of strengths, including the direct comparison of adults with schizophrenia and autism on a multisensory paradigm, the incorporation of spatial measures to complement the numerous studies that have focused on temporal processing, and the inclusion of two well-established visual-tactile interaction paradigms. This study also has some important limitations to consider. The sample sizes are modest, and there was some data loss for the PPS task due to attrition from the study and RTs that could not be fit to a sigmoid function. This data loss may have limited our ability to detect correlations with clinical symptoms. Differential use of medications across groups is an additional limitation that should also be considered, and, relatedly, our SZ cohort was chronic, stabilized, and thus perhaps representative of only one phase of the disease process. Future studies might include first-episode or prodromal patients to address this. Finally, our study was cross-sectional. Peripersonal space representation can be measured shortly after birth (82) and may form the basis of an emerging sense of self in infancy and early toddlerhood (83), the period in which autism symptoms are first evident. Thus, prospective longitudinal studies of this phenomenon and related tests of bodily self-consciousness in infants at high genetic risk for autism or other neuropsychiatric conditions may shed important light on whether and how the development of the sense of self goes awry in these populations.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories: https://osf.io/en3x8/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Vanderbilt University Human Subjects Research Protection Program. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC, J-PN, MW, SP, and RB conceived and designed the study, interpreted the results, and drafted the manuscript. CC oversaw data collection an analyses. J-PN, AZ, JQ-Z, ZW, and MF contributed to data cleaning and analyses. HN, KA, MG, and JT collected the data. SH assisted with coordination of data collection, interpreted results, and drafted the manuscript. JF-F interpreted results and drafted 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.2020.578401/full#supplementary-material

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Cerebellar-Cortical Connectivity Is Linked to Social Cognition Trans-Diagnostically

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Background: Psychotic disorders are characterized by impairment in social cognitive processing, which is associated with poorer community functioning. However, the neural mechanisms of social impairment in psychosis remain unclear. Social impairment is a hallmark of other psychiatric illnesses as well, including autism spectrum disorders (ASD), and the nature and degree of social cognitive impairments across psychotic disorders and ASD are similar, suggesting that mechanisms that are known to underpin social impairments in ASD may also play a role in the impairments seen in psychosis. Specifically, in both humans and animal models of ASD, a cerebellar–parietal network has been identified that is directly related to social cognition and social functioning. In this study we examined social cognition and resting-state brain connectivity in people with psychosis and in neurotypical adults. We hypothesized that social cognition would be most strongly associated with cerebellar–parietal connectivity, even when using a whole-brain data driven approach.

Methods: We examined associations between brain connectivity and social cognition in a trans-diagnostic sample of people with psychosis ($n = 81$) and neurotypical controls ($n = 45$). Social cognition was assessed using the social cognition domain score of the MATRICS Consensus Cognitive Battery. We used a multivariate pattern analysis to correlate social cognition with resting-state functional connectivity at the individual voxel level.

Results: This approach identified a circuit between right cerebellar Crus I, II and left parietal cortex as the strongest correlate of social cognitive performance. This connectivity-cognition result was observed in both people with psychotic disorders and in neurotypical adults.

Conclusions: Using a data-driven whole brain approach we identified a cerebellar–parietal circuit that was robustly associated with social cognitive ability,

consistent with findings from people with ASD and animal models. These findings suggest that this circuit may be marker of social cognitive impairment trans-diagnostically and support cerebellar–parietal connectivity as a potential therapeutic target for enhancing social cognition.

Keywords: bipolar disorder, schizophrenia, psychosis, connectivity, social cognition, cerebellum, imaging, resting state

INTRODUCTION

Psychotic disorders such as schizophrenia (SZ) spectrum disorders and bipolar disorder (BD) with psychosis are characterized by substantial impairment in social cognitive processing (1–3), which is associated with poorer community functioning (4–7). Social cognitive impairments have been reported in people with SZ and BD across multiple domains including various aspects of emotion processing such as facial affect recognition and "higher level" emotional reasoning (8–12), theory of mind (8, 13–15) and attributional style (16–18). Some aspects of social cognition appear to be more severely impaired in people with SZ compared to those with BD including "higher level" emotion processing (19, 20), theory of mind, and attributional style (10, 21), although in general differences appear more quantitative than qualitative, and empirical methods such as cluster analysis have revealed subgroups of patients cross-diagnostically who share similar levels of social cognitive functioning ranging from intact to more severely impaired (11).

Social cognitive impairments are not unique to psychosis but represent hallmark symptoms in other psychiatric disorders as well, including autism spectrum disorders (ASD). Recent evidence indicates that, behaviorally, people with psychotic disorders and ASD exhibit similar widespread social cognitive impairment relative to controls (22–24). Thus, it is possible that neural mechanisms believed to underpin social cognitive impairment in ASD may offer clues to neural substrates underlying similar deficits in SZ and BD. However, the extent to which similar behavioral phenotypes are underpinned by common neurobiological mechanisms across diagnoses is unclear.

Trans-diagnostic studies of neuroimaging and social cognitive impairment in people with SZ-spectrum disorders and ASD participants have been mixed, with some showing similar activation or connectivity patterns and others showing only partial overlap. In studies using fMRI-measured task-based activation, reduced frontolimbic and superior temporal sulcus (STS) engagement during social cognition tasks was a shared feature across diagnoses (25–27). Cortical connectivity abnormalities in default mode network (DMN) and salience networks were also common to both SZ-spectrum and ASD in adults and adolescents (28, 29) which were associated with abnormalities during mentalizing (29) and associated with severity of social impairment (30). However, some findings report diagnostic differences in regional activation even when task performance is similar (31) suggesting that similar behavioral phenotypes may result from different underlying mechanisms. Similarly, the above meta-analysis (27) found diagnosis-specific activation abnormalities including reduced thalamic and amygdala activation and ventrolateral prefrontal dysfunction primarily in SZ, decreased somatosensory engagement in ASD, and some task-specific differences in activation patterns. Overall, these findings suggest that some regional activation and network connectivity abnormalities may be common trans-diagnostically and associated with social cognition and functioning, although no clear mechanistic pathway has been identified within or across disorders. These studies have largely been based on purely correlational experiments, however, making it difficult to determine whether these associations are causal or are reflective of diagnosis-related epiphenomena.

While much work on the neurobiology of social cognition in psychosis has focused on cortical and limbic activation and connectivity (3, 32, 33), abnormalities of the cerebellum have consistently been reported in psychiatric disorders characterized by social cognitive impairments including SZ (34–38) and ASD (39–42). While cerebellum is commonly considered in terms of motor behavior, the cerebellum appears to play an important role in social cognition and emotion processing [e.g., (43–46)] and may be associated with social and emotional processing impairments seen in psychotic disorders and ASD. Few empirical reports have linked cerebellar abnormalities to social cognitive impairments in SZ [see (47)], and there are no such reports we are aware of in BD. However, recent evidence of associations between cerebellum and social cognition in ASD provide evidence of a specific cerebellar-cortical circuit directly related to social cognition.

Stoodley et al. used neuromodulation in humans and mice to demonstrate a *causal* association between connectivity of the Right Crus I (R Crus I) region of the cerebellum (commonly implicated in ASD) and the inferior parietal lobule and social behavior (48). Using neuromodulation, they identified a cerebellar–parietal circuit in neurotypical humans, and abnormalities of functional connectivity in this same circuit in children with ASD. They then went on to demonstrate that chemogenetically mediated inhibition of R Crus I activity in mice produced social behavioral impairment, whereas stimulation of R Crus I in a transgenic ASD mouse model rescued aberrant social behaviors. These novel findings are consistent with previous evidence from lesion studies in humans and animal models (49, 50), and suggest that this cerebellar parietal circuit may be directly and causally associated with social cognition in ASD. Whether this circuit is associated with social cognition in humans with psychotic disorders and thereby represents a trans-diagnostic mechanism for social processing impairments remains unknown.

In this report we aimed to examine whether previous findings of social cognition-connectivity associations in ASD were also present in people with psychotic disorders including SZ and BD. Specifically, we examined social cognition in association with resting-state (rsfMRI) brain connectivity in a trans-diagnostic sample of people with psychotic disorders as well as neurotypical controls using a data-driven, whole brain approach. We hypothesized that (1) people with psychosis would perform worse than neurotypical controls on an emotion management/emotion regulation task of social cognition; (2) social cognitive performance would be positively correlated with connectivity in the cerebellar–parietal circuit identified in people with ASD (48); and (3) associations between social cognitive performance and cerebellar–parietal connectivity would be similar across groups, indicating that this circuit is a common pathway underpinning social cognition.

TABLE 1 | Demographic and clinical information by group.

	Probands ($n = 81$)	Controls ($n = 45$)	Statistical test
Mean age (SD)	26.06 (7.19)	25.57 (5.93)	$t = 0.411$, $p = 0.682$
Sex	54 M, 27 F	22 M, 23 F	$\chi^2 = 3.11$, $p = 0.078$
Diagnosis	21 Bipolar Disorder, 51 Schizophrenia 9 Schizoaffective	–	N/A
Mean CPZE mg (SD)	261 (225)	–	N/A
Mean MSCEIT-ME	46.8 (13.0)	55.8 (9.4)	$t = 4.48$, $p < 0.001$
Mean FSIQ	109.8	110.7	$p = 0.671$

CPZE, chlorpromazine equivalents; F, female; M, male; SD, standard deviation.

MATERIALS AND METHODS

Participants

Participants included people with a diagnosis of SZ or BD with psychosis ($n = 81$) and neurotypical controls ($n = 45$). Participants were recruited at three collaborating health centers via clinical programs including early psychosis specialty care, and through community referral networks, in the context of several separate research studies. Participants recruited from the Boston and Pittsburgh sites participated in a clinical trial (BICEPS, NCT01561859). Only the baseline (pre-intervention) evaluation data for these participants were included for this analysis. At the McLean site participants were recruited in the context of two separate but related studies including a study of cognitive remediation in bipolar disorder (TREC-BD, NCT01470781) and a study of clinical and cognitive characterization of psychosis. For subjects who participated in the cognitive remediation intervention study, only baseline cognitive and imaging data were included here. All procedures were approved by the Institutional Review Boards of the University of Pittsburgh (Pittsburgh, PA), McLean Hospital (Belmont, MA), and Beth Israel Deaconess Medical Center (Boston, MA). Every participant provided written informed consent prior to their participation. A subset of the data analyzed here was previously presented in Ling et al. (51).

Across sites, diagnosis was determined using the Structured Clinical Interview for the DSM-IV (SCID) (52), administered by trained raters of the SCID and confirmed by a doctoral-level clinician. All participants were clinically stable outpatients at the time of assessment. Inclusion criteria for participants at the Pittsburgh and Boston sites were: (1) between 18 and 45 years old; (2) current IQ $\geq$ 80, assessed by the WASI-II (53); and (3) fluent English speaker with the ability read at a sixth grade level or higher. Additional inclusion criteria for the participants with a psychotic disorder were: (1) a SZ or schizoaffective disorder diagnosis, verified using the SCID interview (54); (2) time since first psychotic symptoms of <10 years; and (3) clinically stabilized on antipsychotic medication. Inclusion criteria for psychotic disorder participants at the Belmont site were: (1) age 18–60 years; (2) diagnosis of SZ, schizoaffective disorder, or BD with psychotic features; and (3) clinically stable defined as no psychiatric hospitalization or medication change in the past month. Across sites exclusion criteria included: (1) significant neurological or medical disorders that might cause cognitive impairment (e.g., seizure disorder, traumatic brain injury); (2) persistent suicidal or homicidal behavior; (3) substance abuse or dependence present within the past 3 months; (4) any MRI contraindications; and (5) decisional incapacity requiring a guardian.

Neurotypical participants had never met criteria for any Axis I psychiatric disorder and had no history of head injury resulting in a loss of consciousness, seizure or neurological disorder. **Table 1** summarizes the sample's demographic, clinical, and medication regimen information.

Cognitive Testing

The MATRICS Consensus Cognitive Battery (MCCB) was used to assess cognition (55, 56). This testing battery yields a cognitive composite score and 7 domain scores including processing speed, attention, working memory, verbal learning, visual learning, problem solving, and social cognition. In the MCCB, social cognition is assessed using the Mayer-Salovey-Caruso Emotional Intelligence Test (57) Managing Emotions branch (MSCEIT-ME). The MSCEIT-ME includes a series of vignettes. The vignettes are read aloud to participants as they follow along in their printed materials. Each vignette proposes a series of possible actions related to its scenario. The participants are asked to assess the effects each action would have on the actor's or other characters' mood states or behaviors. Responses follow a Likert-type scale. The MSCEIT-ME and MCCB scoring packages were used to calculate age and sex normed *T* scores.

Participants at the Boston and Pittsburg sites had full-scale (FSIQ) assessed using the Wechsler Abbreviated Scale of Intelligence (WASI). Participants at the McLean site had FSIQ and verbal IQ (VIQ) assessed using the North American Adult Reading Test (NAART).

MRI Data Acquisition

Boston site: Data were acquired on 3T Siemens Trio (TIM upgrade) scanners using a standard head coil. The echoplanar imaging parameters were: repetition time, 3,000 ms; echo time, 30 ms; flip angle, 85°; 3 × 3 × 3-mm voxels; and 47 axial sections collected with interleaved acquisition and no gap. Structural data included a high-resolution T1 image. All participants underwent a resting-state fMRI run. Each functional run lasted 6.2 min (124 time points).

Pittsburgh site: Data were acquired on a 3T Siemens Verio scanner using a standard head coil. The echoplanar imaging parameters were: repetition time, 3,000 ms; echo time, 30 ms; flip angle, 85°; 3 × 3 × 3-mm voxels; and 45 axial sections collected with interleaved acquisition and no gap. Structural data included a high-resolution T1 image. The functional run lasted 6.2 min (124 time points).

McLean site (SZ): Data were acquired on 3T Siemens Trio (TIM upgrade) scanners using a standard head coil. The echoplanar imaging parameters were: repetition time, 3,000 ms; echo time, 30 ms; flip angle, 85°; 3 × 3 × 3-mm voxels; and 47 axial sections collected with interleaved acquisition and no gap. Structural data included a high-resolution T1 image. Each functional run lasted 6.2 min (124 time points) and the participants were given instructions to "remain still, stay awake, and keep your eyes open."

McLean site (BP): Data were acquired on 3T Siemens Trio (TIM upgrade) scanners using a standard head coil. The echoplanar imaging parameters were: repetition time, 2,500 ms; echo time, 24 ms; flip angle, 82°; 3 × 3 × 3-mm voxels; and 42 axial sections collected with interleaved acquisition and no gap. Structural data included a high-resolution T1 image. Each resting-state functional run here lasted 10 min (240 time points) and the participants were given instructions to "remain still, stay awake, and keep your eyes open."

MRI Data Processing

MRI image preprocessing was performed as in presented in Ling et al. (51). DPABI image processing software was used to preprocess the imaging data (58). To minimize the scanner signal stabilization effects, the first images were omitted from all analysis (the first 4 images from 124 time point scans and first 10 images from 240 time point scans). We discarded scans with head motion that exceeded a 3 mm or 3° of maximum rotation threshold during the resting-state run. Functional and structural images were co-registered. Using the DARTEL technique (59), the structural images were normalized and segmented into gray, white and CSF partitions. Head motion effects were regressed out from the realigned data using a Friston 24-parameter model (60). CSF and white matter signals along with the global signal and the linear trend were regressed out. We incorporated the global signal regression because prior demonstration showed that combining it with volume-wise "scrubbing" for head "micromovements" is an effective method to remove motion artifacts (61). Following realignment, slice timing correction and co-registration, framewise displacement (FD) was calculated for all resting state volumes (62). All volumes within a scan that had a FD >0.2-mm were censored. Scans that required censoring half, or more, of their volumes were discarded. After nuisance covariate regression, the resultant data were band-pass filtered to select low frequency (0.01–0.08 Hz) signals. DARTEL normalized the filtered data into MNI space and then the data were smoothed by a Gaussian kernel of 8 mm^3 full-width at half maximum (FWHM). Voxels contained within a group derived gray matter mask were used for further analyses.

After preprocessing, 126 participants, across all sites, remained in the study. 51 participants diagnosed with SZ, 9 with schizoaffective disorder, 21 with BD, and 45 neurotypical participants comprise our sample (**Table 1**).

Functional Connectivity Analysis

Multivariate Distance Matrix Regression

We performed a connectome-wide association study using multivariate distance matrix regression (MDMR) as originally laid out in Shehzad et al. (63). In brief, MDMR tests every voxel to determine if whole-brain connectivity to that voxel is more similar in individuals with similar scores on an independent measure (MSCEIT-ME) than in individuals with dissimilar scores. As described (64–66), MDMR occurs in several stages: First, scan and MSCEIT-ME scores are collected from all participants (**Figure 1A**). Next, a seed-to-voxel connectivity map is generated for every participant. These maps are created by calculating the temporal Pearson's correlation coefficients between each voxel, using its BOLD signal time-course, and all other gray matter voxels (**Figure 1B**). Second, the temporal correlation coefficients for each voxel in the connectivity map are correlated with the values of corresponding voxels in the maps generated for the other participants. This Pearson's correlation coefficient, r, is a measure addressing how similar the whole-brain connectivity to a specific voxel is, for each voxel, between patients. This value is used to calculate between-subject distance (or dissimilarity) using the metric $d_{ij} = \sqrt{2\left(1 - r_{ij}\right)}$ where i and j are two subjects and r is the correlation coefficient above (**Figure 1C**) (67). Third, we test the relationship between the independent variable of interest, here, MSCEIT-ME score, and the inter-subject distances in connectivity generated in the previous stage. Broadly speaking, this process consists of an ANOVA-like hypothesis test between a variable of interest and a matrix of distances. This method was originally named multivariate distance matrix regression by Zapala and Schork while they focused on associations between gene expression and related variables (67). Shezhad et al. then shifted their analytic focus, and used this framework to test the relationship between variables of interest and a matrix of distances, the matrix being similarity between-subject's whole-brain functional connectivity. This test first creates a distance matrix $A = (-\frac{1}{2}d_{ij}^2)_{1\leq i,j\leq n}$ among n participants where $d =$ the between subject distance metric calculated above. Next, this matrix is used to create a Gower's centered matrix $G = \left(I - \frac{1}{n}11^T\right)A\left(I - \frac{1}{n}11^T\right)$, in which n is the number of participants, I is the $n \times n$ identity matrix, and 1 is a vector of n 1s. The F statistic for assessing the relationship between a predictor variable (e.g., MSCEIT-ME score) and dissimilarities in connectivity is calculated as follows: For m predictor variables, let $\boldsymbol{X}$ be a $n \times m$ design matrix of

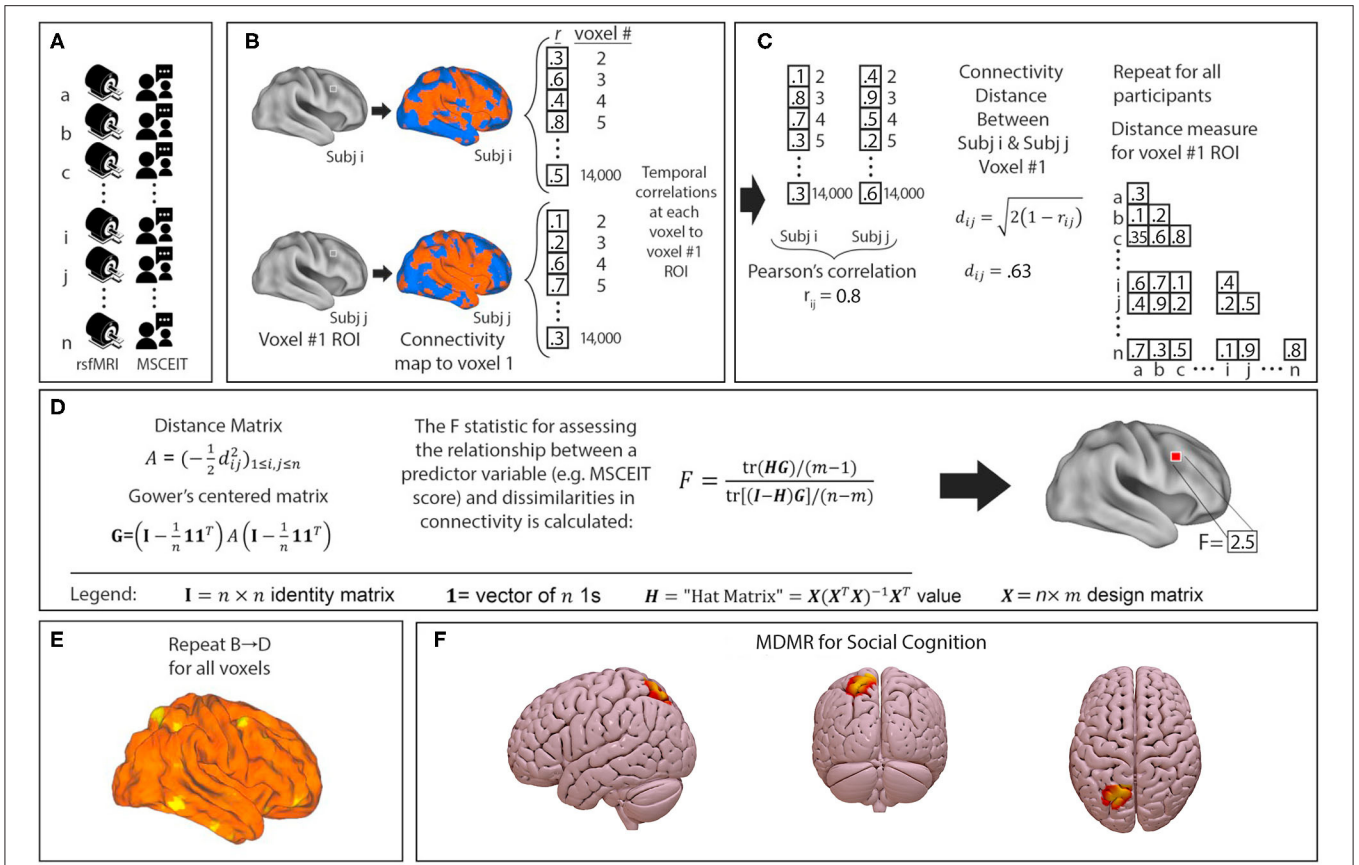

FIGURE 1 | Multivariate distance matrix regression identifies left parietal connectivity as the strongest correlate of social cognitive ability in a trans-diagnostic sample. MDMR procedure: **(A)** rsfMRI and emotional intelligence testing are collected from each participant. **(B)** For each participant a functional connectivity map is generated to an individual voxel. **(C)** Voxelwise temporal correlations between participants are used to generate a Pearson's correlation *r* and a distance metric *d*. This is repeated for all participants to generate a matrix of between subject distances. **(D)** The distance matrix is centered and an ANOVA-like test is used to generate an *F*-statistic to assess the relationship between a predictor variable (MSCEIT-ME score) and dissimilarities in functional connectivity at that voxel. **(E)** This process is repeated for every voxel. This results in a whole brain map of how significantly functional connectivity is related to emotional intelligence. Permutation testing then identifies whole-brain significant clusters in connectivity-MSCEIT-ME relationships. **(F)** In our sample of 126 participants ($n = 60$ with schizophrenia or schizoaffective disorder, $n = 21$ with bipolar disorder with psychosis, and $n = 45$ neurotypical participants), we identified a single region in the left parietal lobule (centered at MNI coordinates $x - 24$ $y - 69$ $z + 57$) whose connectivity correlated significantly with emotional intelligence. In this image, connectivity is thresholded at a voxelwise level of $p < 0.001$ and extent threshold of $p < 0.05$.

predictor values, and let $H = X(X^TX)^{-1}X^T$ be the associated $n \times m$ "hat" matrix.

$F = \frac{tr(HG)/(m-1)}{tr[(I-H)G]/(n-m)}$ (**Figure 1D**) (63). This process is repeated for every voxel. The result is a whole brain map showing how significant the relationship between MSCEIT-ME scores and functional connectivity is at every voxel (**Figure 1E**). From this generated map, ROIs for follow-up analysis are determined based on clusters of significant voxelwise *F*-statistics. To correct for multiple comparisons, a nonparametric permutation is calculated for voxels that exceed the significance threshold of $p < 0.001$ and clusters of such with an extent threshold of $p < 0.05$, with a null distribution calculated from 1,000 such permutations (**Figure 1F**). The voxelwise threshold was selected to maximize the replicability potential.

This MDMR analysis identifies anatomical regions where MSCEIT-ME score is significantly correlated with functional connectivity. Notably, this process does not consider spatial information about the voxels that give rise to between-individual distances. For example, two individuals may be very distant, or dissimilar, in the functional connectivity of a voxel in the precuneus. Such dissimilarity might be driven by differences in precuneus connectivity to the mPFC, temporal lobe, parietal lobe, or perhaps all three. MDMR, as implemented by Shehzad et al. (63), does not present this information. Visualizing this missing spatial information requires follow-on seed-based connectivity analysis. Shehzad et al. and others have defined this follow-on analysis as "*post-hoc*" testing to clarify that this alone, is not sufficient hypothesis testing nor an independent validation of the original MDMR finding (63–66). Following these prior manuscripts, we conducted the MDMR analysis to locate anatomical regions of interest where connectivity significantly correlated with MSCEIT-ME score and then performed follow-on seed-based connectivity analysis to detail the spatial distribution of these connectivity differences.

Seed Based Connectivity Analyses

We used DPABI for our seed-based connectivity analyses. This analysis extracted the BOLD signal time course in a 6 mm spherical ROI centered in the result of the MDMR (MNI x – 24 y – 69 z + 57). We then generated whole brain maps of z-transformed Pearson's correlation coefficients. We entered these maps into SPM12 (Statistical and Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). Next, we regressed these maps against MSCEIT-ME scores. This process generated spatial maps that show how whole brain functional connectivity to the ROI varies with MSCEIT-ME score. We performed these analyses with sex, age, and scanner site as covariates to control for participant variables of non-interest.

In our sample, prescribed CPZE dosage was inversely correlated with MSCEIT-ME score ($r = -0.445$, $p < 0.001$). To control for possible medication regimen effects, this analysis was re-performed with the covariates above (age, scanner site, and sex) plus prescribed anti-psychotic dosage (in chlorpromazine equivalents, CPZE) as an additional covariate (**Supplementary Figure 2**).

ROI to ROI Analyses

To generate a scatter plot of the relationship between functional connectivity and MSCEIT score we extracted the BOLD signal time course between the MDMR centered ROI and the cerebellar cluster (thresholded at voxelwise $p < 0.001$).

Correlations between connectivity and MSCEIT and partial correlations with FSIQ or VIQ or CPZE as covariates were calculated using r.

Figure Generation

SurfIce was used to generate the projections of ROIs and T contrast maps onto cortical surfaces (www.nitrc.org/projects/surfice/).

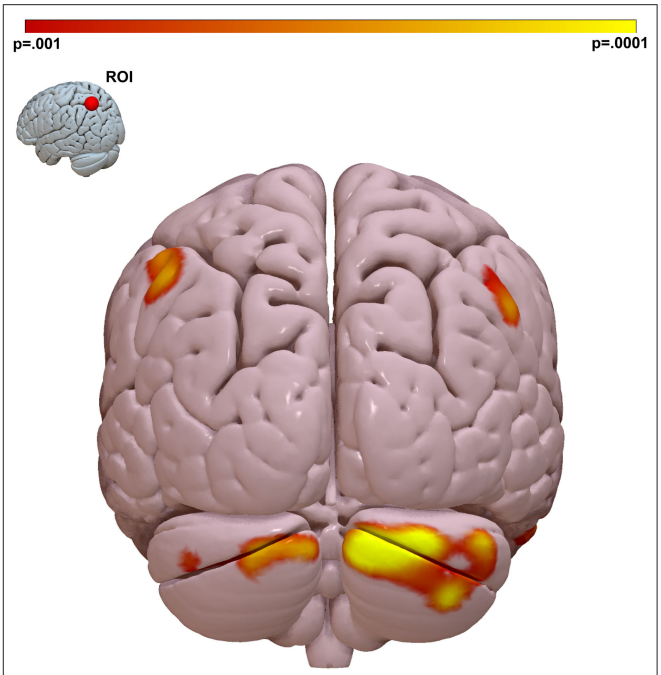

FIGURE 2 | The strongest link between connectivity and social cognitive ability is a parietal Lobe-cerebellar Crus I, II circuit. We visualized the spatial distribution of connectivity that gave rise to the MDMR result in **Figure 1**. We placed a ROI in the left parietal region identified by MDMR and regressed connectivity to this region against MSCEIT-ME score. This identified the right cerebellar Crus I, II region as the region where functional connectivity correlates with social cognitive ability. Peak T-stat $T = 4.99$, $p < 0.001$, MNI x – 12, y – 90, z – 30. Cluster $k = 695$, $p_{FWE} < 0.001$. Color bar = voxel connectivity p-value.

RESULTS

Functional Connectivity in the Superior Parietal Lobule Is Linked to Social Cognition

MDMR analysis performed across all 126 participants (51 SZ, 9 schizoaffective disorder, 21 BD with psychosis, 45 neurotypical) revealed a single region whose intrinsic functional connectivity correlated significantly with MSCEIT-ME social cognition scores. This identified a region in the left superior parietal lobule centered at MNI coordinates x – 24 y – 69 z + 57 (**Figure 1F**).

Parietal–Cerebellar Connectivity Is Linked to Social Cognitive Ability

We performed follow-on analysis using this parietal region in a seed-based connectivity analysis to determine the spatial distribution and directionality of connectivity that gave rise to this result. This analysis revealed that social cognition is positively correlated to functional connectivity between the left parietal lobe and other regions of the DMN including DMN nodes in both bilateral parietal lobes and bilateral cerebellum. This relationship was observed maximally between left superior parietal lobe and the Crus I, II region of the cerebellum (**Figure 2** and **Supplementary Figure 1**).

In our sample participants with a psychotic disorder demonstrated social cognitive ability a full standard deviation below the neurotypical participants (**Table 1**). When we examined individual diagnostic groups, we observed that the relationship between connectivity and cognition was similar for all groups: Neurotypical participants: $r = 0.434$, $p = 0.003$; BD participants: $r = 0.448$, $p = 0.042$. SZ/schizoaffective participants: $r = 0.394$, $p = 0.002$. Comparing the strength of correlation between groups did not reveal significant differences between neurotypical and BD groups ($p = 0.952$), between neurotypical and SZ /schizoaffective groups ($p = 0.810$), or between bipolar and SZ/schizoaffective groups ($p = 0.810$).

To isolate social cognition specific effects we calculated the partial correlation between parietal–cerebellar connectivity and MSCEIT with estimated IQ regressed out as a covariate. We continued to observe the same strong correlation between connectivity and MSCEIT score $r = 0.410$, $p < 0.001$. A subset of the participants ($n = 56$) also had verbal IQ estimated by NAART. In this subset of participants, the partial correlation of connectivity with MSCEIT score with VIQ as a covariate remained highly significant $r = 0.555$, $p < 0.001$.

As reported above (section "Seed Based Connectivity Analyses") we observed a significant inverse correlation between prescribed CPZE dosage and MSCEIT score. We observed the same cerebellar–parietal connectivity-cognition relationship in all diagnostic subgroups (including neurotypical participants not taking antipsychotics) making it unlikely that observed connectivity is caused by medication effects. We calculated the partial correlation between parietal–cerebellar connectivity and MSCEIT with CPZE regressed out as a covariate. We continued to observe the same strong correlation between connectivity and MSCEIT score $r = 0.364$, $p < 0.001$. We also regressed maps of connectivity to the parietal ROI against MSCEIT score with CPZE as an additional covariate (in addition to age, sex, and site) and continued to identify a significant correlation to the right cerebellum (**Supplementary Figure 2**), albeit at a lower voxelwise significance threshold ($p < 0.005$).

DISCUSSION

We present the results of our efforts to identify brain circuit correlates of social cognition. Our approach included a trans-diagnostic cohort of neurotypical adults and participants with psychotic disorders. As predicted, participants with psychosis exhibited significant impairment in social cognition compared to controls. We then used a fully data driven analysis of task-free connectivity at the individual voxel level to find the strongest correlates of social cognitive ability. This approach determined that functional connectivity between left superior parietal cortex and other nodes of the DMN are positively correlated with social cognitive ability. A link between cognition and SPL connectivity was observed in bilateral nodes of the DMN but there was a laterality to the strongest result observed. Specifically, the strongest relationship between functional connectivity and social cognitive ability was observed in a circuit between right cerebellar Crus I, II and left superior parietal cortex. The relationship between cognition and connectivity at those nodes was trans-diagnostic and observed in both neurotypical participants as well as those with psychotic disorders, despite the participants with psychotic disorders performing, on average, a full standard deviation worse than neurotypical adults. This is consistent with a model in which cerebellar–parietal connectivity mediates the relationship between diagnosis and social cognitive ability. This observation is in line with a recent consensus report highlighting the role of the cerebellum in social cognition (68). Interestingly, a recent large study in SZ found robust reductions in cerebellar gray matter volume with the strongest effects in regions that were functionally connected with frontoparietal cortical regions (69) suggesting that not only is cerebellar–parietal connectivity linked to social cognitive processing, but that it is strongly associated with abnormalities in psychosis.

Historically, hypothesis driven neuroimaging has focused on the prefrontal cortex in studies involving complex cognition such as working memory and social reasoning. How can our result be reconciled with the extant literature? Strikingly, this discovery is entirely consistent with prior findings in both human disorders of social cognition (e.g., autism) and in murine models. Case-control studies in ASD have consistently identified abnormalities in the Crus I, II region of the cerebellum but the functional consequence of this finding had been unclear. More recently, through innovative experiments, Stoodley et al. demonstrated that cerebellar neuromodulation in humans can manipulate cerebellar–parietal connectivity. Those investigators were able to extend this result by demonstrating with direct recording that right Crus I Purkinje neurons modulate activity in mouse parietal association cortex (48). Both that study and a subsequent paper demonstrated a critical role for Crus I in social preference in mice (48, 70).

Here we expand on these studies in two critical ways: First, while prior studies demonstrated R Crus I of the cerebellum can modulate parietal activity in humans, we demonstrate that communication between cerebellum and parietal lobe is directly related to human social cognitive ability. Second, we demonstrate that this circuit can account for individual variance in social cognitive ability in disorders of impaired social cognition (e.g., SZ) as well as in neurotypical humans.

Of particular note, we arrive at this circuit using a whole-brain, data-driven analysis, i.e., without limiting ourselves *a priori* to these candidate regions. This circuit is identified as *the strongest* link to social cognition in our sample. Thus, we observe a convergence of results from independent data in humans and mice identifying a trans-diagnostic and *trans-species* cerebellar-cortical circuit with evidence of a *causal* link to social cognitive ability.

We suggest that this convergence of results is also a product of the analytic approach used here. Specifically: The participants of this sample represented a spectrum of social cognitive ability. That variance is presumably linked to a variety of underlying causes, i.e., some participants had social cognitive deficits linked to a primarily genetic disorder (SZ) and other participants whose abilities represent normal population variation not linked to the genetic causes of SZ. In finding a common brain substrate for social cognitive ability irrespective of etiology, we propose that this connectivity-cognition link may be common pathway mediating social cognitive ability. That is, a circuit casually linked to cognition rather than epiphenomena linked to disease severity.

The results presented in these studies link circuit connectivity to social cognition as measured by tests in laboratory conditions. However, data suggest that there may be real-world outcomes linked to this circuit as well. Smith et al. analyzed human connectome project data using canonical correlation analysis to link a wide range of tests and life experiences to functional connectivity (71). This analysis revealed a broad range of outcomes organized along a "positive–negative" axis (e.g., life satisfaction as a positive outcome, and THC use as a negative outcome). Strikingly, the strongest brain link to this axis was functional connectivity between cerebellar Crus I, II and parietal lobule.

These results in murine behavioral tests, human social cognitive test performance, and real-world outcomes are independently derived but all converge on the same consensus cerebellar–parietal circuit. This allows the construction of an empirically derived model in which social cognition is critically dependent on this cerebellar-cortical circuit function (**Figure 3**).

Prior evidence for a cerebellar role in organized cognition has come from lesions and correlational imaging studies (72). A wealth of recent murine studies has demonstrated a critical

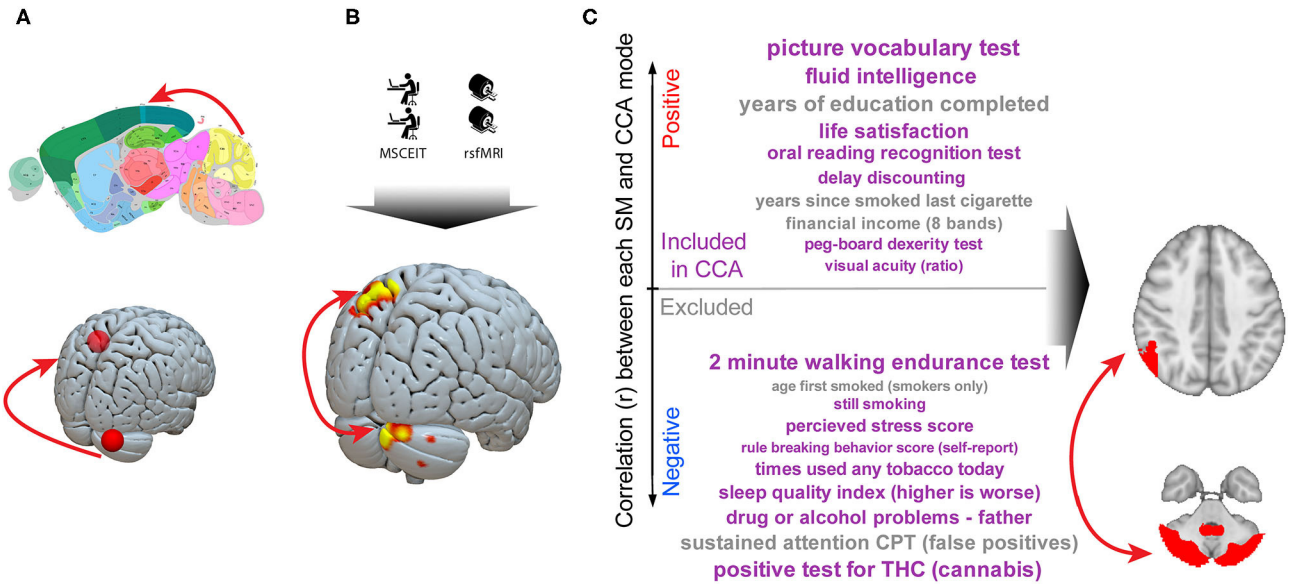

FIGURE 3 | A cerebellar–parietal circuit is causally linked to social cognition both trans-diagnostically and trans-species. A series of murine and human experiments converge on a shared circuit causally linked to social cognition. **(A)** Imaging studies reliably identify cerebellar right Crus abnormalities in autism. Neuromodulation experiments in humans identify a circuit linking right Crus to the left parietal lobe and murine studies demonstrate this circuit is critical to normal social interaction (48). **(B)** We observe that, in a trans-diagnostic sample, connectivity between right cerebellar Crus and left parietal lobe connectivity is directly linked to social cognitive ability. **(C)** In a large (n = 461) dataset, connectivity in this cerebellar Crus–parietal circuit was the strongest link between a broad array of outcomes along a "positive–negative axis" (71). Taken together, these data are consistent with a critical role for a cerebellar–cortical circuit in complex social cognition. Murine image from the Allen Mouse Brain Atlas.

role for the cerebellum in multiple aspects of cognition (73–77). In this model we add social cognition to the growing list of cognitive domains dependent on cerebellar computation. In particular, the MSCEIT-ME branch requires participants to listen to vignettes and make predictions about the emotional or social consequences of various possible actions; the association between performance on this task and the identified cerebellar–parietal circuit is consistent with findings that the cerebellum, and specifically Crus I and II, plays a role in social cognition via social prediction (68).

What is the relevance of this result to disease? The evidence presented here link social cognitive impairment in psychotic disorders to this circuit. We previously demonstrated, in an independent data set, that hypoconnectivity in a cerebellar–Dorso-Lateral Pre-Frontal Cortex (DLPFC) circuit is *causally* linked to negative symptoms (e.g., apathy) in SZ (78). The cerebellar node of that circuit is the *same* Crus I, II region we link to social cognition in the current study. Specifically: connectivity between this Crus I, II region and different cortical regions is linked to different deficits in SZ: the left parietal lobe for social cognition and the right DLPFC for negative symptoms. This allows a mechanistic model for the co-occurrence of these deficits in SZ: Distinct deficits result from dysconnectivity in specific circuits, but all of these circuits have a shared node in the cerebellum.

Importantly, these findings have implications for targeted interventions to improve social cognitive functioning in people across diagnostic boundaries. Our study using transcranial magnetic stimulation (TMS) to target a cerebellar-cortical circuit associated with negative symptoms in psychosis found that neuromodulation at the cerebellar site was associated with both increased connectivity *and* reduction in negative symptoms (78). Our findings, together with others [e.g., (48)], identify a potential neural target for improving social cognition that may be both modifiable and associated with downstream pro-cognitive effects.

One limitation of our study was the use of a single test of social cognitive ability. The MSCEIT-ME test included in the MATRICS consensus cognitive battery was designed to measure a specific aspect of social cognition, higher-order emotional reasoning regarding emotion management and regulation, and does not measure other social cognitive domains such as theory of mind or emotion perception. That said, the managing emotions domain of MSCEIT-ME is linked to real world functional outcomes (79) and the broad adoption of the MATRICS allowed consolidation of samples from across multiple sites (80). The MSCEIT-ME branch was also the only branch of the MSCEIT in which people with psychosis continued to differ from controls after controlling for general cognitive ability (81), suggesting that it is tapping emotional intelligence in a way that is at least partially distinct from general cognitive skills. Additionally, the MSCEIT-ME was among the MSCEIT branches most strongly associated with brain volume measures in people with SZ and related disorders (82). However, associations between this circuit and other domains of social and emotional processing remain to be determined. Another limitation is that we did not have uniform data on social or other functional outcomes across the sample and were

therefore unable to evaluate effects of our findings on real-world social functioning.

Despite these limitations, the convergence of results linking social cognition to a cerebellar–parietal circuit (**Figure 3**) argues (1) dysfunction in this circuit is linked to social cognition trans-diagnostically in psychotic disorders and (2) at the circuit level these deficits lie along a continuum with variation in social cognitive ability in a neurotypical population. Future studies can determine if individual variation in social cognitive ability in ASDs covaries with cerebellar–parietal connectivity. Evidence from murine experiments are consistent with a *causal* relationship between this circuit and social cognition. From a basic science perspective, the convergence of human and murine findings suggest that this circuit is a valid candidate for modeling how circuit dysfunction gives rise to social cognitive phenotypes in psychiatric disorders. Therapeutically, prior work has established that this circuit can be manipulated non-invasively (48) making it a promising candidate target for interventions designed to ameliorate social cognitive deficits.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

These studies were reviewed and approved by the University of Pittsburgh, BIDMC, and McLean Hospital IRBs.

AUTHOR CONTRIBUTIONS

RB was involved in all aspects of this project including study design, statistical analyses, development of tables and figures, and drafting of the manuscript. AB was involved in statistical analyses, development of figures, and drafting of the results, and methods. MN was involved in data collection and analysis. SE was involved in development of studies in which the data were collected. RM-G was involved in design and interpretation of the cognitive data. MK was involved in development of studies in which the data were collected and the analysis plan. KL was involved in development of studies in which the data were collected, development of the present project, and drafting of the manuscript. All authors reviewed and approved 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.2020.573002/full#supplementary-material

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REVIEW
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Facial Expression Processing Across the Autism–Psychosis Spectra: A Review of Neural Findings and Associations With Adverse Childhood Events

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Autism spectrum disorder (ASD) and primary psychosis are classified as distinct neurodevelopmental disorders, yet they display overlapping epidemiological, environmental, and genetic components as well as endophenotypic similarities. For instance, both disorders are characterized by impairments in facial expression processing, a crucial skill for effective social communication, and both disorders display an increased prevalence of adverse childhood events (ACE). This narrative review provides a brief summary of findings from neuroimaging studies investigating facial expression processing in ASD and primary psychosis with a focus on the commonalities and differences between these disorders. Individuals with ASD and primary psychosis activate the same brain regions as healthy controls during facial expression processing, albeit to a different extent. Overall, both groups display altered activation in the fusiform gyrus and amygdala as well as altered connectivity among the broader face processing network, probably indicating reduced facial expression processing abilities. Furthermore, delayed or reduced N170 responses have been reported in ASD and primary psychosis, but the significance of these findings is questioned, and alternative frequency-tagging electroencephalography (EEG) measures are currently explored to capture facial expression processing impairments more selectively. Face perception is an innate process, but it is also guided by visual learning and social experiences. Extreme environmental factors, such as adverse childhood events, can disrupt normative development and alter facial expression processing. ACE are hypothesized to induce altered neural facial expression processing, in particular a hyperactive amygdala response toward negative expressions. Future studies should account for the comorbidity among ASD, primary psychosis, and ACE when assessing facial expression processing in these clinical groups, as it may explain some of the inconsistencies and confound reported in the field.

Keywords: ASD, psychosis, facial expression processing, neuroimaging, childhood adverse events

INTRODUCTION: AUTISM AND PRIMARY PSYCHOSIS AS DISTINCT YET RELATED DISORDERS

Autism spectrum disorder (ASD) and psychosis spectrum disorders are neurodevelopmental disorders characterized by impairments in social cognition. According to DSM-5, ASD is an early-onset disorder characterized by (1) difficulties in social interaction and communication, including deficits in socioemotional reciprocity and deficient nonverbal communicative behavior, and (2) the presence of restrictive and repetitive behaviors and interests and/or atypical sensory processing (1). Psychosis spectrum disorders are marked by positive symptoms, such as hallucinations and delusions, and negative symptoms, such as blunted affect and anhedonia. In addition, cognitive, affective, and social impairments may also be present (1). Psychosis spectrum disorders, which typically arise in young adulthood, include schizotypal personality disorder, delusional disorder, brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, and substance/medication-induced psychotic disorder. As these disorders are very heterogeneous in terms of symptoms, severity, and duration, we will adopt the term primary psychosis to represent all disorders included in psychosis spectrum disorders throughout this paper, except when the evidence is specific to individuals with a particular diagnosis.

Despite clear differences between ASD and primary psychosis, in particular regarding age of onset, historically, both disorders have been considered as closely related pathologies (2, 3). In fact, DSM-II (4) did not differentiate between the two disorders and listed autistic behavior as one of the criteria for childhood schizophrenia (5). Research from the 1970s onwards showed that a reliable distinction could be made between ASD and primary psychosis (6); yet, studies continuously demonstrated a considerable overlap between these two conditions (7). More recently, research has again been focusing on evidence for the connection between ASD and primary psychosis. Recent meta-analyses revealed a significant epidemiological association between both disorders [(8, 9); for an umbrella review, see (10)]. More specifically, the prevalence of primary psychosis in individuals with a childhood ASD diagnosis is significantly higher than in controls (odds ratio = 3.55) (9), with an estimated weighted pooled prevalence of up to 9.5% of primary psychosis in individuals with ASD (8). Vice versa, the prevalence of comorbid ASD in primary psychosis (ranging from 3.4 to 52%) is also higher than in the general population (9). A recent study revealed significantly increased rates of autistic traits in patients with psychosis, with 6.5% scoring above clinical cutoff; yet, there was no significant difference between people with familial risk and healthy controls (11).

Notably, both ASD and primary psychosis are also associated with an increased prevalence of adverse childhood events (ACE) [(12, 13); for reviews, see (14–16)]. On the one hand, ACE, such as physical, sexual, or emotional abuse and physical or emotional neglect, have consistently been shown to be related to the onset of psychotic symptoms and the development of primary psychosis (15, 16). On the other hand, children with ASD may be more prone to experience ACE due to their social and communicative difficulties and their struggles with daily life skills (17, 18). Furthermore, heritability rates for ASD and primary psychosis are high and both disorders share overlapping genetic mechanisms (7, 19, 20).

In addition to overlapping epidemiological, environmental, and genetic components, both disorders display multiple endophenotypic similarities. At a behavioral and cognitive level, individuals with ASD and primary psychosis show overlapping symptomatology, impeding the differentiation between psychosis and ASD symptoms and hampering differential diagnosis [for a review and meta-analysis, see (21)]. In both disorders, social interaction, and communication deficits may be present, as well as theory of mind, mentalizing, and general social–cognitive functioning impairments, such as the lack of socioemotional reciprocity (7, 21, 22). In addition, individuals with ASD often display positive psychotic experiences, while patients with primary psychosis may also show restricted interest, mental inflexibility, and reduced social attunement (7).

At a neural level, similar structural and functional atypicalities have been reported in both disorders, in particular pertaining to social brain areas. For example, both disorders show lower gray matter volumes in the right parahippocampal gyrus, posterior cingulate, putamen, insula, and left thalamus (23). This finding is supported by reduced cortical thickness and surface area in children and adolescents with ASD and early-onset first-episode primary psychosis, which may serve as a potential early neurodevelopmental mechanism in the pathogenesis of both disorders (24). Furthermore, volume loss in prefrontal areas and the temporal–parietal junction, volume gains in the caudate, and reduced fractional anisotropy values (indexing reduced structural connectivity) have been reported in both ASD and childhood-onset primary psychosis (7, 9). Besides these structural similarities, functional similarities have also been reported in individuals with ASD and primary psychosis (25). During social cognition tasks, both groups display reduced activation in medial prefrontal areas, yet this deficit is larger in individuals with ASD. Moreover, individuals with ASD and primary psychosis both exhibit amygdala hypoactivity and reduced activity in the superior temporal sulcus (STS) during social cognition tasks (25).

One of the key processes underlying impairments in social interaction and communication deficits common to ASD and primary psychosis may be facial expression processing. Indeed, accurate facial expression processing is crucial for social communication, as facial expressions convey important social cues and constitute a large portion of nonverbal communication. Consequently, impairments in facial expression processing very likely contribute to poor psychosocial functioning in psychiatric disorders including ASD (26) and primary psychosis (27). In a similar vein, impaired facial expression processing may impact psychosocial functioning in individuals exposed to adversity (28, 29). The development of adequate facial expression processing is largely driven by visual experience during childhood (28, 30). Faces provide important cues about the emotional state of the interacting partner, in particular the primary caregiver, and infants learn to read and interpret this emotional information.

In the case of unsafe social environments, children may become hypersensitive to (facial) cues signaling threat, and this threat signaling may subsequently generalize to more ambiguous emotional cues (30). Therefore, children exposed to atypical emotional environments, such as ACE, are expected to show atypical facial expression processing.

Thus far, the face processing literature has typically been focusing rather exclusively on isolated syndromes, thereby ignoring possible commonalities and associations among various syndrome clusters. Accordingly, the present narrative review aims to adopt a broader more overarching perspective in order to provide a concise overview of commonalities and differences in the current neuroimaging literature on facial expression processing in ASD and primary psychosis, as well as to provide insight into the impact of ACE on facial expression processing.

The studies included in this narrative review were identified through a series of literature searches in online databases (*PubMed*, *ScienceDirect*, *Web of Science*) and *Google Scholar* for papers published within the last 20 years (2000–2020) using a combination of the following keywords: *auti**, *autism*, *ASD*, *psychosis*, *schizo**, *trauma*, *abuse*, *maltreatment*, *advers**, *emotional face processing*, *emotion processing*, *facial expression processing*, *neuroimaging*, *EEG*, and *fMRI*. Additional studies were encountered in the reference lists of selected studies.

As evidenced by the different keywords used in our literature search to define ACE, definitions of ACE vary greatly, ranging from experiences of poverty and neglect to physical, emotional, and sexual abuse. Likewise, there exists a multitude of operationalizations to characterize ACE. For instance, ACE can be assessed prospectively or retrospectively, and these measures are often used interchangeably, even though a recent meta-analysis (31) confirmed that there is only very limited agreement between them. Furthermore, ACE are generally measured via child services reports or via questionnaires and interviews. The latter show a large variability in the type of adversity included and can either be self-report or parent-report [for reviews, see (32, 33)]. As a result, ACE are often recorded differently in different studies, thereby reducing comparability and generalizability of the reported findings. For the present qualitative review, we applied a rather broad definition of ACE, including experiences of neglect and physical, emotional, and sexual abuse. Similarly, facial expression processing serves as an umbrella term, covering various operationalizations to pinpoint individual differences in the sensitivity for processing particular facial emotional cues. This process can be assessed via explicit behavioral tasks (i.e., with explicit attention to the emotional features) or via implicit measures (e.g., via eye-tracking, neuroimaging, autonomic nervous system reactivity, etc.). Furthermore, a large variety of behavioral facial expression processing tasks can be administered, such as labeling facial expressions, matching emotional faces, discriminating or differentiating between different emotions, judging the intensity of emotional expressions, detecting a specific facial expression in a series of faces displaying different emotions, etc. In addition, low-level stimulus features (e.g., spatial frequency) and emotion-specific stimulus dimensions (e.g., intensity, valence) also impact on the emotion processing and can possibly determine whether group differences are observed (34). For the present report, we focused upon behavioral face processing indices and neural face processing mechanisms as measured via electroencephalography (EEG) and functional magnetic resonance imaging (fMRI).

NEURAL MECHANISMS OF FACIAL EXPRESSION PROCESSING

Typically, facial expression recognition develops and improves with age (35, 36), but the developmental trajectories are emotion-specific (35, 37). Happiness, for example, is recognized the earliest, fastest, and most accurate (38), reaching adult levels at 5 to 6 years of age (36), whereas the recognition of anger, for instance, steeply improves (39, 40), with a clear increase in sensitivity from adolescence into adulthood (41).

In addition to behavioral improvement, facial expression processing also matures from early infancy to adolescence at the neural level (42–44). Extensive fMRI research has delineated a core face processing network consisting of the occipital and fusiform gyri [also known as the occipital and fusiform face area (OFA and FFA), respectively] (45) and the posterior STS (46). More specifically, invariant aspects of faces, such as facial identity and gender, are mainly processed by the ventral occipito-temporal cortex (OFA and FFA), whereas dynamic and variant aspects of faces, such as eye gaze and expression, are mainly processed by the posterior STS (47). This core face processing system is activated when processing expressive faces (48–50), along with areas of an extended face processing network involving visual, temporo-parietal, prefrontal, and subcortical areas (51–54) to extract meaning from these faces (55, 56). The amygdala, for instance, plays a crucial role in processing expressive faces and allows prioritizing of processing emotionally salient stimuli (49, 53, 57). In addition to the generally increased neural activation during emotion processing, there also seems to be a differential response pattern for specific emotions. For instance, the limbic system is especially sensitive to fearful and, to a lesser extent, happy expressions, whereas the insula shows increased activation when processing disgusted faces and, to a lesser extent, angry faces (52).

Unlike fMRI, EEG has a very high temporal resolution and is therefore optimal for studying the temporal course of facial expression processing (58). Event-related potentials (ERPs) have been widely used to investigate the neural mechanisms supporting facial expression processing in different populations, including individuals with ASD [for reviews, see (59–62)] and individuals with primary psychosis (63, 64). Research has pinpointed the N170, an ERP component with a negative peak occurring ∼170 ms after stimulus onset, as a consistent marker of face processing as it is more responsive to faces than objects (58, 65, 66). Despite conflicting reports in the literature, a meta-analysis by Hinojosa et al. (65) found that the N170 is especially sensitive to expressive faces, as its amplitude is larger in response to expressive faces compared with neutral faces. Yet, evidence from a recent integrative review did not support the presence of a distinctive discrimination pattern between the different facial emotions, apart from the differential encoding

of emotional expressions from a neutral expression (67). In addition to the N170, a broader range of ERP components—which reflect different stages of neural processing—has been found to be modulated by facial expressions. Other authors have shown that both the latency (68) and amplitude (69, 70) of the P100 are influenced by facial expressions, especially by fear. Likewise, sadness (71), fear, and anger (70) have been found to elicit larger late positive potential responses as compared with neutral faces [for a review, see (72)]. Furthermore, anger (73) and other basic expressions (74) have been shown to evoke larger early posterior negativity.

Facial expression processing is thus guided by a complex, interconnected network of neural structures (49, 52). In the following sections, we will provide a brief summary of findings from neuroimaging studies investigating facial expression processing in ASD and primary psychosis (see **Table 1** for an overview). Considering the extensiveness of the neuroimaging literature and the scope of this paper, for the fMRI data, we will mainly focus on the most commonly investigated brain areas during facial expression processing, more in particular the core and extended face processing network, as well as the social brain areas.

Facial Expression Processing in ASD

Behavioral Findings

An abundance of behavioral studies has investigated the facial expression processing abilities of individuals with and without ASD, yielding, however, mixed and inconsistent results in terms of group differences (34, 75–78). Most studies suggest a general emotion processing deficit in ASD as compared with healthy controls (79–82), yet some researchers only find difficulties with specific—mostly negative—emotions (83–86). Fear has been shown a difficult to recognize expression for individuals with ASD, especially for adults (77, 87). In addition, some studies also reported reduced recognition abilities for positive emotions, such as surprise (84) and happiness (83). Generally, though, individuals with and without ASD perform equally well for happy facial expressions (84–86). In contrast to the findings described before, other studies have reported intact facial expression recognition in ASD (88–90). Intact recognition abilities may indicate the use of verbally mediated or cognitive compensatory mechanisms in ASD to recognize facial expressions, whereas this process is more automatic in typically developing individuals (75). Hence, the interpretation of explicit emotion processing results can be impeded due to mechanisms beyond facial expression processing *per se*. In addition, given that a considerable degree of the conflicting findings on facial expression recognition can be attributed to task demands, the highly variable behavioral results may reflect the variability and limited sensitivity of certain behavioral measures (75).

fMRI Research

To overcome these impediments of behavioral measures and to understand the neural basis of facial expression processing in ASD, many researchers have turned to neuroimaging measures, such as fMRI. However, also fMRI studies generally fail to draw consistent conclusions on the brain anomalies of individuals with ASD. For example, although a previous review (91) and a meta-analysis (92) reported a generally hypoactivated fusiform gyrus in individuals with ASD as compared with healthy controls during facial expression processing, a more recent meta-analysis (93) showed similar activation patterns in both groups. In a similar vein, in contrast to the previously reported hyperactivation of the STS in individuals with ASD as opposed to healthy controls (92, 94), the meta-analysis of Aoki et al. (93) indicated no group differences in STS activation. However, differences in the applied analysis method might (partially) account for the differences in results: the more recent meta-analysis was conducted using seed-based *d* mapping, whereas Di Martino et al. (94) and Philip et al. (92) applied the activation likelihood estimation approach. Moreover, the accumulated number of included empirical studies may also have contributed to the different results.

Pertaining to the amygdala, the amygdala theory of autism postulates that atypicalities in the amygdala are at the root of the characteristic social deficits of individuals with ASD (95). Hypoactivation of this region has, indeed, frequently been found (93, 94), especially when processing fearful faces (96, 97). In addition, substantial evidence points toward a dysfunctional connectivity between the amygdala and the medial prefrontal cortex [(98); for a review, see (99)], possibly resulting in the socioemotional difficulties in ASD. Indeed, as these brain regions are employed when perceiving and assessing socioemotional information, the atypical connectivity might be associated with more severe social difficulties and less social orienting (100). Furthermore, individuals with ASD also display altered functional connectivity between the amygdala and other areas of the social brain, such as the fusiform gyrus and STS, when implicitly processing fearful faces (96) or explicitly processing angry and happy faces (101).

While Ciaramidaro et al. (102) reported differential activation in the temporo-parietal junction and the medial prefrontal cortex—two regions crucially involved in theory of mind processing (103)—in individuals with ASD when processing expressive faces, no general group difference in brain activity has been found in these regions on the basis of a formal meta-analysis (93).

Given that neural activity in social brain regions can be modulated by experimental parameters (91, 92, 94), the methodological variability across studies might contribute to the inconsistent findings (104). For instance, activation in the fusiform gyrus can be influenced by the degree of visual attention to the expressive faces and to the eyes, as evidenced by similar activation patterns in individuals with and without ASD when cues explicitly guided the visual attention of participants with ASD toward the faces (105, 106). These results have been interpreted in light of the social motivation theory of ASD (100), suggesting that hypoactivity in the fusiform gyrus in the absence of guiding cues might reflect the lack of motivation to attend to salient expressive facial features (92). Similar effects have been reported for the amygdala, with enhanced amygdala activity when attention is oriented toward the eyes of the faces (92, 107). In addition, modulatory effects of task demands on

TABLE 1 | Overview of the reported neural alterations in individuals with ASD and primary psychosis when processing facial expressions, in comparison with typically developing individuals.

	ASD	Primary psychosis
fMRI STUDIES		
Amygdala	**Activation** Hypoactivation **Functional connectivity** Altered connectivity between amygdala and -Medial prefrontal cortex -Fusiform gyrus -STS	**Activation** Hypoactivation Hyperactivation **Functional connectivity** Altered connectivity between amygdala and -Precuneus -Temporo-parietal junction
Fusiform gyrus	**Activation** Hypoactivation	**Activation** Hypoactivation
STS	**Activation** Hyperactivation	
Other brain regions	**Activation** Hypoactivation in -Temporo-parietal junction -Medial prefrontal cortex	**Activation** Hypoactivation in -Hippocampal region -Anterior and middle cingulate cortex -Dorsolateral and medial frontal cortex -Insula -Thalamus -Caudate -Lentiform nucleus -Putamen -Basal ganglia Hyperactivation in -Left middle occipital gyrus -Cuneus -Left precuneus -Inferior parietal lobule -Precentral gyrus -Right middle frontal gyrus -Dorsolateral prefrontal cortex
ERP STUDIES		
P100	**Latency** Delayed response **Amplitude** Reduced amplitude	**Amplitude** Reduced amplitude
N170	**Latency** Delayed response **Amplitude** Reduced amplitude	**Amplitude** Reduced amplitude
Other ERP components	**N300 latency** Delayed response **N400 latency** Faster response **N400 amplitude** Reduced amplitude **NSW amplitude** Less differentiated amplitude in function of facial expression	**N250 amplitude** Reduced amplitude **P300 amplitude** Reduced amplitude
FREQUENCY-TAGGING EEG STUDIES		
	Oddball response Reduced neural sensitivity for angry and fearful faces	

STS, superior temporal sulcus; NSW, negative slow wave.

neural activation during facial expression perception have also been reported (91, 92, 94). For example, explicit vs. implicit facial expression processing elicit differential responses in the amygdala, fusiform gyrus, or STS, both in individuals with (102, 108) and without ASD (48). Furthermore, also stimulus characteristics, such as intensity of the expressions (83, 96), familiarity of the faces (109), or static vs. dynamic expressions (54), have been found to influence the neural responses.

EEG Research

In addition to fMRI, EEG is a suitable method for ASD research, given its noninvasive nature and the nonrequirement of verbal or motor responses (110). ERPs have been widely used to investigate perceptual mechanisms supporting face and emotion processing abilities in individuals with and without ASD (60, 62). However, up until now, ERP studies have also generally failed to draw consistent conclusions on facial expression processing in ASD (59, 75). Similar ERP patterns in children, adolescents, and adults with and without ASD have been found (111–114), yet others have reported differences. Differences in the latency and/or amplitude of early ERP components, such as P100 (81, 115), N170 (113, 116–118), and N300 (119), for different facial expressions have frequently been found in individuals with ASD, suggesting reduced or delayed facial expression processing. However, anomalies have also been reported in later ERP components [e.g., N400 (117, 120) or negative slow wave (119)], which are believed to be more related to emotion categorization than to affective processing

(62, 67). Differences in ERP components, particularly in the N170, between both groups have often been reported for fearful faces (117–119).

Recently, the N170 has been put forward as a possible biomarker of the underlying neural face processing deficits in individuals with ASD (61). However, standard ERP techniques are seriously limited in objectively defining components in the time domain and quantifying responses of interest at the individual subject level (121). Moreover, observed group differences in N170 latency and/or amplitude could merely reflect a slower general processing of social stimuli in individuals with ASD (44, 116, 121), or they could be caused by carryover effects from changes in the amplitude and/or latency of the immediately preceding P100 component (122). In addition, atypicalities in this ERP component (i.e., delayed and/or reduced response) may not be autism-specific: similar atypical N170 responses have been observed in other neurological and psychiatric disorders, in particular in primary psychosis, hence, possibly rather indicating facial expression processing dysfunction as a symptom of these diagnoses, than a disorder-specific deficit (58).

To meet some of the methodological limitations of the standard ERP approach, a novel fast periodic visual stimulation frequency-tagging EEG approach was recently introduced in the autism field [see (123) for a review]. This novel tool offers great advantages in terms of objectivity in the identification and quantification of selective responses of interest in the frequency domain of the EEG spectrum, as well as high sensitivity (i.e., high signal-to-noise ratio). A pioneering study by Van der Donck et al. (124, 125) applied a frequency-tagging EEG oddball paradigm to assess the neural sensitivity for rapid changes in emotional expressions, revealing reduced neural discrimination responses for fearful and angry faces in children with ASD and predicting clinical status with an 87% accuracy at the individual level.

Although the previously described findings provide insights in the underlying neural nature of facial expression processing difficulties in ASD, multimodal imaging (i.e., integrating imaging methodologies) might advance our understanding of these mechanisms even further. In recent years, this powerful approach has increasingly been applied to study the main characteristics of ASD (126, 127). However, to date, the number of studies investigating facial expression processing in ASD using multimodal imaging is limited [for example, see Corbett et al. (128)]. In particular, complementing EEG and fMRI face processing studies with white matter structural connectivity diffusion-weighted MRI tractography might be a promising avenue for ASD research, as reduced white matter integrity has been observed in the occipito-temporal cortex (129) and specifically along the inferior longitudinal fasciculus (130, 131), a tract which is crucially involved in neural face processing. Altogether, despite the inconsistencies in the neuroimaging literature regarding facial expression processing in individuals with and without ASD, overall, both fMRI and EEG findings seem to indicate a differential, possibly reduced, facial expression processing ability in individuals with ASD.

Facial Expression Processing in Primary Psychosis

Behavioral Findings

In contrast to the mixed and inconsistent findings of behavioral facial expression processing in ASD, behavioral studies have consistently reported social cognition deficits in individuals with primary psychosis compared with healthy controls, including deficits in facial expression perception (27). Impaired facial expression perception in primary psychosis has been demonstrated across a variety of tasks, including emotion identification and higher-level social judgments, and is especially apparent for negative emotions. Moreover, these deficits are present early in the course of psychosis, as they have been reported in first-episode psychosis, and have been related to functional outcomes (27, 132).

fMRI Research

Overall, individuals with primary psychosis have been shown to display hypoactivity along the core face processing network, more specifically the fusiform gyrus, as well as structural abnormalities and hypoactivity along the extended face processing network. Furthermore, there is evidence of some compensatory hyperactivity along areas that do not typically belong to the social brain network.

During facial expression perception, individuals with primary psychosis display reduced activity in early visual processing regions, the amygdala/hippocampal region, anterior cingulate cortex, dorsolateral frontal cortex, and medial frontal cortex. A recent meta-analysis revealed decreased activity in two clusters during facial expression processing: one extensive cluster including the right ventrolateral prefrontal cortex, cingulate, insula, amygdala, thalamus, caudate, lentiform nucleus, and putamen and a cluster with the anterior and middle cingulate cortex (133). Similarly, Kret and Ploeger (134) described reduced activity in the fusiform gyrus, amygdala, and basal ganglia, as well as a reduced functional connectivity between the amygdala and precuneus and temporo-parietal lobe. Activity in the bilateral fusiform gyrus and right superior frontal gyrus is also significantly impaired in individuals with primary psychosis (135). These findings seem to depend on task demands however, as, for instance, hypoactivation in the fusiform gyrus is mainly found during implicit tasks (136). Yet, atypical amygdala activity is reported both in implicit and explicit tasks, indicating a robust impairment in individuals with primary psychosis (135).

Pertaining to atypicalities in amygdala functioning, functional differences during facial expression processing have consistently been reported, especially in response to negative emotions, yet the reported direction of these abnormalities is highly inconsistent. Whereas meta-analyses have mainly demonstrated reduced amygdala activity (133–135), some studies also revealed increased amygdala activity in individuals with primary psychosis (137).

These inconsistent results in terms of hypo- vs. hyperamygdala activity can be explained by differences in the applied baseline contrast used to calculate responses to expressive faces, i.e., whether expressive faces are contrasted

vs. a neutral face or whether they are contrasted vs. a nonface baseline. In line with the aberrant salience hypothesis (138), it is hypothesized that individuals with primary psychosis assign too much emotional salience to neutral stimuli, thus also to neutral faces (136). Studies assessing neural activity in response to neutral faces have indeed found increased activity in amygdala, as well as in prefrontal, cingulate, and parahippocampal regions, in individuals with primary psychosis as compared with healthy controls (137, 139). Consequently, the relative hypoactivity in amygdala found in many studies assessing primary psychosis may well be a methodological artifact induced by contrasting expressive faces with faces with a neutral expression. This particular interpretation was corroborated by a formal meta-analysis of amygdala activation in individuals with primary psychosis, identifying methodological heterogeneity as an explanatory factor of the inconsistent findings (140). In general, bilateral amygdala activity in response to expressive faces was significantly reduced, but this hypoactivity was only apparent in studies using the expressive minus neutral face contrast. This finding suggests that the true difference in amygdala activity between individuals with primary psychosis and healthy controls might be an elevated amygdala response toward emotionally neutral stimuli rather than decreased activity to emotional faces (140).

In contrast to the underactivity in the emotion processing areas described above, individuals with primary psychosis often demonstrate increased activation in other areas not typically associated with facial expression processing. Recent reviews revealed increased activity in the left middle occipital gyrus, cuneus, left precuneus, inferior parietal lobule, precentral gyrus, right middle frontal gyrus, and dorsolateral prefrontal cortex (133, 134, 136). Hyperactivation in these areas could be interpreted as a compensatory mechanism for the disrupted neural activity during behavioral performance on explicit facial expression processing tasks in primary psychosis.

Generally, neural atypicalities during facial expression processing in individuals with primary psychosis are robust and have also largely been observed in individuals at high risk for psychosis (i.e., familial risk or high clinical risk) (141, 142). More specifically, abnormal functional activation in risk groups has been reported in the prefrontal cortex, anterior cingulate cortex, amygdala, and temporal cortex (141, 142). Notably, also reduced amygdala volumes have been found in individuals at risk of psychosis (137, 142, 143), emphasizing the role of amygdala alteration as a potential liability to developing primary psychosis in those risk groups.

EEG Research

As the occipito-temporally recorded N170 ERP component is regarded as the primary component of face processing, the majority of ERP research on facial processing in primary psychosis has focused on this component (63, 144). A smaller N170 amplitude in individuals with primary psychosis compared with controls when processing expressive faces has been reported (58, 63, 145), and this effect seems to be independent of method of component extraction (mean vs. peak amplitude) or task requirements. Similarly, individuals with primary psychosis display smaller N250 and P300 amplitudes than healthy controls (63, 145).

A recent review by Earls et al. (144) suggested that N170 alterations in facial expression processing in primary psychosis may however stem from deficits in earlier visual processing, as for instance indexed by the P100. Indeed, also the P100 component is sensitive to facial stimuli and already shows emotional modulation. Individuals with primary psychosis display reduced P100 amplitudes when processing facial stimuli, indicating early sensory processing deficits. This effect, however, seems to depend on the emotional valence of the faces, as the difference between primary psychosis and controls was limited to neutral and happy faces, not fearful faces (144). Interestingly, a recent study revealed selectively decreased P100 amplitudes in individuals with negative schizotypy for all facial expressions, while there were no group differences in N170 amplitude. This finding underscores the early visual processing impairment in primary psychosis and thereby questions to what extent neural alterations are specific for expressive faces (146).

In line with the fMRI findings, to date, it is unclear whether EEG atypicalities in primary psychosis are specific to the processing of expressive faces or whether they arise when processing faces in general (63). In this regard, Murashko and Shmukler (64) and Shah et al. (145) reported reduced N170 amplitudes in individuals with primary psychosis when processing neutral faces, and this N170 amplitude to nonemotional faces also correlated with social functioning.

Altogether, EEG research shows robust alterations in face processing in primary psychosis. The high temporal resolution of EEG indicates that face processing impairments in primary psychosis are evident in the earliest ERP components and persist throughout processing (63). Yet, in line with the fMRI findings, it is questionable to what extent these alterations are specific to facial expression processing and do not merely result from altered face processing *per se*. To dissociate these alternatives, EEG paradigms directly contrasting neutral and emotional facial expressions are needed. A particularly promising approach for this would be the administration of a fast periodic visual stimulation oddball frequency-tagging paradigm, as has been applied in ASD (124, 125). Thus far, this method has not been applied in primary psychosis, but it was recently administered in patients with velocardiofacial (22q11.2 deletion) syndrome, which is a well-known high-risk group for psychosis (147). Interestingly, this study revealed significantly reduced emotion discrimination responses in the patient group (in particular for anger, disgust, and sadness) while showing slightly increased general visual face processing responses. Moreover, the neural response magnitude to expression changes was inversely associated with the severity of positive symptoms, pointing to a potential endophenotype and/or biomarker for psychosis risk (147). In this regard, this study strongly points toward emotion-specific facial processing impairments in psychosis-prone individuals while also echoing the findings of increased neural salience of faces *per se*.

A large number of studies have evaluated facial expression processing in primary psychosis using either fMRI or EEG, thereby contributing to our understanding of the neural

nature of facial expression processing difficulties in this population. Nonetheless, multimodal imaging combining both methodologies is required to provide a deeper understanding of these mechanisms (148).

THE IMPACT OF ADVERSE CHILDHOOD EVENTS ON FACIAL EXPRESSION PROCESSING

ACE Alter the Broader Face Processing Network

Face perception is in part an innate process but is also guided by visual learning and extensive social experiences (28, 149). As pointed out by the social motivation theory of ASD, early-onset impairments in social attention and social reward may initiate a developmental cascade that may ultimately deprive children of adequate social learning experiences, thereby also impacting on the neural sensitivity for facial expression processing (100). In a similar vein, extreme environmental factors, such as ACE, can disrupt these normative developmental experiences and can have detrimental effects on the neural basis of facial expression processing (29). Especially, due to the prolonged maturation of brain areas involved in the face processing network, these social brain regions are particularly vulnerable for the impact of stress during childhood (150–152).

These alterations in neurocognitive systems are hypothesized to be adaptive for survival in the face of adversity (151, 152). More specifically, according to the latent vulnerability theory, children exposed to adverse experiences show heightened neurocognitive vigilance to threat, including the processing of threatening social cues such as angry facial expressions (153). Whereas this hypervigilance may be adaptive in early at-risk environments, it may lead to psychiatric difficulties later in life (151–153).

In the past decades, research has focused on the impact of ACE on brain development (154, 155), and several structural and functional changes have been identified in individuals with a history of ACE. Structural changes partially depend on the age at ACE exposure (152) and include reduced brain volume in hippocampus, anterior cingulate, dorsolateral prefrontal cortex, and orbitofrontal cortex, amygdala alterations, and reduced white matter fiber tract integrity (151, 152). As can be expected based on the psychological impact of ACE and the involved structural alterations, ACE may alter behavioral face processing performance. More specifically, a majority of studies report deficits in facial expression recognition of both positive and negative emotions in children with a history of ACE. Furthermore, individuals with ACE exposure are more reactive toward negative expressions, especially anger, as they require lower levels of emotional intensity to recognize anger (156).

In terms of functional alterations, the most consistent observation is the increased responsivity of the amygdala in individuals with a history of ACE. Amygdala hyperactivity in response to expressive faces, especially threatening faces, has consistently been found in both children and adults with a history of ACE (157, 158). This finding is independent from psychiatric diagnosis, indicating that this hyperactivity may be inherent to the experience of adversity in itself (151, 152). Similar to behavioral studies, this hyperactivity suggests increased awareness for social threats and emotional sensitivity.

A recent meta-analysis by Hein and Monk (150) revealed significantly increased activation in the bilateral amygdala, right superior temporal gyrus, bilateral parahippocampal gyrus, and right insula in individuals with a history of ACE. Children and adolescents, but not adults, additionally show increased activity in the left lentiform nucleus and globus pallidus. In line with the behavioral studies indicating hypervigilance for negative or threatening emotions, this increased activation might facilitate rapid identification of threatening stimuli (150). Focusing specifically on individuals with a history of neglect, a recent review by Doretto and Scivoletto (29) revealed amygdala hyperactivity when processing fearful, angry, and sad faces, as well as greater hippocampal and ventromedial prefrontal cortex activation in response to fearful faces.

Pertaining to functional connectivity, increased functional communication in the fronto-limbic circuitry was reported in adults with a history of ACE performing an emotion-matching task. In particular, increased connectivity of the amygdala toward the orbitofrontal cortex, ventrolateral prefrontal cortex, dorsomedial, and dorsolateral prefrontal cortex, and hippocampus has been shown (159).

EEG research also shows substantial differences in individuals exposed to ACE compared with unaffected control populations. On the one hand, reduced face-specific ERPs (i.e., P100, N170, and P400) are observed in children exposed to extreme psychosocial deprivation in institutional rearing when processing faces, regardless of the displayed expression (157). One longitudinal study assessed facial expression processing in institutionalized vs. family-reared children at baseline (i.e., between the age of 5 and 31 months) and 30 and 42 months old (160). Institutionalized children displayed reduced ERPs at baseline compared with family-reared children. Furthermore, children that are placed into foster care following institutionalization had intermediate ERP amplitudes and latencies compared with institutionalized and family-reared children at 30 and 42 months. On the other hand, increased ERP amplitudes, indicative of social hypervigilance, are observed in individuals with an effective history of ACE. A review by da Silva Ferreira et al. (156) revealed that a majority of studies found higher ERP amplitudes in response to angry faces in maltreated children. Some studies in individuals with a history of ACE also revealed larger N170 amplitudes when processing any type of expressive faces. Remarkably, this increased amplitude was not limited to negative emotions, indicating increased vigilance during facial expression processing irrespective of the valence of the facial expression (161). Similarly, adults with a history of interpersonal childhood adversity fail to show a reduced N170 amplitude toward subconscious happy relative to angry faces, again suggesting hypervigilance toward expressive faces and a failure to differentiate between threatening and nonthreatening stimuli (162).

Altogether, the findings reported above indicate robust altered facial expression processing in children, adolescents, and adults with a history of ACE. Considering the characteristic general

facial expression processing difficulties in individuals with ASD and primary psychosis, and given the substantially increased prevalence of ACE in these particular populations, we may contend that a history of ACE in these individuals might even further hamper and complicate face processing skills in these populations and add to the reported inconsistencies in the literature. In the following, we will briefly explore the sparse literature discussing the impact of ACE on social processing in individuals with ASD and/or primary psychosis.

Increased Prevalence of ACE in Individuals With ASD

Youth with developmental disabilities, such as ASD, have 1.5 to 3 times more chance of encountering ACE than their peers (17) and are twice as likely to experience four or more different types of ACE (14). Especially their sociocommunicative characteristics (e.g., difficulties with emotional insight and information processing, mental rigidity, etc.), as well as their predisposition for experiencing large levels of familial stress, make them more susceptible to ACE (18). Despite the increased vulnerability of individuals with ASD for trauma, literature on the association between ASD and ACE is still in its infancy (18, 163). One factor that may contribute to the lack of studies investigating this association is the overlap in diagnostic criteria for ASD and posttraumatic stress disorder (1), hampering the identification of trauma in individuals with ASD (17, 163). For example, individuals who experienced ACE may struggle with social interactions, may display hyperarousal to sensory stimuli, and may show circumscribed interests and reduced affect, which are all core symptoms of ASD. In light of these similarities, it is not surprising that a history of ACE has been found to be related to a delay in ASD diagnosis (14).

Probably because this research field is still emerging, we could not find any study investigating behavioral or neural facial expression processing in individuals with ASD and a history of ACE. Nevertheless, as pointed out in the discussion, integration of both research fields might be highly elucidating, in particular because investigation of the counteracting effects on facial expression processing (e.g., amygdala hypoactivation in ASD and hyperactivation in ACE) could possibly clarify some of the existing inconsistencies in the field.

The Impact of Comorbid ACE and Primary Psychosis on Facial Expression Processing

Primary psychosis develops as a result of a complex interplay between genetic and environmental factors, including childhood adversity (164). ACE are associated with a two- to fourfold increased risk of primary psychosis, and the prevalence of ACE in individuals with primary psychosis is consistently higher than in the general population (15, 165, 166). Furthermore, exposure to ACE is higher and more severe in individuals at ultra-high risk of psychosis, with prevalence rates ranging from 54 to over 90% (167). Several studies have shown a dose–response relationship between the severity of ACE and the severity of (positive) psychotic symptoms such as hallucinations and delusions, suggesting a causal association between ACE and primary psychosis (15, 16, 166, 168).

Despite consistent evidence of the impact of ACE on facial expression processing, despite the large comorbidity between ACE and primary psychosis, and despite the potential confounder of this comorbidity for findings on facial expression processing in the psychosis literature, only a limited number of studies have assessed facial expression processing in individuals with psychosis and a history of ACE. At the behavioral level, Mrizak et al. (169) showed that adults with primary psychosis and a high exposure to ACE perform significantly worse on facial emotion recognition tasks compared with adults with primary psychosis without a history of ACE. Furthermore, the authors suggested that the type of abuse could be associated with specific emotion recognition deficits. In particular, in this study, sexual abuse was associated with poor recognition of anger and disgust, and emotional abuse and physical neglect were associated with poor recognition of happy and sad faces (169).

Aas et al. (170) applied fMRI to assess neural activation during a facial expression processing task in individuals with primary psychosis with vs. without ACE exposure. Patients with higher ACE exposure displayed a relatively stronger neural activation in response to negative expressions (i.e., angry and fearful faces) in the right lateral occipital cortex (i.e., fusiform gyrus), middle temporal gyrus, angular gyrus, and supramarginal gyrus. As such, individuals with primary psychosis and a high ACE exposure might show an activation pattern closer to that reported in healthy individuals, yet no comparison with healthy controls could be made in this study. Nonetheless, this difference in neural activation between individuals with high and low ACE was associated with poorer daily life functioning. Behaviorally, individuals with primary psychosis and high ACE exposure evaluated negative faces as more negative, and positive faces as less positive than those with low ACE exposure (170).

Pertaining to EEG findings, Gong et al. (146) presented expressive (i.e., happy, angry, fearful, and disgusted) and neutral faces to individuals with high and low levels of negative schizotypy with and without a history of ACE using a dot-probe task. Individuals with negative schizotypy and a history of ACE displayed a longer P100 latency independent of emotion, indicating a general dysfunction of the visual pathway. This study found no differences in P100 amplitude nor in N170 amplitude and latency.

In sum, ACE seem to alter facial expression processing impairment in individuals with primary psychosis. On the one hand, Aas et al. (170) reported increased neural activation in response to negative faces in individuals with primary psychosis and a history of ACE. On the other hand, individuals with negative schizotypy and ACE exposure have a longer P100 latency to faces, revealing a general dysfunction in visual processing (146). More research is needed to elucidate the relation between ACE, primary psychosis, and facial expression processing.

DISCUSSION

The aim of this narrative review was twofold: we aimed to (i) provide a concise overview of the currently reported neural commonalities and differences in individuals with ASD and primary psychosis when processing expressive faces and (ii) explore and provide insight into how ACE might influence facial expression processing in ASD and primary psychosis.

Altered Neural Facial Expression Processing in ASD and Primary Psychosis

Although the neuroimaging literature on facial expression processing in ASD appeared to entail many more inconsistencies in comparison with the literature on primary psychosis, both disorders show altered neural facial expression processing as compared with healthy controls. Indeed, individuals with ASD, as well as individuals with primary psychosis, activate the same brain regions as healthy controls during facial expression processing, albeit to a significantly lesser and/or different extent (133–135, 171). Overall, when compared with healthy controls, individuals with ASD and individuals with primary psychosis mainly display altered activation in the fusiform gyrus and amygdala as well as altered connectivity among the broader face processing network, probably indicating reduced facial expression processing abilities.

Reduced activation in the fusiform gyrus—and indirectly also atypical amygdala functioning—might be associated with delayed or reduced N170 responses, often reported in individuals with ASD (61) or primary psychosis (58, 63, 145), respectively, as this ERP component is mostly recorded over occipito-temporal sites where the fusiform gyrus is located. Studies assessing facial expression processing using multimodal imaging (i.e., integrating imaging methodologies) are invaluable to enhance our understanding of the neural underpinnings of facial expression processing in ASD and primary psychosis.

In addition to reduced activity in the fusiform gyrus, also altered activity of the amygdala is generally found in ASD and primary psychosis. According to the amygdala theory of autism (95), atypicalities in the amygdala (such as the observed hypoactivation) are at the root of the social deficits characteristic for ASD. Similarly, the severity of blunted affect (i.e., one of the negative symptoms) has been found to be associated with amygdala activation during facial expression processing in individuals with primary psychosis (172). However, the reduced amygdala activation in primary psychosis vs. healthy controls is mostly found when expressive faces are contrasted to neutral faces (136, 137, 139) and potentially results rather from an enhanced brain response to neutral faces, than a decreased response to expressive faces (140). This aligns with the aberrant salience hypothesis, stating that salience is attributed to irrelevant stimuli (here, neutral faces), which then attract more attention (138). Whereas individuals with primary psychosis might thus attribute too much salience to socially irrelevant stimuli, thereby masking the salience of truly relevant social stimuli, individuals with ASD show an overall reduced tendency to orient to social stimuli [social motivation theory; (100)].

Experiences Tuning the Brain Toward Social Signals: the Case of ASD and Primary Psychosis

As the progressive tuning of the neural system involved in facial expression processing (30, 42) is enhanced by social experiences (173), deprivation of social interaction might hamper further specialization of this system. Hence, in ASD, the reduced tendency to orient to social stimuli and/or to participate in social interactions (174) might hamper acquirement of the facial expression processing experiences necessary for typical maturity of these abilities and of this neural system. Likewise, in primary psychosis, the progressive decline in face processing abilities with increasing age and increasing illness duration [(64, 132); but see (27)] may partially result from the progressive social withdrawal typical for this population.

Additionally, both in ASD and primary psychosis, the maturation of facial expression processing abilities—and, thus, the activation of the corresponding brain regions—might be hampered by deficits in general visual perception (175), as difficulties in emotion processing may occur when one fails to inspect the most relevant facial cues (176). Indeed, similar to ASD [e.g., (177, 178)], neuroimaging and eye-tracking studies in individuals at risk of psychosis and those with primary psychosis have revealed more local and fragmented processing of faces as well as avoidance of crucial face areas such as the eyes, nose, and mouth [e.g., (179)].

Experiences Tuning the Brain Toward Social Signals: the Case of ACE

With the exception of studies assessing the impact of neglect and extreme social deprivation, which results in a uniformly blunted response for all socioemotional cues (157, 160), the majority of studies investigating the impact of ACE clearly show an increased sensitivity for facial expressions, in particular negative emotions such as anger and fear (156, 161). At the neural level, this hypervigilance for social cues signaling a potential threat seems to be driven by a hyperactive amygdala, which may continuously alert and arouse the broader social brain through a hyperexpressed functional connectivity (150, 151). As a result, and somewhat in line with the aberrant salience hypothesis in primary psychosis (138), too much undifferentiated salience is attributed to any social signal, thereby impeding a more thorough and fine-grained discrimination between social cues. However, to our knowledge, only one study assessed facial expression processing in individuals exposed to adversity and followed them up longitudinally (160). Longitudinal studies are crucial to draw strong conclusions regarding the causal effects of ACE on facial expression processing.

The robust effects of ACE on facial expression processing may be reversible to some extent if early intervention, such as good rearing circumstances, is applied. For instance, children that were reared in institutions but eventually placed in good foster care had intermediate P100, N170, and P400 amplitudes as compared with institutionalized and family-reared children (157, 160). Likewise, there is emerging but still highly conflicting evidence for the neuroplasticity of facial expression processing abilities in

ASD and primary psychosis via social cognition training or via targeted expression processing [(180–184); but see (185)]. Yet, it remains questionable to what extent this training may generalize to daily life face processing and may effectively improve social functioning outcomes.

Need for Integrative Studies Across Multiple Clinical Conditions

As stated previously, ASD and psychosis represent spectrum disorders with a considerable epidemiological, phenotypical, and neural overlap. Likewise, individuals with ASD, as well as individuals with primary psychosis, have a much higher chance to encounter ACE as compared with their peers. Against this background, it seems imperative to design studies that explicitly contrast the three clinical conditions or that at least control for comorbidity and/or presence of dimensional (sub)clinical characteristics. This is *a fortiori* the case for facial expression processing research, as it yields atypical findings among the three populations, but with distinctive flavors in each of the particular populations. Such an approach might eventually also account for some of the inconsistencies and confound reported in the field.

Thus far, only very few studies directly contrasted facial expression processing in individuals with ASD vs. individuals with primary psychosis, or in individuals with primary psychosis with vs. without a history of ACE. To our knowledge, no face processing studies accounted for the presence of ACE history in individuals with ASD.

Direct comparisons of facial expression processing in samples with ASD vs. samples with primary psychosis are scarce. In general, individuals with primary psychosis tend to perform slightly better than individuals with ASD on behavioral face processing tasks, yet this group difference seems to decline with increasing age [(22, 175); but see a recent study by Pinkham et al. (186)]. Probably, this decreasing group difference with age can be understood as follows: on the one hand, because increasing age and thus illness duration may be associated with more severe impairment in primary psychosis; on the other hand, because more learning experiences due to increasing age may ultimately improve facial expression processing in adults with ASD.

The few studies investigating facial expression processing in individuals with primary psychosis with vs. without a history of ACE show mixed results. On the one hand, an enhanced neural processing of negative stimuli [i.e., increased brain activity; (170)] has been reported, but this does not seem to translate in improved behavioral processing. Indeed, behaviorally, individuals with primary psychosis, and a history of ACE perform significantly worse on emotion recognition tasks than adults with primary psychosis without ACE exposure (169). This pattern may suggest that ACE may further boost the general aberrant salience in primary psychosis, thereby causing overarousal and impeding a differentiated behavioral facial expression processing performance. On the other hand, the single study assessing ERPs in individuals with primary psychosis and a history of ACE revealed a longer P100 latency when viewing expressive and neutral faces, suggesting a larger deficit in visual processing (146).

Altogether, these few studies may suggest an additional aggravating effect of ACE on facial expression processing impairments in primary psychosis. Thus far, no studies investigated facial expression processing in ASD while accounting for individual differences in ACE experiences. However, given the opposite and possibly counteracting pattern of neural atypicalities, with reduced neural responses toward especially negative emotional expressions in ASD and enhanced neural responses toward especially negative and threatening facial expressions in individuals with a history of ACE, this integrative approach would be particularly informative. Eventually, it may possibly account for the large interindividual heterogeneity in the autism population and may explain (part of) the observed inconsistencies across studies.

Preferentially, these future studies should not only incorporate interindividual variability and comorbidity of the target populations but should also account for variability in research methods and designs, as these may also partially account for the differences and inconsistencies encountered in the neuroimaging literature. Task demands, for example, have been found to influence neural responses. Indeed, differences in facial expression processing in healthy controls vs. individuals with ASD (75) or primary psychosis (179) have most frequently been reported when tasks are more demanding, or when tasks involve implicit automatic processing instead of explicit facial expression processing (102, 108, 136). Furthermore, stimulus characteristics, such as the intensity of the expressions (83, 96), familiarity of the faces (109), or the use of static vs. dynamic expressions (54), have also been found to modulate the neural responses and may therefore differentially impact on individuals with different clinical status.

The Unfulfilled Search for a Selective Biomarker of Facial Expression Processing Impairments and/or Socioemotional Dysfunctioning

Overall, individuals with ASD or primary psychosis display impairments in facial expression processing, both at a behavioral and at a neural level. This has led researchers to suggest that impaired facial expression processing may be a vulnerability marker for primary psychosis (27) or ASD (61). In the past decades, greater affordability and accessibility of noninvasive brain imaging techniques have led to an intense quest for an objective brain-based biomarker that could predict risk, support clinical diagnosis, or monitor treatment effects (138, 185, 187). This urge is particularly strong in the field of neurodevelopmental disorders, such as ASD, in which standardized behavioral assessment options are often limited and access to clinical expertise is not always readily available.

Against this background, the N170 ERP component has often been put forward as a promising biomarker, both within the psychosis literature (27, 58) and within the ASD research field (61), and often largely independent from each other. Multiple reports have indeed suggested that N170 amplitudes are generally smaller and latencies slower regardless of psychiatric disorder. Accordingly, the N170 component has been proposed to index

impairments in the extraction of facial expression information, an impairment that is common across disorders and could be related to social functioning (58).

However, it should be noted that the N170 is a very rough index that is not specific for facial expression processing and that lacks specificity, objectivity, sensitivity, and reliability, as pointed out in a number of recent reports (121, 147, 185, 188). Most importantly, the N170 does not consistently categorize individuals and does not measure a specific impairment (facial expression processing) related to a specific clinical profile (e.g., ASD). Moreover, disentangling the specific neural response to the facial expression from the general neural face processing response is challenging, especially since deficits in general (neutral) face processing have also been reported in both ASD (177, 189) and primary psychosis (64, 145, 179). Accordingly, and in spite of many studies claiming otherwise [e.g., (58, 61)], it is highly questionable whether the N170 may ever fulfill its promise of being a sensitive biomarker for aberrant socioemotional sensitivity and definitely not for disorder-specific dysfunction [e.g., (121, 185, 190)].

In the past years, an alternative EEG approach, called fast periodic visual stimulation frequency-tagging EEG, has been put forward, yielding promising findings pinpointing selective facial expression processing impairments in individuals with ASD (124, 125) and primary psychosis (147). This novel approach reveals an objective, selective, reliable, and behavior-free signature of impaired visual coding of facial expression, implicitly quantified from brain activity with high signal-to-noise ratio at the individual subject level. Given the strength of the obtained effects, the implicit nature, the rapid application, and straightforward analysis, this novel tool may open avenues for clinical practice, potentially providing a biomarker for individual assessment of aberrant socioemotional sensitivity across syndrome boundaries.

Future integrative multipopulation studies looking into the associations of aberrant facial expression processing among ASD and primary psychosis, and the modulating impact of adverse childhood events, might benefit of incorporating this pioneering frequency-tagging EEG approach.

LIMITATIONS

With this narrative review, we hope to have identified the gaps and inconsistencies in the existing literature on facial expression processing in ASD and primary psychosis, and the possible impact of ACE upon this, which could encourage and inspire future researchers to further investigate this topic. While we aimed to cover this field in a comprehensive manner, the possibility of a subjective selection bias cannot be fully excluded. In addition, given the extensiveness of the literature on facial expression processing in ASD and primary psychosis, we specifically focused on behavioral emotion processing and on neural activity and connectivity patterns as investigated via EEG and fMRI.

AUTHOR CONTRIBUTIONS

CS and SV wrote the first draft of the manuscript. RW and BB provided thorough feedback to the first draft. All authors contributed to manuscript revision and approved the submitted version.

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Social Cognition and Friendships in Adolescents With Autistic-Like Experiences and Psychotic-Like Experiences

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Autism spectrum conditions (ASC) and schizophrenia spectrum conditions (SSC) are both characterized by changes in social-cognitive functioning. Less is known about the overlap and the differences in social-cognitive functioning when comparing individuals with subclinical levels of ASC and SSC, while studies in non-clinical samples have the benefit of avoiding confounds that are present in clinical groups. Therefore, we first examined how autistic-like experiences, positive psychotic-like experiences and the co-occurrence of both correlated with the performance on an extensive battery of social cognition tasks in young adolescents. Second, we examined the effect of autistic-like experiences, psychotic-like experiences and their co-occurrence on friendships in daily life. A total of 305 adolescents (*M*age = 12.6, *sd* = 0.4, 147 boys) participated in the current study. A battery of social cognition tasks, comprising the Reading the Mind in the Eyes task, Dot perspective task and trust game were individually administered in a classroom setting, along with a friendship peer nomination questionnaire. Results indicated no evidence for a relationship between the performance on the social cognition battery and subclinical experiences of autism and/or psychosis. However, results did show that the amount of autistic-like experiences of adolescents were associated with being less often selected as a friend by their peers. By contrast, no relationship between self-reported friendships and autistic-like experiences was found. Neither a relationship between friendships and psychotic-like experiences was reported. This study provides initial evidence that information provided by peers may shed light on (altered) social behavior associated with autistic-like experiences that is not apparent on performance measures, as well as elucidate possible differences between autistic- and psychotic-like experiences.

Keywords: autistic-like experiences, psychotic-like experiences, social cognition, friendships, non-clinical samples

INTRODUCTION

Both autism spectrum conditions (ASC) and schizophrenia spectrum conditions (SSC) are neurocognitive conditions characterized by altered social-cognitive functioning. Since their early conception, much attention has been paid to describing the overlap and differences between ASC and SSC (1, 2). Both conditions and their subclinical expressions are related to a decrease in social or emotional understanding, difficulties during social interactions and problems in interpersonal relationships (3–6). Research in non-clinical populations may help to further elucidate the nature of difficulties in social functioning and the relationship between the two conditions (7). Adolescence is a particularly interesting period for this research, as this phase is characterized by extensive changes in social cognition (8) and by significant increases in the prevalence of psychopathology (9, 10). Furthermore, altered social functioning in non-clinical samples may impact peer relations, which typically increase in quantity and in meaning during adolescence (11). Therefore, the first aim of the current study was to examine the overlap and differences between autistic-like experiences and psychotic-like experiences on a battery of social cognition tasks in young adolescents. Secondly, we tested how subclinical experiences impact adolescent friendships within the classroom. The study was conducted in a non-clinical sample, which avoids confounds that may arise in clinical groups, for example use of medication, differences in attention and motivation which can impact the performance on cognitive tasks, and the presence of comorbidities or interacting cognitive difficulties (7).

Studies on social cognition in clinical samples have demonstrated altered Theory of Mind (ToM) abilities in both ASC (12, 13) and SSC (14). Theory of mind is the ability to understand that people have their own mental states, such as thoughts and desires, and that these affect behavior (13). There is evidence for other social-cognitive dysfunctions as well. A recent meta-analysis revealed similarly decreased performance between ASC and SSC on measures of emotion recognition, emotional intelligence, social skills and ToM abilities (15). The only differences between the groups were found on tasks of facial emotion perception, where those with SSC outperformed those with ASC. A number of studies have examined the social-cognitive changes associated with either ASC or SSC phenotypes in non-clinical groups (16–20). Most findings support the suggestion that those with subclinical experiences have similar (though milder) difficulties in social interactions to those who have been diagnosed with either condition. Thus, poorer ToM, emotion recognition and social skills have been associated with higher levels of autistic-like experiences (17, 20–22) and psychotic-like experiences have been associated with decreased ToM performance in adolescents and adults (16, 18, 19, 23). According to a recent meta-analysis ToM difficulties are related to both positive and negative psychotic-like experiences (24).

Evidence from non-clinical samples suggests that childhood autistic-like experiences are associated with psychotic-like experiences during adolescence [(25, 26), mean age of both studies was 12 years]. Little is known about the co-occurrence of autistic-like experiences and positive psychotic-like experiences in relation to social cognition. In a previous study, perspective-taking skills in a non-clinical young adult sample (mean age 21) were examined (27). Results showed that having either autistic-like experiences or psychotic-like experiences was associated with increased perspective-taking errors, but this effect was reduced in the group with a combination of both high autistic tendencies and high psychosis proneness. The performance of the latter group was similar to that of those with low autistic tendencies and low psychosis proneness (27). These findings provide initial support for the diametric model, which suggests that the relationship between ASC and SSC can be viewed as that ASC and SSC are on opposite extremes of a social-cognition continuum, in which social-cognitive skills are underdeveloped in ASC and overdeveloped in SSC (2, 28). According to the diametric model, having both subclinical symptoms of ASC and SSC may result in typical levels of performance as these may have an ameliorating effect on one another (2, 28). These results emphasize the importance of examining the co-occurrence of ASC and SSC symptoms.

It has been suggested that differences in social and communication skills between those with and without autistic-like experiences make it more challenging to foster and maintain friendships (5). Studies have shown that having autistic-like experiences is related to a poorer quality of friendships and to fewer friendships (5, 6). Having psychotic-like experiences that consist of unusual beliefs about other people (such as being persecuted) can make someone reluctant to socialize with others (3). A study has shown that having psychotic-like experiences is associated with having problems in peer relationships (3). Early adolescence is a critical period for social development, during which peers become increasingly important and friendships are formed (29). As adolescents spend a substantial amount of their time at school, the classroom is an important social environment for the formation of friendships. These social relationships can be examined using social network analysis in which both the adolescent and their classmates report on their friendships. This method accounts for the adolescent's own view on their friendships, but also asks their peers to report these relationships. As mentioned by Wainer et al. (6), relying solely on self-report data when examining associations between subclinical experiences and friendships may result in biased results (commonly referred to as common-method variance), and therefore peer report data may add valuable, and possibly new, insights. Social network analysis provides a measure that indicates the number of peers a person selects as friends (outgoing ties: one's own perspective) and how many peers select the person as a friend (incoming ties: peer's perspective).

In the current study, 305 young adolescents were tested on a battery of social cognition tasks combined with measures of their social relationships within their classroom. First, we examined how young adolescents with autistic-like experiences, with positive psychotic-like experiences and with the co-occurrence of both perform on social cognition tasks, specifically visual perspective taking (the Dot perspective task), mental state recognition (the Reading the Mind in the Eyes task), and interpersonal trust (the trust game). We expected a negative association between autistic-like experiences and performance

on social cognition tasks and between psychotic-like experiences and performance on social cognition tasks. Based on the results of the study of Abu-Akel et al. (27), we investigated if the co-occurrence is related to better performance on social cognition tasks compared to high levels of either autistic-like experiences or psychotic-like experiences, as the combined traits would have an ameliorating effect on one another, supporting the diametric model. Second, we examined the effect of autistic-like experiences, psychotic-like experiences, and the co-occurrence of both on friendships in the classroom setting. For both autistic-like experiences and psychotic-like experiences we hypothesized a negative association with the number of friendships (for both outgoing ties and incoming ties).

METHODS

Participants

Participants in the current study were taken from wave 1 and wave 2 of the second cohort of the longitudinal #SOCONNeCT project. A total of 647 adolescents provided written informed consent before the start of wave 1 of the #SOCONNeCT project. Data collection within the #SOCONNeCT project consisted of six waves, twice per school year, starting in the first year of high school. Participants were recruited from eight high schools across The Netherlands. All participants were enrolled in the senior general secondary educational track or a pre-university educational track, which constitute the higher tracks within the Dutch education system (top 40% of pupils based on academic achievement). Participants from the larger sample were included in the analyses of the current study if they were in classes where a minimum of 70% of pupils participated and had complete data on all relevant variables, that is the Diagnostic Interview for Children (DISC-C), the Autism Symptom SElf-ReporT for adolescents and adults (ASSERT), the Reading the Mind in the Eyes task (RMET), the Dot perspective task, the trust game, the Raven's Progressive Matrices (SPM), and the urbanization and SES measures. A minimum of 70% participants within a class is advised to create reliable social network positions, although this cut-off is under continuous discussion (30, 31). From a total of 33 classes, 15 met the 70% cut-off rate. Based on these criteria 305 participants (Mage $= 12.6$, $sd = 0.4$, 147 boys) were included in the final sample. Schools received €7.50 per participating pupil per wave to use for a class activity. The #SOCONNeCT project was approved by the Scientific and Ethical Review Board of the Faculty of Behavioral and Movement Sciences of the Vrije Universiteit Amsterdam.

Procedure

Both the participant and the parent(s)/caregiver(s) of the participant gave active informed consent (either via e-mail or a printed version) for participation in the #SOCONNeCT project. Pupils and parents were contacted via schools and informed about the project with a letter and an information evening in which the aims and the procedure of the project were explained. To make sure the participants understood the protocol of the study and the research aims, data collection started with an extensive explanation of what research entails and on the rights that participants have. Every participant then signed an informed consent.

Data collection was done at school under supervision of researchers and trained research assistants and lasted about 90 min, including classroom explanations and the administration of tasks and questionnaires not analyzed in the current study. To make sure participants understood the questionnaires and tasks, the explanation was adjusted according to feedback received by several focus groups of adolescents. Also, the researchers covered frequently asked questions that were created after discussion with the focus groups (these questions were mostly about what research is, and whether the research was part of the education curriculum of their school). Furthermore, for the trust game a joint, extensive explanation was given beforehand. Then, on a laptop, each participant individually had to answer multiple questions about the method of the game correctly before the participant was able to start the game. The Dot perspective task started with 10 practice rounds (five per block) and these were repeated until the correct answer was given. Afterwards, a researcher or research assistant went by every participant individually to make sure the method of the game was clear and only then, the participant was able to start the task. Furthermore, throughout data collection participants were given the opportunity to ask questions to the researchers at all times. Each participant completed the tasks and questionnaires individually on a laptop and on an iPad provided by the researchers. All materials that were administered on laptops were tested and validated on laptops during the focus groups and the same was true for the materials that were administered on iPads. The RMET, the Dot perspective task, the trust game, the peer nomination questionnaire and the urbanization and SES measures were administered in wave 1 and the DISC-C, the ASSERT and the SPM were administered in wave 2. Wave 1 and wave 2 were administered within the same school year (∼6 months apart).

Materials

Diagnostic Interview for Children (DISC-C)

Four items from the self-report DISC-C (schizophrenia section) (32) were used to assess subclinical positive psychotic-like experiences which could be answered with "yes" or "no": (1) "Some people believe in mind reading or being psychic. Have other people ever read your mind?", (2) "Have you ever had messages sent just to you through television or radio?", (3) "Have you ever thought that people are following you or spying on you?", (4) "Have you ever heard voices people cannot hear?" (33). The sum score on the DISC-C was used as an indication of psychotic-like experiences (range 0–4). The items were administered in Dutch (34) using an iPad. A longitudinal study showed that the four items at age 11 predicted the presence of adult psychosis at age 26 (33).

Autism Symptom SElf-ReporT for Adolescents and Adults (ASSERT)

The self-report ASSERT questionnaire was used to assess subclinical autistic-like experiences (35). The ASSERT consists of seven items on a three point scale ("not true", "somewhat true",

and "certainly true"): (1) "Do you find it difficult to socialize with, or get in touch with people, especially people of your own age?", (2) "Do you prefer to be alone rather than being together with other people?", (3) "Do you have difficulties perceiving social cues?", (4) "Do other people tell you that your behavior or your emotional responses are inappropriate or hurtful?", (5) "Do you have a strong interest or hobby that absorbs so much of your time that it hampers other activities?", (6) "Do you or do other people feel that you have very set routines or that you are very immersed in your own interests?", (7) "Do you or do other people feel that you impose your routines or interests on others?". The sum score on the ASSERT was used as indication of autistic-like experiences (range 0–14). A previous study found that the validity of the ASSERT as a screening instrument for the diagnosis ASC in adolescents was good (sensitivity of 0.80 and specificity of 0.86 for scores ≥8) (35). The items were translated to Dutch by a bilingual native Dutch/English speaker (including back translations and discussion of possible uncertainties) and administered using an iPad.

Reading the Mind in the Eyes Task (RMET, Child Version)

The child version of the RMET questionnaire consisted of 28 pictures and was used to examine mental state recognition (36). Each picture displays human eyes surrounded by four words describing mental states. The participant was asked to choose which word best described the expression of the human eyes. The items were translated to Dutch by a bilingual native Dutch/English speaker (including back translations and discussion of possible uncertainties). To analyze the effect of autistic-like experiences and psychotic-like experiences on mental state recognition skills, a sum score of correct trials on the RMET questionnaire was calculated. The RMET was administered on an iPad and took 10 min to complete. A previous study found that the validity and reliability of the RMET was good (37).

Dot Perspective Task

The Dot perspective task (38) was used to measure perspective taking skills and consisted of two blocks (the arrow block and the avatar block) which were administered in counterbalanced order. The arrow block served as a control condition but was not relevant to the current analyses so it will not be described here. A trial went as follows. The participant saw a room with an avatar in the middle. Dots were shown on the walls in front of and/or behind the avatar. A trial started with a fixation cross (750 ms) and this was followed by a screen that showed the word "you" or "he/she" (750 ms). The word was replaced by a digit between one and three and, after that, the room with the avatar was shown. The word "you" indicated that one had to adopt his/her own perspective to judge whether the digit corresponds to the total number of dots one sees on all of the walls. The word "he/she" meant that the participant had to adopt the perspective of the avatar to indicate whether the digit corresponds to the number of dots that the avatar is able to see (so only the number of dots on the wall that the avatar is facing). In case of correspondence between the digit and the number of dots, the participant pushed a green button on the keyboard of the laptop. In case the digit and the number of dots did not correspond, the participant pushed a red button. The participant was told to respond as quickly as possible and had a maximum of 2 s to do so. In case the participant did not respond on time, it was counted as an incorrect response. The avatar block consisted of four different trials: self-consistent trials, self-inconsistent trials, other-consistent trials, and other-inconsistent trials. In the self-consistent trial and in the other-consistent trial, the number of dots that the participant sees and the avatar is facing are the same. In the self-consistent trial the participant should take his/her own perspective and judge whether the digit and the dots on the walls correspond. Conversely, in other-consistent trials, the participant is asked to adopt the perspective of the avatar and judge whether the digit and the number of dots correspond. In the self-inconsistent trial and the other-inconsistent trial, the number of dots that the participant sees and the avatar is facing are different (because there are also dots on the walls behind the avatar) which could cause interference of one's own perspective and the perspective of the avatar. Similarly as in the consistent trials, the participant should take their own perspective in self-inconsistent trials and the avatar's perspective in the other-inconsistent trials. Within the avatar block there are 12 trials of each category of trial (so 48 trials in total) and they appear intermixed within the block. Taking into account the age of our sample, we have, compared to the original version of the Dot perspective task by Santiesteban et al. (38), shortened the number of trials based on a study by Surtees and Apperly (39). Five practice trials were played before each block and these were repeated until the correct answer was given. The Dot perspective task was administered on a laptop and took ∼10–15 min to complete.

To analyze the effect of autistic-like experiences and psychotic-like experiences on perspective-taking skills, two different measures of perspective-taking were calculated and used as dependent variables. First, a measure called the "altercentric intrusion rate" was calculated by dividing the reaction time of the response in the correctly answered self-inconsistent trials by the reaction time of the response in the correctly answered self-consistent trials (40). Values >1 indicate that the avatar's perspective interfered with the participant's judgement when they had to adopt their own perspective. A second measure was called the "egocentric intrusion rate" and was calculated by dividing the reaction time of the response in the correctly answered other-inconsistent trials by the reaction time of the response in the correctly answered other-consistent trials (40). Values >1 indicated that the participant's perspective interfered with their judgement when they needed to adopt the avatar's perspective.

Trust Game

The multi-round trust game was used to measure trust behavior in a dynamic, simulated social interaction (41). Two conditions of a multi-round trust game were administered in counterbalanced order. The multi-round trust game is a simulated repeated social interaction in which a trustor and a trustee share money on the basis of trust. Both conditions consisted of 15 trials. A trial starts with the trustor, the participant, sharing an amount of

money between 0 and 10 euros with the trustee (the partner). The invested amount is multiplied by three and received by the trustee. Next the trustee decides how much money to keep and how much money to return to the trustor. This outcome is shown to the trustor, after which the trial ends and a new trial starts. The behavior of the trustee was modeled by a computer algorithm and the trustee's return was determined by the trustor's investment multiplied by a factor (explained below). Participants were informed they were playing with an avatar, as opposed to a human partner, as we did not want to use deception.

The computer algorithm was programmed such that the trustee's behavior was equally trustworthy in the beginning of both conditions and that the trustee's behavior changed after the first five trials. From the sixth trial onwards, the behavior of the trustee in the untrustworthy condition was modeled to be untrustworthy and the behavior of the trustee in the trustworthy condition was modeled as trustworthy. The algorithms were programmed as follows. As mentioned, the trustee's return was determined by the trustor's investment multiplied by predefined factor. For the first five trials in both conditions the factor was randomly selected between 1.2 and 1.4 (in steps of 0.1). The minimum and maximum value that the factor could reach in the first five trials was 1.2 and 1.4. The factor for the second up until the fifth trial in both conditions increased with 0.1 when the trustor's investment increased compared to the investment of the previous trial. The factor stayed the same when the investment decreased or when it did not change compared to the previous trial. Then, the factor for the sixth trial in the trustworthy condition was randomly chosen between 1.5 and 2.0 (in steps of 0.1). The minimum value of the factor became 1.5 and the maximum value became 2.0. For the seventh trial up to the fifteenth trial in the trustworthy condition, the factor increased by 0.1 when the trustor's investment increased compared to the investment of the previous trial. When the trustor's investment decreased or stayed the same compared to the previous investment, the factor did not change. So, the trustee's return was always more than the trustor's investment meaning that the behavior of the trustee was trustworthy. In the untrustworthy condition, the factor for the sixth trial was randomly chosen between 0.7 and 1.3 (in steps of 0.1). The minimum value of the factor became 0.7 and the maximum value became 1.3. The factor for the seventh to the fifteenth trial decreased by 0.1 when the trustor's investment increased compared to the previous investment. The factor stayed the same when the trustor's investment decreased or when it did not change. This setup means that the trustee becomes more untrustworthy, specifically when the trustor shows trust behavior. The trust game was administered on a laptop and took 10–15 min to complete.

To analyze the effect of autistic-like experiences and psychotic-like experiences on trust behavior we used three measures of trust behavior namely baseline trust (the mean of the first trial investment in the trustworthy condition and the first trial investment in the untrustworthy condition) and average trust behavior in both conditions (the average investment of all trials separately for the two conditions).

Friendship Measures

A peer nomination questionnaire was used to measure social relationships in daily life. For this study, the question "Who are your friends in your class?" was used. All participants within a class answered this question, which provided us information on the dynamics of a complete social network. The names of all participating pupils in the classroom were listed on an iPad screen and participants could select a maximum of 15 friends. The indegree measure was based on the sum of incoming friendship nominations (that is, the number of pupils selecting a participant as a friend). The outdegree measure was based on the sum of outgoing friendship nominations (that is, the number of pupils a participant selects as friends). Additional peer nomination questions were administered as part of the #SOCONNeCT project, but were not used in the current analyses. The peer nomination questionnaire was administered on an iPad and took 5–10 min to complete.

The Raven's Standard Progressive Matrices Test (SPM)

The SPM was administered to assess non-verbal intelligence (42). The SPM consists of five sets covering 60 analogy problems. Each problem displayed an array of pictures with one picture missing. The order of the pictures was based on a rule which the participant had to deduce. The participant was asked to choose from multiple pictures which one best fitted the missing picture in the array. A sum score of correctly solved problems was calculated and added to the analyses as a control variable. The SPM test was administered on an iPad and lasted between 15 and 25 min.

Urbanization

A measure of urbanization was used to assess the population density in the areas where participants lived. This measure was based on the postal code that participants provided and using data from the Central Agency for Statistics, a Dutch governmental institution, a categorical variable was created that indicated the density of home addresses per postal code (ranging from 1 to 5: higher numbers indicating more addresses, so higher urbanization, per km^2) (43). The measure was added to the analyses as a control variable. The question about the postal code was administered in a demographics questionnaire on the iPad.

Socioeconomic Status (SES)

A measure of SES was calculated based on the average yearly gross income per income receiver per household, separated per postal code areas. Postal codes were provided by the participants and information on the average yearly gross income was provided by the Central Agency for Statistics (43). The measure was added to the analyses as a control variable.

Statistical Analysis

For the statistical analyses, multi-level models were used to allow for the nested structure of the data that implies dependency between the observations within the school classes. First, the overlap between autistic-like experiences and psychotic-like experiences was tested by regressing the DISC-C score on the

ASSERT score, and we added a possible moderation by sex. A random intercept for class was added to allow for the nested structure of the data. Second, multi-level regression analyses were performed to investigate the effect of autistic-like experiences, psychotic-like experiences and the co-occurrence of both on the social cognition measures and the friendship measures. Two modeling procedures were created. Each of these procedures were repeated for the RMET, the two measures of the Dot perspective task, the three measures of the trust game and the two friendship measures. In all models, the social cognition measures and friendship measures served as the dependent variable. A first modeling procedure was created to examine the relationship between the dependent variable and the co-occurrence of autistic-like experiences and psychotic-like experiences. This was done by adding an interaction between the ASSERT score and the DISC-C score as predictor. A random intercept for class was added to allow for the nested structure of the data. A second modeling procedure was created to separately examine the relationship between the dependent variable and having autistic-like experiences or positive psychotic-like experiences. This was done by adding a main effect the ASSERT score and a main effect of the DISC-C score and a random intercept for class. Additionally, sex, the SPM score, the urbanization measure and the SES measure were added as control variables but removed in the final model when the predictors were not significant. Results of the final model of all modeling procedures are reported (and so, only when control variables were significant, they are reported). All models were fitted using the full maximum likelihood estimation method. Analyses were done in R version 3.5.1 using the R package "nlme" (44).

RESULTS

Descriptives

First, we tested whether autistic-like experiences as measured with the ASSERT and positive psychotic-like experiences as measured with the DISC-C are related. The ASSERT score significantly predicted the DISC-C score [$t_{(289)} = 3.2, p < 0.01$]. See **Table 1** for descriptive statistics per questionnaire and task.

TABLE 1 | Descriptive statistics (mean and standard deviation) per questionnaire and task.

Questionnaire/task	Mean score (standard deviation)
DISC-C	0.8 (0.87)
ASSERT	3.92 (2.17)
RMET	18.1 (2.7)
Dot perspective task altercentric intrusion rate	1.05 (0.15)
Dot perspective task egocentric intrusion rate	1.07 (0.17)
Baseline trust behavior	3.9 (2.1)
Average trust behavior in the trustworthy condition	5.9 (3.01)
Average trust behavior in the untrustworthy condition	4.34 (2.93)
Indegree friendship	6.94 (2.92)
Outdegree friendship	8.05 (3.82)
SPM	44.51 (6.3)

RMET Task

The RMET was used to test for mental state recognition skills. First, we tested the relationship between the RMET and the co-occurrence of autistic-like experiences and psychotic-like experiences. Results indicated no significant interaction effect of autistic-like experiences and psychotic-like experiences on the RMET score [$t_{(272)} = -0.23, p = 0.82$]. Second, we separately tested the relationship between the RMET and having autistic-like experiences or psychotic-like experiences. Results indicated no significant main effect of autistic-like experiences on the RMET score [$t_{(273)} = -1.31, p = 0.19$]. Results also showed no significant main effect of psychotic-like experiences on the RMET score [$t_{(273)} = -1.51, p = 0.13$]. A significant main effect of sex on the RMET score was found [$t_{(273)} = -3.02, p < 0.01$] with girls scoring higher compared to boys. A significant main effect of urbanization was found [$t_{(273)} = 2.09, p < 0.05$] with participants living in a more densely populated area scoring higher compared to participants living in a less densely populated area.

Dot Perspective Task

The Dot perspective task measures perspective taking skills. The altercentric intrusion rate indicates the extent to which the avatar's perspective interfered with the participant's judgement when the participants had to adopt their own perspective. We first tested the relationship between the altercentric intrusion rate and the co-occurrence of autistic-like experiences and psychotic-like experiences. Results indicated no significant interaction effect of autistic-like experiences and psychotic-like experiences on the altercentric intrusion rate [$t_{(287)} = 1.39, p = 0.17$]. Second, we separately tested the relationship between the altercentric intrusion rate and having autistic-like experiences or psychotic-like experiences. Results indicate no effect of autistic-like experiences on the altercentric intrusion rate [$t_{(288)} = -0.55, p = 0.59$] and no effect of psychotic-like experiences on the altercentric intrusion rate [$t_{(288)} = -0.03, p = 0.97$]. The second measure we examined was called the egocentric intrusion rate and indicated the extent to which the participant's perspective interfered with their judgement when the participant needed to adopt the avatar's perspective. Results showed no significant interaction effect of autistic-like experiences and psychotic-like experiences on the egocentric intrusion rate [$t_{(287)} = -1.17, p = 0.24$]. Also, there was no significant main effect of autistic-like experiences on the egocentric intrusion rate [$t_{(288)} = 0.3, p = 0.76$] and no significant main effect of psychotic-like experiences on the egocentric intrusion rate [$t_{(288)} = -0.56, p = 0.57$].

Trust Game

Baseline trust was calculated as the mean of the first trial investment in the trustworthy condition of the trust game and the first trial investment in the untrustworthy condition of the trust game. We first tested the relationship between baseline trust and the co-occurrence of autistic-like experiences and psychotic-like experiences. Results indicated no significant interaction effect

of autistic-like experiences and psychotic-like experiences on baseline trust behavior [$t_{(286)} = -0.82$, $p = 0.41$]. We then tested the separate effects of having autistic-like experiences or psychotic-like experiences on baseline trust. Neither a significant effect of autistic-like experiences on baseline trust behavior [$t_{(287)} = 0.76$, $p = 0.45$] nor a significant effect of psychotic-like experiences on baseline trust behavior was found [$t_{(287)} = -0.72$, $p = 0.47$]. Results did show a sex difference in baseline trust with boys scoring higher compared to girls [$t_{(287)} = 3.23$, $p < 0.01$].

Average trust in the trustworthy condition of the trust game was indicated by the average investment of all trials in the trustworthy condition. Results indicated no significant interaction effect of autistic-like experiences and psychotic-like experiences on the average trust behavior in the trustworthy condition [$t_{(286)} = 0.61$, $p = 0.54$]. Also, no significant main effect of autistic-like experiences on average trust in the trustworthy condition was found [$t_{(287)} = 1.52$, $p = 0.13$]. The main effect of psychotic-like experiences on average trust behavior in the trustworthy condition was also not significant [$t_{(287)} = 0.56$, $p = 0.58$]. A main effect of sex on average trust behavior in the trustworthy condition was found with boys scoring higher than girls [$t_{(287)} = 3.3$, $p < 0.01$].

The average trust in the untrustworthy condition of the trust game was based on the average investment of all trials in the untrustworthy condition. No significant interaction effect of autistic-like experiences and psychotic-like experiences on the average trust behavior in the untrustworthy condition was found [$t_{(286)} = -0.64$, $p = 0.52$]. Furthermore, results did not indicate a significant main effect of autistic-like experiences on average trust in the untrustworthy condition [$t_{(287)} = 0.19$, $p = 0.85$] and no significant main effect of psychotic-like experiences on the average trust behavior in the untrustworthy condition [$t_{(287)} = 1.11$, $p = 0.27$]. Results did show a sex difference in average trust in the untrustworthy condition with boys scoring higher compared to girls [$t_{(287)} = 3.71$, $p < 0.001$].

Friendship Measures

The outdegree measure of friendship indicated the number of pupils a participant selects as friends. We first examined the relationship between the outdegree measure and the co-occurrence of autistic-like experiences and psychotic-like experiences. Results indicated no significant interaction effect of autistic-like experiences and psychotic-like experiences on the outdegree score [$t_{(287)} = -1.02$, $p = 0.21$]. Furthermore, we separately tested the relationship between the outdegree measure and having autistic-like experiences or psychotic-like experiences. Results indicated no significant main effect of autistic-like experiences on the outdegree score [$t_{(288)} = -1.24$, $p = 0.21$] and no significant main effect of psychotic-like experiences on the outdegree score [$t_{(288)} = 1.55$, $p = 0.12$].

The indegree measure indicated the number of pupils selecting a participant as friend. Results showed no significant interaction effect of autistic-like experiences and psychotic-like experiences on the indegree score [$t_{(287)} = 0.2$, $p = 0.84$]. Also, results showed no significant effect of psychotic-like experiences on the indegree score [$t_{(288)} = 0.21$, $p = 0.83$]. Results did show a significant, negative effect of autistic-like experiences on the indegree score [$t_{(288)} = -2.51$, $p = 0.01$]. This means that those participants who showed higher overall levels of autistic-like experiences were selected as a friend less often by their classmates (see **Figure 1**), but there is no evidence that they themselves select fewer friends in their class.

DISCUSSION

In the current study, we examined performance on a comprehensive battery of social cognition tasks in a non-clinical sample of young adolescents with autistic-like experiences, positive psychotic-like experiences and with the co-occurrence of both. Secondly, we examined the effect of autistic-like experiences, psychotic-like experiences and their co-occurrence on friendships in daily life. Results showed a significant, positive relationship between autistic-like experiences and psychotic-like experiences. However, the current study did not find evidence for an association between autistic-like experiences, psychotic-like experiences, or the co-occurrence of both and the performance on any of the social cognition tasks. While psychotic-like experiences showed no significant positive or negative relationship with real-life friendships, social relationships were affected by autistic-like experiences. Specifically, we found a negative relationship between self-reported autistic-like experiences and the indegree measure of friendship, i.e., the number of classmates that selected the adolescent as their friend. Interestingly, we did not find evidence for this relationship with the outdegree measure of friendship, which reflects the number of classmates the adolescent themselves nominated as their friends.

Social Cognition and Autistic-Like Experiences and Psychotic-Like Experiences

Both autistic-like experiences and positive psychotic-like experiences were reported by the participants, confirming previous research that these difficulties can also be found in samples that are considered to be typically developing. With regards to autistic-like experiences, the levels in our sample ($M = 3.92$, $sd = 2.17$) were slightly higher than those previously reported using the same instrument (35), though significantly below the suggested cut-off score of 8 for clinical diagnosis. While levels of reported psychotic-like experiences were low ($M = 0.8$, $sd = 0.87$), the prevalence was similar to earlier work using the same instrument in an early adolescent sample (34), as well as studies using other measures which have estimated the prevalence of psychotic symptoms at 17% in this age range (45).

In line with earlier studies in non-clinical groups, autistic-like experiences and psychotic-like experiences were significantly and positively associated in our sample (25, 26, 46–50). The result of the current study and of previous studies may indicate shared etiological mechanisms that drive increases in both autistic-like experiences and psychotic-like experiences due to genetic and environmental risk factors (2, 25). We hypothesized that this overlap would also be reflected in social-cognitive abilities but our results did not reveal any significant relationships

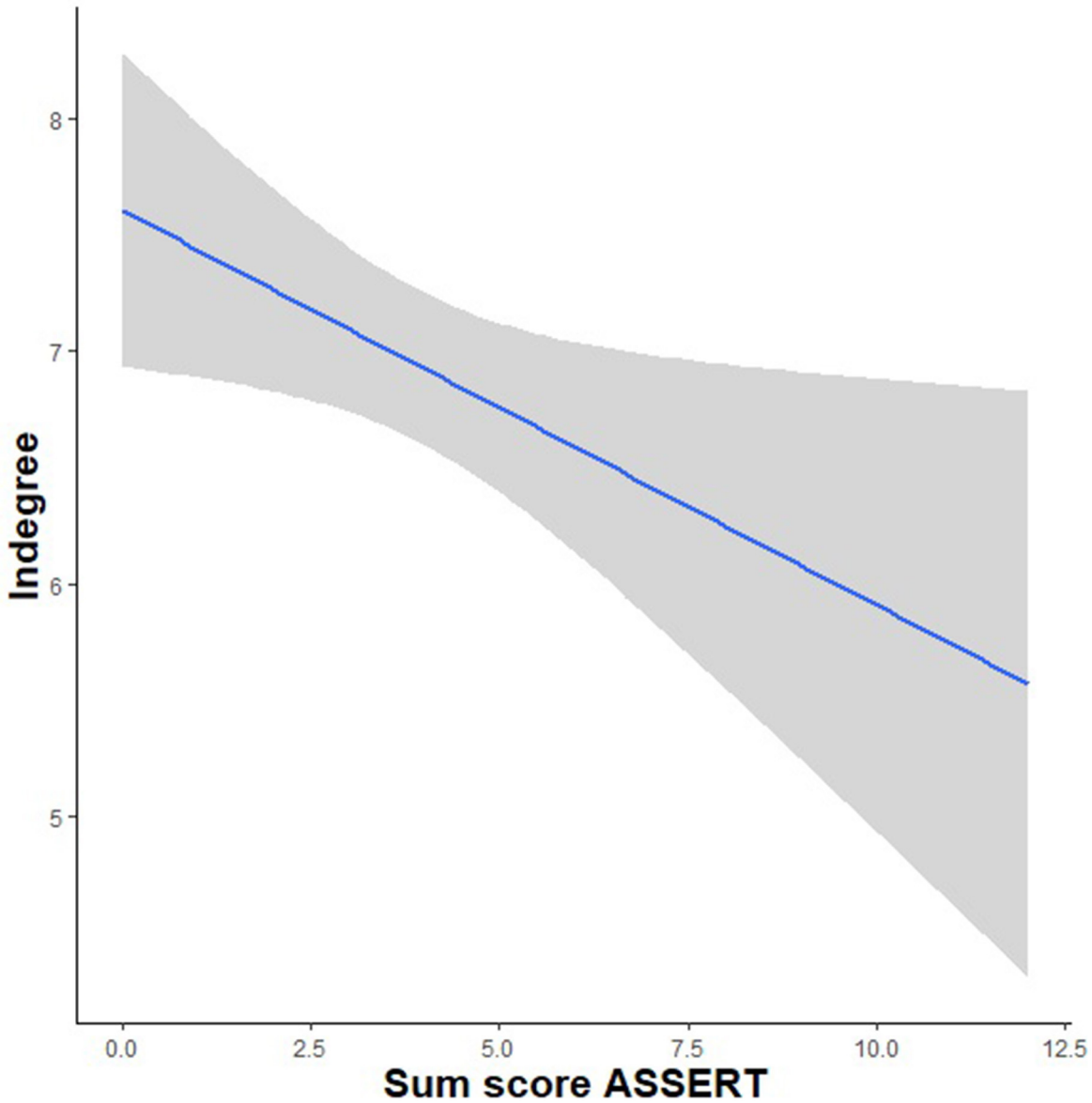

FIGURE 1 | A significant, negative relationship between autistic-like experiences and the indegree friendship measure.

between social cognition and autistic-like experiences, psychotic-like experiences or the combination of the two. The results of the current study underscore the probable shared etiology, however, in the current sample no altered functioning was found on a comprehensive battery of social cognition tasks in relation to either autistic- or psychotic-like experiences, so we cannot conclude how social cognition contributes to this shared etiology. Furthermore, we found a relationship between autistic-like experiences and social behavior (in terms of friendships) while no evidence for such an association was found for psychotic-like experiences. This shows the importance to not only look at the overlap and differences between ASC and SSC in terms of social cognition but also examine social behavior using daily life indicators. Specifically, friendship data provided by adolescents and also by their peers may shed light on alterations in social behavior that are not evident on the lab-based performance measures.

As described, previous studies in non-clinical samples of autism and psychosis did find that autistic-like experiences or psychotic-like experiences at a subclinical level are related to decreased ToM, emotion recognition and social skills (16–24). Several methodological factors may contribute to this discrepancy. For example, one of the measures we used was the trust game, which has not been used in previous studies examining subclinical experiences of ASC and SSC. Furthermore, the RMET is subject to debate on the exact social-cognitive

processes that are involved (51). Another explanation for the differences in results could be the age of the sample as prior work was conducted in late adolescent and adult samples while the adolescents in the current study were around age 12. At this age, the foundational aspects of social cognition, such as following and interpreting the movements and gaze of others, and understanding their basic intentions are well-developed (52), but the higher-level aspects of social cognition, as well as the associated networks in the brain, continue to develop throughout adolescence and into adulthood (8, 53). These include the more complex forms of intentionality and ToM (54, 55), the ability to understand mixed and complex emotions (56, 57), and to flexibly adapt trust behavior based on social information (58). As we did not find evidence for an association between subclinical experiences and altered complex forms of social cognition, we hypothetically suggest that altered complex forms of social cognition in relation to these subclinical experiences may only be expressed during late adolescence or early adulthood but future research is needed to confirm this. In addition to these developmental considerations, it is important to note that the participants in our study were enrolled in the higher tracks of the Dutch educational system. The Dutch educational system has three main educational tracks based on academic performance. Schools from the lower track did not participate in the current study. Therefore, the enrolled participants had a relatively high level of education and cognitive performance, factors which are positively related to social cognition abilities and may have offset the potentially deleterious effects of autistic-like experiences and psychotic-like experiences (59).

The current sample provided the opportunity to test the oft-cited diametric model of (subclinical) autism and psychosis, which predicts that the co-occurrence of ASC and SSC symptoms have an ameliorating effect on one another toward normality (2, 28). The study by Abu-Akel et al. (27) found support for the diametric model, as the performance on a social cognition task of people with both high autistic tendencies and high psychosis proneness was similar to that of people with low autistic tendencies and low psychosis proneness. As we did not find evidence for an association between performance on the social cognition tasks and subclinical experiences of autism or subclinical experiences of psychosis, we consequently also did not find evidence for a relationship between the co-occurrence of autistic-like experiences and psychotic-like experiences and the performance on the social cognition tasks, and thus did not find support for this model in our early adolescent sample. More studies are required to better understand the effect of the co-occurrence of both subclinical experiences to improve distinction and diagnoses.

Friendships and Autistic-Like Experiences and Psychotic-Like Experiences

The current results showed that the more autistic-like experiences someone has, the less often the adolescent is selected as a friend by their peers. This may suggest that peers experience altered social behavior in young adolescents with autistic-like experiences while we did not find evidence that those adolescents themselves experience altered friendship behavior. Using peers as informants about the social behavior of adolescents with subclinical expressions of ASC or SSC has not often been done in prior work but the current study implicates peers can be a useful source of information. The current study also did not find evidence for an association between autistic-like experiences and the performance on computerized tasks tapping into social cognition. This implies that the computerized social cognition tasks do not tap into the mechanisms that make that the adolescents with autistic-like experiences are less often nominated as friends by their peers. If replicated, future studies could set out to further investigate these mechanisms, for example by using social cognition tasks with higher ecological validity or measured in the context of daily life using ecological momentary assessment and by using other informants (e.g., teachers, parents) to assess the social networks. Furthermore, we did not find evidence for an association between psychotic-like experiences and the two measures of friendship used, suggesting a possible difference in the social behavior in daily life of young adolescents with autistic-like experiences and young adolescents with psychotic-like experiences.

Limitations and Future Directions

In the present study we used self-reported measures of autistic-like experiences and positive psychotic-like experiences. This requires the ability to assess and reflect on own behavior, which may have differed among the young adolescents in our sample. It should be noted, however, that these self-report measures are validated questionnaires also for this age group (33, 35). Further research using multiple informants (teacher, parents) would allow potential differences in assessment of subclinical experiences to be examined in more detail. In addition, future studies could use a measure of schizotypal traits rather than psychotic-like experiences. The current study was based on a homogenous sample in terms of age and level of education. This may limit the generalization of the results. At the same time, this homogeneity has likely reduced the differences between participants in the ability to reflect on their autistic-like and psychotic-like experiences and their social network ties. Due to the general design of this longitudinal study, some measures were administered at a 6-month interval. Furthermore, the peer nomination questionnaire was administered within classrooms. Using well-defined groups is a prerequisite for measuring (the dynamics of) complete social networks. However, this also implies that friendship ties outside the classroom could not be taken into account. Consequently, our measures will underestimate the total number of friends for most of the adolescents in our sample. However, as young adolescents spend a large amount of their time at school and all classes are taken with the same classmates, this social environment provides reliable information about a large part of their social interactions. Future research may add information about egocentric networks, as well as examine qualitative aspects of peer relationships.

Conclusions

The current study did not find evidence for a relationship between autistic-like and/or positive psychotic-like experiences

and social-cognitive functioning in young adolescents. Furthermore, there was no evidence for a relationship between psychotic-like experiences and friendships. In contrast, having autistic-like experiences was negatively related to the number of times being selected as a friend by peers even though there was no evidence for a lower number of self-reported friends. This study provides initial evidence that information provided by peers may shed light on (altered) social behavior associated with autistic-like experiences that is not apparent on performance measures, as well as elucidate possible differences between autistic- and psychotic-like experiences.

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 Vaste Commissie voor Wetenschap en Ethiek, Faculty of Behavioral and Movement Sciences, Vrije Universiteit Amsterdam (VCWE). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LK, NL, and HS developed the main conceptual idea. HS, MH, and RW collected the data. HS and BB developed the analytical models and carried out all analyses. HS wrote the initial draft of the paper. NL, MH, RW, BB, MB, and LK provided feedback on the draft and approved the final version. All authors contributed to the article and approved the submitted version.

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Abnormally Large Baseline P300 Amplitude Is Associated With Conversion to Psychosis in Clinical High Risk Individuals With a History of Autism: A Pilot Study

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Psychosis rates in autism spectrum disorder (ASD) are 5–35% higher than in the general population. The overlap in sensory and attentional processing abnormalities highlights the possibility of related neurobiological substrates. Previous research has shown that several electroencephalography (EEG)-derived event-related potential (ERP) components that are abnormal in schizophrenia, including P300, are also abnormal in individuals at Clinical High Risk (CHR) for psychosis and predict conversion to psychosis. Yet, it is unclear whether P300 is similarly sensitive to psychosis risk in help-seeking CHR individuals with ASD history. In this exploratory study, we leveraged data from the North American Prodrome Longitudinal Study (NAPLS2) to probe for the first time EEG markers of longitudinal psychosis profiles in ASD. Specifically, we investigated the P300 ERP component and its sensitivity to psychosis conversion across CHR groups with (ASD+) and without (ASD–) comorbid ASD. Baseline EEG data were analyzed from 304 CHR patients (14 ASD+; 290 ASD–) from the NAPLS2 cohort who were followed longitudinally over two years. We examined P300 amplitude to infrequent Target (10%; P3b) and Novel distractor (10%; P3a) stimuli from visual and auditory oddball tasks. Whereas P300 amplitude attenuation is typically characteristic of CHR and predictive of conversion to psychosis in non-ASD sample, in our sample, history of ASD moderated this relationship such that, in CHR/ASD+ individuals, enhanced – rather than attenuated - visual P300 (regardless of stimulus type) was associated with psychosis conversion. This pattern was also seen for auditory P3b amplitude to Target stimuli. Though drawn from a small sample of CHR individuals with ASD, these preliminary results point to a paradoxical

effect, wherein those with both CHR and ASD history who go on to develop psychosis have a unique pattern of enhanced neural response during attention orienting to both visual and target stimuli. Such a pattern stands out from the usual finding of P300 amplitude reductions predicting psychosis in non-ASD CHR populations and warrants follow up in larger scale, targeted, longitudinal studies of those with ASD at clinical high risk for psychosis.

Keywords: autism spectrum disorder, psychosis, P300, EEG, conversion, prodrome

INTRODUCTION

While autism spectrum disorder (ASD) and the schizophrenia spectrum disorders (SCZ) are considered diagnostically distinct, they share phenotypic features, genetic overlap, and a common historical background (1, 2) that highlight the possibility of related neurobiological substrates. As a neurodevelopmental disorder, ASD diagnosis –characterized by impaired social interaction and communication, alongside repetitive and restricted behaviors and interests (3) occurs in early childhood. SCZ is also characterized by impairments in social interactions, but hallmark symptoms of delusions, hallucinations, disorganized thought and behavior, and a constellation of negative symptoms, typically emerge in late adolescence and early adulthood (4). Yet, epidemiological studies also point to considerable overlap between the two disorders. Estimates of SCZ rates in ASD, for example, are 5–35% higher than in the general population (5–7), while rates of ASD diagnoses in SCZ patients range from <1–52% (8). Importantly, prodromal symptoms of SCZ that precede full-blown illness also include social deficits (9) that share some overlap with core features of ASD. In addition, cognitive deficits are pervasive in both ASD and SCZ, as well as in prodromal SCZ. Indeed, tasks that probe attention, memory, and executive functioning find differences in processing speed, accuracy, and perceptual discrimination/detection thresholds compared to typically developing (TD) control cohorts across disorders (10–12).

Recent trends in the schizophrenia field have focused on examining clinical and neurobiological characteristics in individuals at clinical high risk for psychosis (CHR) in order to identify which features are most predictive of transition to full-blown psychosis. Clinically, some of the best predictors of conversion to psychosis include genetic risk, history of substance abuse, and severity of social impairment (13). Neurologically and neuropsychologically, brain volume abnormalities (14, 15), reduced processing speeds and worse verbal memory (16) are associated with increased risk and an earlier psychosis conversion in CHR individuals. Until recently, it was unknown whether individuals with ASD who presented at CHR services showed similar prodromal features and conversion rates to those seen in the broader CHR general population. However, a recent study from the second wave of the North American Prodrome Longitudinal Study (NAPLS2) revealed that CHR individuals with prior ASD diagnoses had more social impairment than other CHR individuals, but similar positive symptoms of psychosis and similar rates of converting to co-morbid psychotic illness (17). However, it is not yet known whether neurological profiles and predictors of conversion to psychosis are similar between CHR individuals with and without ASD.

Event-related potentials (ERPs) have been widely used in understanding altered information processing in clinical vs. non-clinical populations. In SCZ, reduced P300 amplitude during detection of an infrequent target stimulus is among the most reliable and replicable findings (18–20). P300 is a positive-going ERP associated with shifting and allocation of attention, as well as stimulus salience (21–27), where larger amplitudes reflect larger resource allocation toward these processes. The robust amplitude reduction in SCZ suggest that the P300 might be a possible biomarker for the illness (28). Moreover, attenuated P300 is also seen in CHR individuals (29, 30) and may be useful as a predictive tool when identifying individuals at risk for psychosis conversion (31–33) and considering preventative interventions.

P300 can be divided into two subcomponents: P3a and P3b. P3a is maximal over frontocentral scalp and reflects attention orienting toward novel stimuli that are not behaviorally-relevant, in other words, distractors requiring no response (34–38). P3b, on the other hand, is maximal over central-parietal scalp and reflects allocation of attention toward infrequent stimuli that require behavioral response. In schizophrenia, P3b amplitude deficits are well-replicated, particularly in the auditory modality (18, 19, 39–43). Auditory P3a amplitude deficits have also been detected (19, 29, 42, 44–50), though they may be less robust (44, 51, 52). In CHR, both P3a and P3b amplitude reductions have been identified (29, 46, 50, 53–60), with emerging evidence that auditory P3b amplitude may be predictive of conversion to psychosis (33, 60).

The P300 literature in ASD is less clear than in SCZ and CHR. A recent meta-analysis of the P3a and P3b found only reduction in P3b amplitude to be a reliable alteration, whereas P3b latency and both P3a amplitude and latencies were generally similar to controls (61). Clear differences in P300 response to auditory vs. visual stimuli have not been reported, though in general there are more systematic findings of impaired auditory processing and enhanced visual perceptual functioning in the ASD literature broadly. Whether there is a particular pattern of P300 alterations that characterizes individuals with ASD and CHR or predicts who in this population will develop full-blown psychotic illness has not been examined.

The present study leveraged a large, longitudinal study of CHR individuals to examine whether the neural profile and predictors of conversion to psychosis are comparable between individuals with and without co-morbid ASD. In particular, we

focused on early attention-modulated indices in response to both attended (P3b) and task-irrelevant (P3a) sensory input. By testing both auditory and visual sensory modalities, we further examined whether, as in CHR more generally, sensory domain affects the predictive utility of brain-based measures dependent on ASD status. We hypothesized that whereas consistent P300 amplitude attenuations are predictive of conversion to psychosis in general CHR populations, P3b deficits may be more specific in those with ASD history and visual P300 deficits may be lacking regardless of conversion. Because there have been no longitudinal studies of neural markers of psychosis risk and development in ASD, this study capitalized on a large-scale study in order to identify a rare subset of individuals with both ASD and CHR. Though our sample size is small and our findings preliminary, this exploratory work offers the first window into brain-based predictors of psychosis conversion in individuals with ASD and a launching point for future, larger studies.

METHOD

Participants

EEG data were available from the baseline visits of 304 patients who participated in the North American Prodrome Longitudinal Study (NAPLS2) (62), a consortium of eight research centers studying CHR between 2009 and 2013, comprising help-seeking individuals ages 12–35 years, observed for up to 2½ years. These patients represent a subset of the full NAPLS2 cohort who completed both the auditory and visual oddball tasks (see below) at baseline and either converted to psychosis anytime within the 24-mo follow-up period or were followed through to the 24-month visit without converting. All CHR individuals met one or more of the three Criteria of Prodromal Syndromes (COPS): attenuated positive symptom syndrome (APSS), genetic risk and deterioration (GRD), and/or brief intermittent psychotic syndrome (BIPS). APSS requires at least one attenuated positive psychotic symptom, begun or worsened in the past year, and of insufficient severity to meet diagnostic criteria for a psychotic disorder. GRD is defined in NAPLS2 as a combination of functional decline (30% or greater drop in Global Assessment of Function score over the month preceding the baseline visit, as compared to 12 months prior) and genetic risk, defined as either schizotypal personality disorder or a first-degree relative with a schizophrenia spectrum disorder. BIPS reflects the presence of a one or more positive psychotic symptom meeting severity threshold but too brief to meet diagnostic criteria for psychosis (63). There was no formal testing or screening for peripheral sensory deficits as part of study procedures or exclusion criteria.

For this study, CHR participants were grouped based whether or not they had a comorbid ASD diagnosis noted at baseline (ASD+: comorbid ASD; ASD–: no ASD) to predict whether they converted to psychosis (Conv+: converter; Conv–: non-converter) within the 2 years following their baseline visit. All patients in the ASD+ group met DSM-IV criteria for Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) using a combination of DSM-IV checklist during baseline clinical interview, medical records, and caregiver report of historical diagnosis. All patients designated as Conv+ experienced conversion from CHR state to psychosis, determined by meeting the Structured Interview for Psychosis-Risk Syndromes (SIPS) (64, 65), Presence of Psychotic Symptoms criteria (13). Conversion decisions were discussed and approved on a weekly consensus call. In total, of the 304 participants with included data, 290 did not have ASD (ASD–) and 14 had previous ASD history (ASD+). Within the ASD– group, 71 converted to psychosis (Conv+); conversion to psychosis occurred in four participants within in the ASD+ group. **Table 1** summarizes demographic information and assessment scores by group. The sample yielded closely age-matched groups (Main Effect Conversion: $F_{1,300} = 0.61$, $p = 0.44$; Main Effect ASD: $F_{1,300} = 3.69$, $p = 0.056$; Conversion × ASD Interaction: $F_{1,300} = 0.042$, $p = 0.84$). Illness level also did not differ among groups at baseline. In particular, across SIPS positive, negative, disorganization, and general subscales, there were no main effects of conversion status (Positive: $F_{1,298} = 0.60$, $p = 0.44$; Negative: $F_{1,300} = 0.24$, $p = 0.68$; Disorganization: $F_{1,299} = 0.037$, $p = 0.85$; General: $F_{1,298} = 0.24$, $p = 0.88$) or ASD diagnosis (Positive: $F_{1,300} = 0.14$, $p = 0.71$; Negative: $F_{1,298} = 0.017$, $p = 0.90$; Disorganization: $F_{1,299} = 0.45$, $p = 0.50$; General: $F_{1,298} = 0.48$, $p = 0.49$), and no significant interaction effects between conversion status and ASD (Positive: $F_{1,300} = 1.96$, $p = 0.16$; Negative: $F_{1,298} = 0.97$, $p = 0.22$; Disorganization: $F_{1,299} = 1.48$, $p = 0.23$; General: $F_{1,298} = 0.072$, $p = 0.79$) (see **Table 1**).

The Institutional Review Boards of the eight participating sites approved all study protocols. All adult subjects gave informed consent. Minor subjects provided verbal assent while their parents/guardians provided written informed consent.

Oddball Paradigm

The experiment consisted of two (visual, auditory) three-stimulus oddball paradigms, where in addition to the frequent, standard stimulus and the rare, target stimulus, there were also rare novel, task-irrelevant stimuli (37). Each oddball task (i.e., visual and auditory) comprised three blocks of 150 trials, of which 80% of trials were standards (visual: small blue circle presented at the vertical and horizontal meridian; auditory: 500 Hz, 50 ms tone with a 5 ms rise/fall time at 62 dB). An additional 10% of trials were target stimuli (visual: large blue circle presented at the vertical and horizontal meridian; auditory: 1,000 Hz, 50 ms tone with a 5 ms rise/fall time at 62 dB), and 10% were novel stimuli (visual: fractal images; auditory: man-made and natural sounds) that were, on average, 250 ms in duration and presented at 62 dB (66). All visual stimuli were presented for 500 ms and the difference in radius between the target and standard circle was ∼104:67 in ratio. Stimuli were presented in the same pseudorandom order for all participants. Target and novel stimuli were not allowed to repeat in a sequence such that two deviant stimuli could not occur in a row.

Participants were instructed to respond to the target stimulus and withhold a response to both standard and novel stimuli. Participants indicated their response by pressing a button on a Cedrus® response box using the index finger of their dominant hand. Incorrect trials were excluded from EEG analysis. There was a fixed, 1,250 ms stimulus onset asynchrony

TABLE 1 | Participant demographics.

Group	N	Age (SD)	Females (%)	Mean SOPS scores (SD)			
				Positive	Negative	Disorganized	General
Conv–/ASD– (non-converter)	219	19.56 (4.63)	101 (46.11)	11.60 (4.23)	11.71 (6.14)	4.87 (3.23)	8.96 (4.29)
Conv+/ASD– (converter)	71	18.79 (3.67)	29 (40.85)	13.54 (3.84)	12.10 (6.48)	6.31 (3.75)	9.52 (4.40)
Conv–/ASD+ (non-converter)	10	17.28 (2.91)	1 (10)	13.80 (3.23)	13.80 (4.49)	6.80 (2.62)	8.40 (5.70)
Conv+/ASD+ (converter)	4	15.98 (2.56)	0 (0)	12.25 (3.10)	10.50 (5.51)	5.75 (5.50)	8.25 (0.96)

(SOA) between auditory oddball trials such that each block lasted approximately 3 min. Visual oddball trials were jittered between 1,500 and 2,500 ms (mean SOA = 2 s) to avoid simultaneous presentation with auditory stimuli from a background mismatch negativity task. Stimulus presentation was implemented with Presentation® software (Version 13.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com).

Electroencephalographic Data Acquisition and Pre-processing

Participants sat in front of a computer monitor with a screen resolution of 1,024 × 768 and a refresh rate of 60 Hz. As described in (32), EEG was recorded at 1024 Hz using either a 32-channel (4 NAPLS2 sites) or 64-channel (remaining 4 sites) BioSemi ActiveTwo recording system (BioSemi, Amsterdam, Netherlands). Additional electrodes were placed on the nose and mastoids with vertical electrooculogram (VEOG) recorded at electrodes placed above and below the right eye and horizontal (HEOG) electrodes at the outer canthus of each eye.

Continuous EEG data were re-referenced to averaged mastoids and high-pass filtered (0.1 Hz). Data were then processed using a modified version [see (32) for detail] of the Fully Automated Statistical Thresholding for EEG artifact Rejection (FASTER) Routine (67), with additional modification of ICA component selection as per previous literature [see (68)] to ensure proper removal of visual artifacts in the visual oddball task where blinks and saccades may be temporally correlated with ERP components. Continuous EEG data were segmented from −1,000 to 2,000 ms time-locked to the onset of the stimulus during FASTER pre-processing. Last, ERP data were baseline corrected (−100 to 0 ms) and low-passed filtered at 30 Hz.

Statistical Analysis

The measure of interest in the oddball task was P300 amplitude, which was disambiguated by computing difference waveforms by subtracting the standard ERP form target (P3b) and novel (P3a) ERPs separately for the auditory and visual tasks. P300 amplitude was defined based on previous literature (32, 69) as the peak amplitude, elicited between 235 and 400 ms follow stimulus onset for auditory stimuli and 230–500 ms for visual stimuli. Peak amplitude was identified within each of these windows at Cz for P3a (in response to task-irrelevant, non-target stimuli) and at Pz for P3b (in response to target stimuli), based on previous literature showing these sites are where P3a and P3b, respectively, have maximal amplitude. Average amplitude value within a 30 ms window centered around this peak was extracted. Thereafter, a statistical correction was applied to all ERP measures to adjust for normal aging effects and data collection site (32). In short, the age-corrected P300 amplitude z-score describes the amount, in standard units, that a participant's amplitude deviates from the value expected for a healthy individual of a given age assessed at a specific consortium site (70–72).

TABLE 2 | Oddball behavioral data ANOVA summary.

	df	F	*p*	η_p^2
Accuracy				
Modality	1,300	0.26	0.61	0.001
Conversion status	1,300	0.21	0.65	0.001
ASD status	1,300	0.10	0.75	<0.001
Modality × Conversion	1,300	0.87	0.35	0.003
Modality × ASD	1,300	0.047	0.83	<0.001
Conversion × ASD	1,300	0.14	0.71	<0.001
Conversion × ASD × Modality	1,300	0.028	0.87	<0.001
Reaction time				
Modality	1,300	<0.001	1.00	<0.001
Conversion status	1,300	0.009	0.93	<0.001
ASD status	1,300	1.62	0.93	<0.001
Modality × Conversion	1,300	0.88	0.35	0.003
Modality × ASD	1,300	0.44	0.51	0.001
Conversion × ASD	1,300	2.83	0.20	0.005
Conversion × ASD × Modality	1,300	0.46	0.83	<0.001

A binomial logistic regression model was applied to examine whether the relationship between baseline P300 amplitude and later psychosis conversion status (Conv+, Conv–) was moderated by whether or not individuals had a prior ASD diagnosis. The effects of interest were the main effect of P300 amplitude and the interaction term between ASD and P300 amplitude. Separate models were used for the four conditions (modality: auditory, visual; stimulus type: target, novel) to prevent collinearity of predictors. Main effects of amplitude would replicate prior findings showing that P300 predicts conversion to psychosis in CHR samples. A statistically significant ASD × P300 amplitude interaction would suggest the association between P300 amplitude and converting to psychosis changes based on ASD status. The ASD+ group was used as the reference condition, and bootstrapping procedures with 1,000 resamples were used to assess statistical significance and model stability. When significant interactions between P300 amplitude and ASD diagnosis were present, follow up analyses with simple

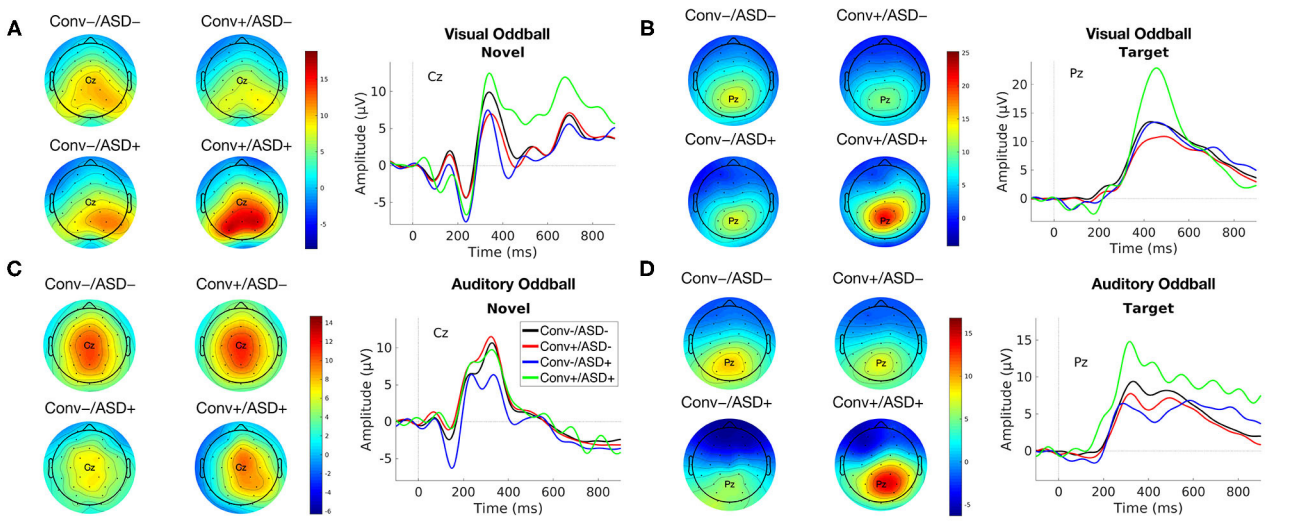

FIGURE 1 | Group average ERP waveforms for modality [Visual **(A,B)** and Auditory **(C,D)**] and Stimulus Type [Novel **(A,C)** and Target **(B,D)**] for Conv−/ASD− (black), Conv−/ASD+ (blue), Conv+/ASD− (red), and Conv+/ASD+ (green). Stimulus onset occurred at 0 ms. Scalp topographic maps of the mean P3a/P3b amplitude in response to the Target/Novel stimulus type around the mean latency ± 10 ms.

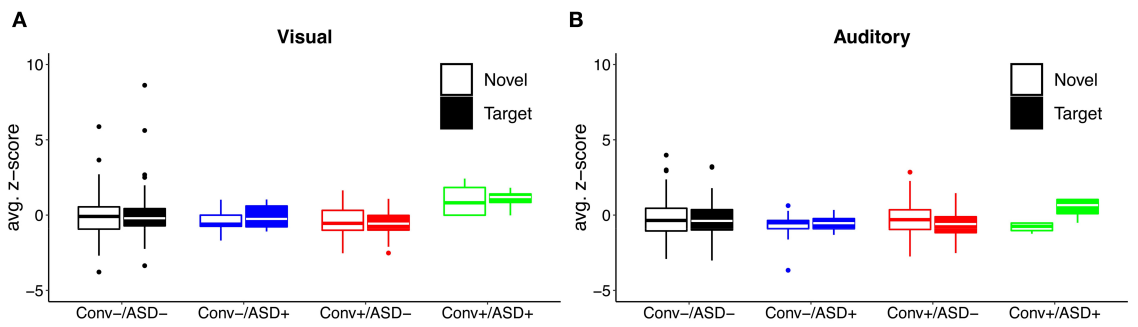

FIGURE 2 | Distribution of **(A)** visual and **(B)** auditory P300 amplitude as a function of ASD history and conversion status.

slopes were computed to better understand the moderating effect of ASD.

To ensure any neural differences detected weren't simply downstream effects of differing behavioral performance across participants, behavioral measures of accuracy and reaction time of target detection were analyzed separately using a 3-way [ASD diagnosis (ASD+, ASD−) × Conversion status (Conv+, Conv−) × Modality (auditory, visual)] repeated measures analysis of variance (ANOVA). Accuracy was calculated as percent correct and comprised total hits [i.e., responding to (70, 71) the target] and correct rejections (i.e., withholding a response to novel, task-irrelevant stimuli and frequent standards) given as the following formula: $\frac{Rejections_{standard}+Rejections_{novel}+Hits_{target}}{All_{standard}+All_{novel}+ALL_{target}}$. Reaction time reflected the time taken to press the button (i.e., respond) to Target stimuli in each modality.

Significance testing was conducted with an alpha level of $p = 0.05$, with p-values generated from bootstrapping with 1,000 resamples. Since this study was designed to be hypothesis-generating given the small number of individuals with ASD history in the NAPLS2 cohort, we did not correct for multiple comparisons in order to reduce the chance of type two error.

RESULTS

Oddball Behavioral Data

Behavioral performance is summarized in **Table 2**. The analysis of response accuracy revealed no significant main effects or interactions between ASD and conversion status, and all participants were highly accurate. Results indicated that, across groups, participants were equally accurate on the visual [(0.99 ± 0.008), (Mean ± SE)] as they were on the auditory (0.98 ± 0.006) oddball task ($F_{1,300} = 0.26$, $p = 0.61$). There were no differences in accuracy between groups based on Conversion status ($F_{1,300} = 0.65$, $p = 0.646$; Conv−: 0.99 ± 0.006; Conv+: 0.98 ± 0.009) or ASD diagnosis ($F_{1,300} = 0.10$, $p = 0.75$; ASD−:

TABLE 3 | Binomial logistic regression summary with bootstrapping of oddball ERP data.

Model	B	SE	OR	*p*
Visual – Novel				
P3a Amplitude	1.47	0.78	4.36	0.004
Amplitude × ASD Diagnosis	−1.80	0.80	–	0.001
Visual – Target				
P3b Amplitude	1.56	0.72	4.73	0.004
Amplitude × ASD Diagnosis	−2.16	0.75	–	0.001
Auditory – Novel				
P3a Amplitude	−0.12	0.47	0.89	0.78
Amplitude × ASD Diagnosis	0.12	0.48	–	0.80
Auditory – Target				
P3b Amplitude	2.98	1.54	19.70	0.045
Amplitude × ASD Diagnosis	−3.37	1.56	–	0.039

0.98 ± 0.002; ASD+: 0.99 ± 0.01). Analysis of reaction time also showed no significant main or interaction effects (see **Table 2**). Across conversion status (Conv–: 486.35 ± 13.70 ms; Conv+: 483.94 ± 21.78 ms), ASD diagnosis (ASD–: 501.51 ± 5.78 ms; ASD+: 468.78 ± 25.07 ms), and modality (Auditory: 485.15 ± 15.25 ms; Visual: 485.15 ± 13.50 ms), groups were comparable in their reaction time.

ERP Data

There were no significant differences in the number of included ERP trials between groups, overall or as a function of stimulus type or modality (Conversion: $F_{1,300} = 0.52$, $p = 0.47$; ASD: $F_{1,300} = 0.007$, $p = 0.94$; Conversion × ASD: $F_{1,300} = 0.63$, $p = 0.63$; 2-way interactions with Conversion: $p > 0.05$; 2-way interactions with ASD: $p > 0.05$; 3- and 4-way interaction with Conversion and ASD status: $p > 0.05$).

Our central question was whether the predictive relationship between P300 amplitude and conversion status was moderated by history of ASD diagnosis. **Figure 1** shows waveforms by modality and condition, as a function of ASD and Conversion status. **Figures 2A,B** show z-score corrected P300 amplitudes for auditory and visual modalities, respectively. The estimated regression parameters are summarized in **Table 3**. A main effect of P300 amplitude predicting conversion status was significant in the visual modality (P3a: $p = 0.004$; P3b: $p = 0.004$) and in the auditory modality for P3b ($p = 0.045$), but not P3a ($p = 0.78$).The ASD × P300 Amplitude interaction significantly predicted conversion status in models of both Novel (P3a: $p = 0.001$) and Target (P3b: $p = 0.001$) stimuli in the visual modality, and for Target stimuli (P3b) in the auditory modality ($p = 0.039$), but not for auditory novel stimuli (P3a: $p = 0.80$).

Simple slopes analyses indicated that, within the ASD+ group, more enhanced P300 amplitudes (relative to the TD sample against which they were z-scored) were significantly associated with conversion to psychosis for both auditory and visual target stimuli, as well as for visual novel stimuli (Auditory P3b: OR = 16.72, β = 2.82, SE = 1.49, $p = 0.011$; Visual P3b: OR = 7.80, β = 2.05, SE = 1.21, $p = 0.025$; Visual P3a: OR = 4.47, β = 1.50, SE = 0.83, $p = 0.008$). There was no association between Auditory P3a amplitude and psychosis conversion in the ASD+ group ($p = 0.93$). See **Figure 3** for individual waveforms by condition from all four Conv+/ASD+ participants. These findings contrast with the ASD– CHR subset, wherein P300 enhancements were significantly associated with decreased risk of conversion to psychosis (Auditory P3b: OR = 0.67, β = −0.39, SE = 0.16, $p = 0.006$; Visual P3a: OR = 0.72, β = −0.32, SE = 0.13, $p = 0.015$; Visual P3b: OR = 0.55, β = −0.60, SE = 0.17, $p = 0.001$), consistent with previous literatures wherein attenuated P300 amplitudes typically associate with conversion to psychosis.

DISCUSSION

In this paper, we present exploratory analyses of the utility of EEG markers for predicting conversion to psychosis in a unique, albeit small, sample of individuals with ASD at clinical high risk for psychosis, followed longitudinally for two years. We find that P300 amplitude profiles to visual target and novel and auditory target stimuli in CHR patients differentially predict conversion to psychosis as a function of ASD status. In the general CHR population, previous literature shows that reduced P300, and particularly P3b response to behaviorally-relevant auditory stimuli, is both characteristic of the group as a whole and predictive of later conversion to psychosis. Here, we find preliminary evidence that history of ASD diagnosis moderates this relationship. In particular, enhanced – rather than attenuated - P300 response to visual and target stimuli appears to be a unique profile associated with conversion to psychosis among CHR individuals with ASD history. Whereas, intact or enhanced P300 response is typically a positive prognostic marker in the CHR literature, we show that, for every one standard deviation increase in P300 amplitude above the mean in healthy controls, CHR individuals with ASD history have between 4 and 16 times greater chance of developing psychosis. Such pattern was not characteristic of either CHR individuals without ASD, or CHR individuals with ASD who did not convert to psychosis. Moreover, the observed odds ratios for P300 predicting conversion to psychosis in ASD are strikingly large compared to those often seen in studies examining predictors of psychosis in broader CHR groups. Neither accuracy nor reaction time during task performance differed between CHR patients with ASD who converted to psychosis and any of the other study groups, and the amount of data retained for analysis also did differ by group. These factors contribute to early confidence that observed differences in ERP response likely reflect true differences in brain response, rather than being artifactual as a function of differences in behavior response patterns or data quality.

Our oddball task findings in CHR patients without ASD align with previous work showing that P300 amplitude is reduced in psychosis (18, 19), in CHR (29, 30, 73), and in those with CHR who convert to psychosis (32, 33, 60, 74). In patients with CHR who have a prior ASD history but do not convert to psychosis, we also see P300 reductions that are consistent

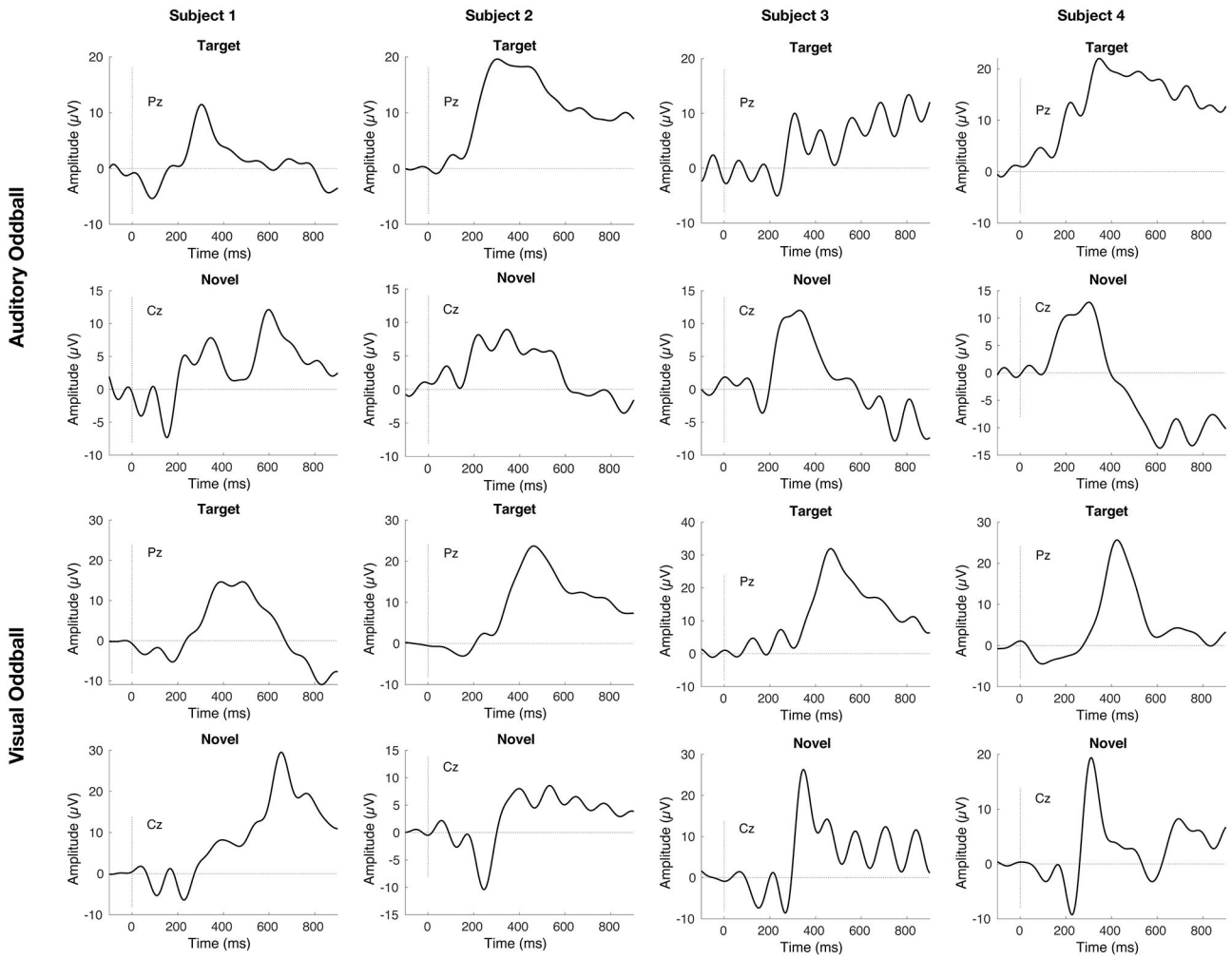

FIGURE 3 | Individual waveforms for $n = 4$ CHR participants with ASD history who convert to psychosis within 2 years of their baseline visit and EEG.

with both the broader CHR group and the general literature on P300 in ASD without psychosis (61, 75). Indeed, the pattern of enhanced P300 to visual and target stimuli appears to be unique to those with CHR and ASD whose illness trajectory results in full-blown psychosis within 2 years. It may reflect allocation of an aberrantly large degree of attention to sensory input, in the visual domain, regardless of behavioral relevance of stimuli, as well as when sensory input is behaviorally relevant, regardless of sensory domain. Of note, as accuracy of responding to target stimuli did not differ among participants as a function of ASD or conversion status, post-attention decision making steps may still function similarly, at least in the context of a simple detection task, despite differential attentional allocation at the neural level.

These results provide initial evidence suggesting that ASD status may be important to account for when evaluating neural markers that may predict later transition to psychosis in CHR individuals. This finding is interesting in light of the fact that clinical predictors of conversion to psychosis do not seem distinct in CHR individuals with ASD vs. those without (17), suggesting additive information from the neural data. Based on prior literature (32), more attenuated P300 amplitude in CHR individuals ought to raise greater concern about future conversion to psychosis. Thus, with such literature as background and without knowledge of prior ASD status, discovering *enhanced* P300 amplitude to oddball stimuli in a CHR individual might be cause for optimism about prognosis and recovery. If borne out in larger studies, our results suggest that knowing the ASD history of these individuals may therefore be of import: only if one know the individual's prior ASD diagnosis can one make the more nuanced interpretation, raising concern about conversion as a function of the P300 enhancement. Combined with clinical and demographic indicators of risk for conversion to psychosis, this information from EEG could in turn contribute to more accurate predictions about disease trajectory.

Study findings are of course limited by our small sample of CHR individuals with ASD, particularly for those who

converted to psychosis. However, the large odds ratios we uncovered support the import of this hypothesis-generating work. In addition, our sample consists only of help-seeking individuals, who are plausibly not entirely representative of the broader population of those with ASD and psychotic-like symptoms. Finally, CHR itself is a broad category, and the range of concerning symptoms expressed at baseline was likely heterogenous both within our ASD subset and within the broader CHR group. Due to our small sample size, we did not look at individual clinical symptom associations, but baseline symptoms did not differ among those with or without ASD, or who did or did not convert to psychosis. Despite study limitations, the striking dissociation among groups that we discovered provides an exemplar of why this line of work is critically important, as our findings would be entirely masked were ASD status not considered. Samples of ASD individuals with CHR symptoms followed longitudinally are exceedingly rare to date, making our findings important, even if preliminary. Future studies in larger samples of CHR individuals with ASD and comparing to non-CHR ASD are needed in order to validate our preliminary findings and ensure they are not spurious. Should they replicate in larger samples, our results could mean new insight into prevention and intervention in patients presenting to CHR clinics with ASD history, and for those presenting to ASD clinics with early signs of psychosis.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: data belongs to the NAPLS2 consortium and may be available upon request. Requests to access these datasets should be directed to daniel.mathalon@ucsf.edu.

ETHICS STATEMENT

Study procedures were reviewed by and approved across all eight sites of the NAPLS2 consortium. Written informed consent to participate in this study was provided by the participant, or by the participant's legal guardian for those under 18 years of age.

AUTHOR CONTRIBUTIONS

JF-F, EV, PB, AB, GL, MN, KC, TM, DP, LS, SW, TC, and DM: concept and design. JF-F, SG, BR, HH, PB, RC, ED, JJ, GL, MN, JA, CB, KC, BC, LS, WS, MT, EW, SW, TC, and DM: acquisition, analysis, or interpretation of data. JF-F, SG, BR, HH, and DM: drafting of the manuscript. JF-F, SG, BR, EV, HH, PB, AB, RC, ED, JJ, GL, MN, JA, CB, KC, BC, TM, DP, WS, MT, EW, SW, TC, and DM: critical revision of the manuscript for important intellectual content. JF-F, SG, BR, and DM: statistical analysis. JA, CB, KC, BC, DP, LS, EW, TC, and DM: obtained funding. HH, BR, PB, RC, ED, GL, MN, JA, CB, KC, BC, LS, WS, EW, TC, and DM: administrative, technical, or material support. All authors contributed to the article and approved the submitted version.

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