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Women in psychiatry 2023: autism

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The role of the broader autism phenotype in anxiety and depression in college-aged adults

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The current study examines the relationship between the presence of autistic traits and anxiety and mood disorders in young adults from different racial groups. A representative sample from a predominately white university (2,791 non-Hispanic White (NHW) and 185 Black students) completed the broad autism phenotype questionnaire (BAPQ), a measure of depression (Patient Health Questionnaire, PHQ-9), and anxiety (Generalized Anxiety Disorder, GAD-7). Statistical Package for Social Sciences (SPSS) was used to perform two multiple regression analyses to determine the association between race, BAPQ score and anxiety and depression symptoms. The current study found a stronger association between autistic traits had depression and anxiety symptoms in Black participants than did NHW participants. These findings underscore the association between autistic traits and anxiety and depression in Black communities, and the need for further studies on this topic area. Additionally, it highlights the importance of improving access to mental health care for this population.

KEYWORDS

autistic traits, anxiety, depression, race, socioeconomic status

Introduction

Prior to 2020, mental health disorders were included as one of the top 10 leading causes of burden worldwide, with depression being the fourth leading cause (1). Mental health disorders, specifically anxiety and depression, are often associated with decreased quality of life (2, 3) and increased mortality rates (4). Additionally, the prevalence of mood and anxiety disorders in the general population is high. A study based on data collected in 2012 through 2013 found that among a population of 36,309 US adults, approximately 10.4% experienced a 12-month Major Depressive Disorder and 20.6% experienced a lifetime Major Depressive Disorder (5). (6) Reported that 33.7% of the general population experience an anxiety disorder during their lifetime. Several studies have also shown that the overall rate of mood disorders in the general population has increased over the past decade. One study found that there was a 63% increase in the number of individuals aged 18–25 years who reported experiencing a major depressive episode between 2009 and 2017 (7). Similarly, among undergraduates specifically, the number of students who experienced severe depression, engaged in self-harm, and attempted or planned suicide doubled between 2012 and 2018. Additionally, rates of moderate to severe anxiety increased by approximately 92% (8). These findings emphasize the importance of studying the underlying mechanisms responsible for the increase in anxiety and mood disorders among adult

and college age populations as well as developing better mental health care and more effective treatment and intervention plans.

Internalizing problems – increased depression and anxiety symptoms – are also very prominent in individuals with autism spectrum disorder (ASD) as well as those with broader autistic phenotypic (BAP) traits. ASD is a neurodevelopmental condition characterized by restricted and repetitive behaviors and interests, and difficulties with social communication and interactions (9). Research suggests relatives of autistic individuals often display autistic tendencies but do not experience the same functional impairment as those with the condition. Therefore, these individuals do not meet criteria for a clinical diagnosis. The sub-diagnostic autistic traits are referred to as BAP (10). BAP traits include pragmatic difficulties, broadly defined stereotyped behaviors and communication difficulties, social skill and emotion recognition differences, rigidity, and aloofness (11–13). While the BAP is often seen in relatives of autistic individuals, they are also present amongst the general population without autistic relatives (14–16). However, less research has examined the relationship between mood and anxiety symptoms and those with sub-diagnostic autism traits. The BAP is associated with increased rates of psychological disorders and difficulties in a variety of cognitive domains. For example, individuals with the BAP often experience difficulties with cognitive functions such as central coherence, executive function, and neurological processing in general (17). Additionally, (18) reported higher rates of obsessive–compulsive disorder in relatives of autistic individuals. Research has also shown a relationship between anxiety and mood disorders and those with the BAP. For example, those with the more autistic traits are shown to exhibit more symptoms of depression and anxiety than those with less autistic traits (19–22). Furthermore, adults who reported a history of depression reported more autistic traits than those without a history of depression (23). Because depression is often linked to suicidal ideation and suicide attempts, it is important to note that studies have also found an increased risk of suicide in individuals with autistic traits (24). For example, through a survey that targeted suicide prevention websites and social media, Richards et al. (25) found that autistic traits, as measured by the Autism Spectrum Quotient (AQ), were higher in those who had attempted suicide.

The prevalence of mood and anxiety disorders among Black populations compared to Non-Hispanic White populations has been reported to be lower, although the chronicity and severity are typically higher. In the Twenge et al. (7) study that reported increases in those who had experienced a major depressive episode, the largest increase came from White Americans, followed by Hispanic and Black Americans, respectively. A study by Hasin et al. (5) examined prevalence rates among 36,309 American adults in 2012 and 2013 and reported the odds of a 12-month Major Depressive Disorder were lower among African American, Asian, and Hispanic adults compared to Non-Hispanic White adults. Despite the lower prevalence, the persistence of these disorders is often higher in Black populations (26, 27). One study found that, out of a group of Black males diagnosed with a mood disorder, only half of them made contact with a medical or mental health provider regarding their mental health condition. A large portion of these males with a mood or anxiety disorder had one that could be classified as lifetime or chronic (28). A similar study found that 12-month prevalence of mood and anxiety disorders were lower among Non-Hispanic Black participants compared to Non-Hispanic White participants, but that the overall persistence of these disorders was greater in the Non-Hispanic Black population (29). Recent data have also reported that Black adolescents had an increase in the rate of suicide attempts (30, 31). This increase was observed even though the rate in non-Hispanic White (NHW) adolescents was unchanged (32).

The previous work examining increased suicide attempts in both autistic and Black communities, while not the main topic of the current work, motivated the current study. The goal of the current, exploratory study was to lay a foundation for further research examining the differential outcomes and experiences of Black individuals with autistic traits. Specifically, in relation to mood and anxiety symptoms in this population. Black individuals experience high levels of social stress, including racial stress (33). This increased level of stress is expected to contribute to increases in frequency of anxiety and mood symptoms and is expected to interact with the presence of autistic traits to result in poorer outcomes. The current study aims to examine the prevalence of autistic traits and their relationship to depression and anxiety symptoms in Black and non-Hispanic white populations, in which autistic traits were measured using the Broad Autism Phenotype Questionnaire (BAPQ) in a sample of college students from a large Midwestern university.

Method

Participants

This sample comprised of 2976 College-age adults (903 male; 2073; female). Their ages ranged from 17 to 46 years ($M = 19.06$, SD = 1.658). Participants completed a series of surveys and questionnaires as part of an introductory psychology course at Midwestern University. The study was conducted in a span of 18 months (between 2015 and 2017). Informed consent was obtained from all participants prior to their participation. The research protocol was approved by the Institutional Review Board for Human subjects research at the Midwestern university. Participants who did not complete the BAPQ were excluded. Additionally, because of the focus of the study, only participants who identified as non-Hispanic White (NHW; $N = 2791$; 73% of original sample) and Black/African American ($N = 185$; 4.8% of original sample) were included in the analyses (see Table 1 for summary); this distribution of race matches the university's demographics. The sample included seven individuals with a reported diagnosis of ASD (all NWH). Additionally, although the sample was limited to undergraduates, 20 were over the age of 25 (0.67% of the sample).

Measures

A family history survey was administered to obtain a family history of anxiety, depression and autism [responses were binary (yes/no, e.g., "Has your parent or grandparent been diagnosed with ____?"), annual family income (multiple choice: (1) under $25k, (2) $25–50k, (3) $50–100k, (4) $100–150k, or (5) over $150k) and the highest level of parental education (multiple choice: (1) did not complete high school, (2) high school, (3) some college, (4) no degree, college graduate (4 or 2 year), or (5) professional/graduate school)]. Participants' race, gender, and age were also obtained (Figure 1).

TABLE 1 Demographic information by group.

Demographic information by group (n=2,976)								
Variable	Black (n =185)			NHW (n =2,791)			T-test comparing Black and NHW	
	M	SD	Range	M	SD	Range	t	p
Age (years)	19.3	1.31	17–25	19.04	1.68	17–46	−2.03	0.47
Annual family income	3.0 ($50–100k)	1.71		4.0 ($100–150k)	1.27		–	–
Parental education	3.7 (some college)	1.49		3.6 (some college)	0.98		–	–
BAPQ	3.4	0.53	0.0–4.1	3.37	0.56	0.0–4.4	−0.847	0.02*
PHQ9	1.69	2.28	0–8	1.29	1.98	0–8	−2.604	<0.001***
GAD7	0.95	1.56	0–6	0.7	1.31	0–6	−2.409	0.002**
	n (%)			n (%)				
Male	47 (25.4)			856 (30.7)				
Female	138 (74.6)			1935 (69.3)				
Family history depression	15 (8.1)			541 (19.4)				
Family history anxiety	5 (2.7)			192 (6.9)				
Family history autism	1 (0.5)			88 (3.2)				

BAPQ, Broad Autism Phenotype Questionnaire; PHQ9, Patient Health Questionnaire; GAD7, General Anxiety Disorder; NHW, Non-Hispanic White. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

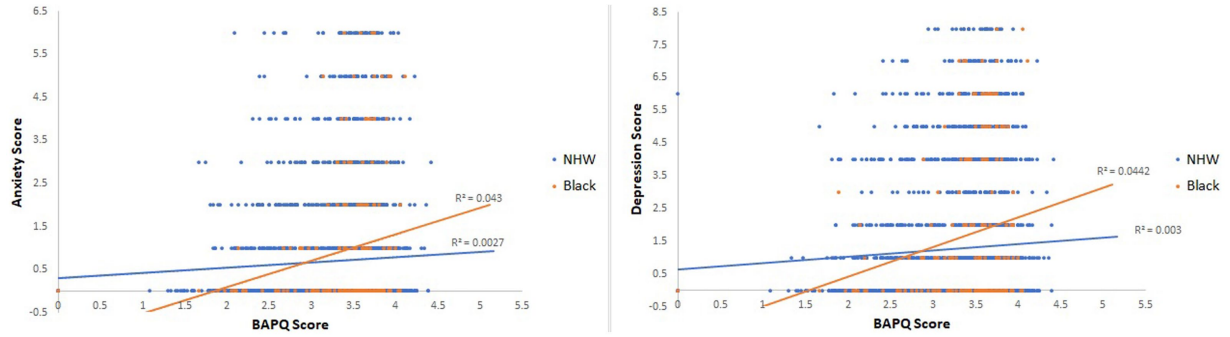

FIGURE 1
Scatterplots depicting the interaction between race and BAPQ for anxiety and depression symptoms.

Broad autism phenotype questionnaire

The Broader Autism Phenotype (BAP) is a set of autistic traits in individuals who do not necessarily have an autism diagnosis, particularly relatives of autistic individuals (34). Therefore, the BAPQ can be utilized in assessing the overall autistic traits of a population when obtaining clinical assessment for all participants is not possible (34, 35). The BAPQ is a 36-item assessment divided among three subscales: *social behavior, stereotyped-repetitive behavior, and communication*, with a six-point scale for responding to each question. For example, one of the items says, "I find it hard to get my words out smoothly" (34). The overall score ranges from 1 to 6 and is averaged from all 36 questions. A cut-off of 3.13 was used to label high and low scores based on the cutoff previously reported by Hurley and colleagues (2006), which resulted in 715 low and 2261 high-scores (see Supplementary Data for an analysis using a higher cutoff of 3.5).

Patient Health Questionnaire (PHQ-9)

Depressive symptoms were assessed using the PHQ-9 (36–39). Each of the nine PHQ-9 depression items describes one symptom corresponding to one of the nine diagnostics in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-4). Participants are asked to rank how often in the last 2 weeks they have experienced that symptom from "Not at all" to "Nearly every day." For example, one of the items is "Little interest or pleasure in doing things" (38). The PHQ-9 is a valid measure of depression severity due

TABLE 2 Summary of multiple regression analysis for variables predicting anxiety scores.

Variable	*B*	*t*	*Df*	*p*
BAPQ (main effect)	0.15	3.4	2973	<0.001***
Race (main effect)	0.24	2.4	2973	0.02*
BAPQ*Race	0.49	2.57	2972	0.01**
BAPQ at NHW	0.12	2.71	2972	0.01**
BAPQ at Black	0.61	3.31	2972	<0.001***

BAPQ, Broad Autism Phenotype Questionnaire; NHW, Non-Hispanic White. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 3 Summary of multiple regression analysis for variables predicting depression scores.

Variable	*B*	*t*	*Df*	*p*
BAPQ (main effect)	0.23	3.53	2973	<0.001***
Race (main effect)	0.39	2.55	2973	0.01**
BAPQ*Race	0.72	2.50	2972	0.01**
BAPQ at NHW	0.19	2.85	2972	0.004**
BAPQ at Black	0.91	3.25	2972	0.001**

BAPQ, Broad Autism Phenotype Questionnaire; NHW, Non-Hispanic White. **$p < 0.01$, ***$p < 0.001$.

to its correlation with the DSM-4 requirements for a depression diagnosis and is useful when gathering a clinical diagnosis is not feasible (36).

General Anxiety Disorder-7 (GAD-7)

Anxiety symptoms were assessed using the GAD-7, which consists of 7 items asking participants to rate how frequently in the last 2 weeks they have experienced a specific anxiety symptom from "Not at all" to "Nearly every day" (37). For example, one of the items is "Not being able to stop or control worry." Scores can range from 0 to 27, with 5 representing mild, 10 representing moderate, and 15 representing severe anxiety symptoms. The GAD-7 has been found to be a valid measure of generalized anxiety symptoms based on DSM-4 criteria and is useful when a clinical diagnosis is not feasible (37).

Statistical analyses

Statistical Package for Social Sciences (SPSS) for Windows, version 28 was used for statistical analysis. Descriptive statistics were computed to evaluate participant characteristics (i.e., mean, standard deviation, and frequencies). Additionally, multiple regression analyses were performed to determine the association between race (Black and NHW), BAPQ scores, and anxiety and depression symptoms (An ANOVA is presented in the Supplementary materials).

Results

A multiple regression analysis was conducted to examine the relationship between anxiety scores, autistic traits, and race. The results revealed a main effect of BAPQ scores ($b = 0.147$, $t(2973) = 3.4$, $p < 0.001$) and race ($b = 0.24$, $t(2973) = 2.4$, $p = 0.02$). These main effects indicate that, on average, Black participants and participants with more autistic traits experienced more anxiety symptoms. However, there was a significant interaction between BAPQ scores and anxiety symptoms ($b = 0.49$, $t(2972) = 2.57$, $p = 0.01$). Specifically, the slope relating BAPQ to anxiety scores was $b = 0.12$, $t(2972) = 2.71$, $p = 0.0068$ in NHW participants and $b = 0.61$, $t(2972) = 3.31$, $p < 0.001$ in Black participants. While both groups showed a significant effect of BAPQ on anxiety scores, the significant interaction indicates that the relationship was stronger for Black participants (Table 2).

A multiple regression analysis was conducted to examine the relationship between depression scores, autistic traits, and race. The results revealed a main effect of BAPQ scores ($b = 0.23$, $t(2973) = 3.53$, $p < 0.001$) and race ($b = 0.39$, $t(2973) = 2.55$, $p = 0.01$). These main effects indicate that, on average, Black participants and participants with more autistic traits experienced more depression symptoms. However, there was a significant interaction between BAPQ scores and depression symptoms ($b = 0.72$, $t(2972) = 2.50$, $p = 0.01$). Specifically, the slope relating BAPQ to depression scores was $b = 0.19$, $t(2972) = 2.85$, $p = 0.004$ in NHW participants and $b = 0.91$, $t(2972) = 3.25$, $p = 0.001$ in Black participants. While both groups showed a significant effect of BAPQ on depression scores, the significant interaction indicates that the relationship was stronger for Black participants (Table 3).

Discussion

The goal of the present study was to examine whether autistic traits differentially affect Black undergraduate college students. The results revealed that although BAPQ scores were not different between Black and NHW participants (see Supplementary materials), there was a significant difference in the relationship between anxiety and mood symptoms and BAPQ. The current study found an interaction between race and BAPQ scores, suggesting that Black individuals with more BAP traits may be at a higher risk for experiencing symptoms of depression and anxiety than NHW individuals with BAP traits. These findings are significant given the already increased rates of anxiety and mood disorders (40–42) and attempted suicide (25, 43–45) in autistic individuals. This, coupled with prior findings of an increase in suicide attempts in Black adolescents (32) suggests higher rates of mood disorders and suicide attempts may be even greater among Black individuals with BAP traits. This is surprising considering consistent previous findings of a lower rate of psychological disorders, including depression, in Black compared to NHW populations [see (33) for review]. This is despite findings that Black populations have higher levels of psychosocial stress (46), which is positively correlated with psychological disorders.

It is important to consider the possible role of stress, particularly race-related stressors in this sample. Previous studies have reported that individuals with ASD and BAP have higher levels of perceived stress and lower perception of coping ability (47). This would suggest that the consequences of stress, including increased internalizing

symptoms would be greater for those with higher BAP traits. Studies indicate Black individuals frequently encounter negative racial experiences, such as microaggressions from peers and faculty at primarily white institutions (PWIs) (48). Furthermore, research has shown that race-related stressors have a negative impact on Black individuals' mental health and psychological well-being (49, 50). For instance, Black individuals who pursue psychotherapy, listed race-related stressors as a problem that led them to pursue psychotherapy (51). In addition, (52) found that psychological well-being was negatively correlated with autistic traits. Given the current study was conducted at a PWI, it is possible the interplay between autistic traits and race-related stressors are impacting the likelihood that Black individuals with autistic traits are at a greater risk for experiencing anxiety and mood disorders.

Limitations

One primary limitation of this study is that the sample utilized is not fully representative of a larger population; it is composed primarily of white, female undergraduates from a Midwestern university. Additionally, while representative of the population from which it was drawn, the sample contains a much larger number of NHW participants than Black participants, making it difficult to draw definitive conclusions related to race.

Implications

The current exploratory study is a first step in developing an understanding of the underlying mechanisms responsible for the racial disparities in mental health care and the relationship between autistic traits and anxiety and mood disorders, specifically in Black populations. Overall, these findings suggest BAP traits may exacerbate anxiety and mood symptoms in Black populations and highlight the importance of thoroughly assessing the relationship between these disorders and individuals with BAP traits. The results of the current study have also precipitated a few additional questions that are worthy of further exploration. For example, the participants in this study were all college students at a PWI in a predominately White college town, likely making the environment itself more stressful for many Black participants. However, it is unclear how this stress may interact with the presence of BAP traits. Future studies should examine how race-related stress may impact those with BAP traits. There is also the question of how socioeconomic status may interact with the relationship between BAP traits and anxiety and mood symptoms. Socioeconomic factors include both educational attainment as well as income and while parental educational attainment was similar across race, income was different which may contribute to racial stress. Future research should explore the role of this complex SES finding and how race may interact with it to affect mood disorders and BAP traits in larger, and more diverse samples.

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 Indiana University IRB. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SN was responsible for the design of the study, data collection, directing the analysis, interpretation, and writing of the manuscript. MK was involved in data analysis and writing. RK contributed to interpretation of results. DR contributed to data analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1187298/full#supplementary-material

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Binocular rivalry in autistic and socially anxious adults

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Background: Social anxiousness is a pervasive symptom in both social anxiety disorder and autism spectrum conditions. Binocular rivalry, which occurs when different images are presented to each eye, has been used to explore how visual and cognitive processing differs across various clinical diagnoses. Previous studies have separately explored whether individuals with autism or anxiety experience binocular rivalry in ways that are different from neurotypical individuals.

Methods: We applied rivalry paradigms that are similar to those used in previous studies of autism and general anxiety to individuals experiencing symptoms of social anxiousness at clinical or subclinical levels. We also incorporated rivalrous stimuli featuring neutral and emotional facial valances to explore potential overlap of social processing components in social anxiety and autism.

Results: We hypothesized that higher levels of social anxiousness would increase binocular rivalry switch rates and that higher levels of autistic traits would decrease switch rates. However, stimulus condition did not affect switch rates in either diagnostic group, and switch rate was not significantly predictive of dimensional measures of either autism or social anxiety.

Discussion: This may suggest a common mechanism for atypical visual cognition styles previously associated with social anxiety and autism. Alternatively, differences in switch rates may only emerge at higher trait levels than reported by the participants in our studies. Furthermore, these findings may be influenced by sex differences in our unique sample.

KEYWORDS

binocular rivalry, autism, social anxiety, social anxiousness, switch rates

Introduction

Social anxiety, defined as concern or avoidance of social situations in response to a fear of negative evaluation by others, can cause significant disruption to everyday routines and sense of well-being. For example, due to the social nature of daily living demands in many communities, social anxiety is associated with greater barriers to employment, including less educational attainment, less work experience, fewer job-specific skills, and fewer skills that involve human interaction in the workplace (1). Individuals with social anxiety are more than twice as likely to be unemployed or underemployed compared to those diagnosed with major depressive disorder, non-social anxiety disorders, or alcohol dependence (2, 3). Success in forming romantic relationships (4, 5) as well as adaptive friendships (6) is likely to be affected.

Social Anxiety Disorder (SAD) is diagnosed when anxiety significantly disrupts daily function, with a prevalence rate estimated at 6.80% of American adults (7). Furthermore, up to 20% of the general population experiences subclinical levels of social anxiety symptoms, which may still be detrimental to function and quality of life (8–10).

Social anxiety often co-occurs with other diagnostic profiles. For example, up to 50% of autistic[1] adults in the United States also experience significant social anxiousness[2] associated with decreased success in everyday endeavors and additional obstacles to quality of life (12–14). While social anxiety and autism have distinct clinical profiles, one potential area of overlap is the link between social information processing and sensory processing, including early visual processing. Social anxiety disorder and autism are both linked with atypical sensory experiences (15, 16). Higher levels of social anxiety are associated with higher levels of sensory hypersensitivity in autistic and neurotypical participants (17, 18), and sensory hypersensitivity has been found to mediate the relationship between socially anxious traits and autistic traits (18). This finding suggests that part of the difficulty autistics face in social interactions is related to the increased sensory load inherent to social settings rather than the social nature of the exchanges themselves (18). Within the subgroup of autistic females, sensory traits do not fade over time and persist into adulthood (19). Tsuji et al. (20) also found sensory sensitivities persisting into adulthood to be associated with more internalizing disorders in autistic females (20).

Social anxiety disorder has been similarly associated with hypervigilance (i.e., increased attunement to certain sensations), especially in the presence of stimuli deemed threatening. Such sensory sensitivity has been linked to harm avoidance and agoraphobic tendencies in social anxiety disorder (21). For example, a recent eye-tracking study found that when experiencing anxiety, individuals diagnosed with social anxiety disorder demonstrated increased scan path lengths compared to a non-anxious comparison group. However, this same scanning effect was not present under emotionally neutral conditions (22). The authors theorized that this longer fixation path denoted less attentional control under threatening conditions, which inhibited effective environmental search. Electroencephalography has also shown that individuals with high levels of social anxiety experience greater sustained amplitude enhancement in early visual cortices associated with face-evoked signals than do low-social-anxiety controls (23).

In co-occurring autism and SAD, differences in sensation and perception may be related to shifts in global versus local processing. One study of autistic children performing a block design task found that the relationship between local processing and social skills was significantly moderated by anxiety levels (24). More dominant local-level processing may be in line with the Weak Central Coherence Theory of autism which suggests that individuals with autism show a greater preference for details rather than overarching themes of stimuli (25). A meta-analysis suggests that preference for local stimuli in autism might be related to unpruned synapses (25). The authors speculate that this reduced neuronal attenuation may explain the correlation between heavier brains and the likelihood of autism diagnosis. This phenomenon may result from decreased top-down modulation within early visual systems, leading to more intense sensory inputs than those experienced by neurotypical individuals (25). While local processing has yet to be thoroughly studied in social anxiety specifically, Hagenaars et al. (26) found that greater fixation on local-level inputs is associated with more intense recall and greater fear in those with anxiety-related to trauma and post-traumatic stress disorder (PTSD) (26). This finding may be suggestive of a role in threat response.

Binocular rivalry tasks may be especially well suited to explore similarities and differences in visual cognition associated with social difficulties in autism and social anxiety, given their ability to simultaneously assess local/global processing, threat bias, and sensory sensitivity. As individuals with autism or SAD can find verbal reports challenging, another benefit of utilizing binocular rivalry tasks is that they are a non-verbal measure of visual and cognitive processing (27, 28).

Binocular rivalry paradigms focus on the brain's process for resolving differences in images presented to each eye. In day-to-day visual processing, resolving minor differences associated with eye position is common and automatic. Binocular rivalry tasks explore what occurs when the images presented to each eye are so distinct that they cannot be merged. During an experimental trial, individuals generally perceive rhythmic switching between the left eye's and the right eye's image. The rates at which this switching occurs seem to depend on stimulus conditions, with the visual system sometimes prioritizing one image over the other so that one percept is available for longer processing.

At the same time that competition in areas associated with early visual processing is necessary for switching to begin, altered inhibition and excitation associated with rivalry can also be observed in higher cortical structures (29, 30). While there is debate around the reason for binocular rivalry oscillations, or in other words, how rivalry phenomena may be related to extrinsic traits and symptoms, researchers theorize that perceptual switching results from variance in inhibition and excitation throughout the attention and visual systems (31, 32) and is especially modulated by GABA levels in the visual cortex (32). Computational models have similarly linked reduced inhibition with longer alternation rates (33) as well as with increased dysmetria and hypometria previously associated with autism spectrum conditions (34). Many genetic, postmortem, animal-model, and manipulation studies indicate that modulation of inhibitory and excitatory processes may also be a key component of other neural differences observed in autism (31, 35–37). Similar findings have also been mirrored in subjects with social anxiety (35) and anxiety generally (36–40). However, these conditions are rarely studied in tandem or with more than one stimulus type at a time.

Using rivalrous images of gratings stimuli, Nagamine and colleagues demonstrated that binocular rivalry induced higher switch rates in a high anxiety group (38). This faster switching may indicate that those with higher anxiety experience more perceptual competition between the two competing images and potentially less sensory suppression (38). Using similar geometric stimuli, Wykes et al. (39) found that neurotypical young adults with more autistic traits experienced slower switching than subjects with fewer autistic

1 We use this term as recommended by many self-advocates we know who prefer the identify-first label "autistic" over person-first terminology "individual with autism spectrum disorder (or condition)" (11).

2 We use "anxiousness" to refer to the symptoms or traits and "anxiety" to refer to the clinical diagnosis.

traits (39). However, this correlation was not present when more complex images of objects were used. This lack of effect is consistent with the findings of Said et al. (40) who found that binocular rivalry with geometric images did not reliably differentiate high-functioning autistic adults from control participants and did not predict symptom severity (40). It is also consistent with the findings of Karaminis et al. (41) who found that neither rivalrous geometric nor rivalrous object images elicited significantly different switch rates in autistic children as opposed to same-age controls (41). On the other hand, Robertson and colleagues found that when viewing rivalrous images of objects, autistic adults experienced longer periods of unresolved perceptions between switches, which resulted in slower switch rates (31). Additionally, the duration of mixed perceptual states was positively correlated with increased levels of autistic traits, while switch rate was negatively correlated with autistic traits. These findings have also been replicated using object images, verified with electroencephalography, and associated with changes in neurotransmitter levels as measured by magnetic resonance spectroscopy, with slower switch rates and more persistent mixed percepts predicting participants' diagnostic status with 87% accuracy (37, 42).

When specifically interested in social symptoms, researchers often prefer studying responses to faces (e.g., expressing hostility or friendliness) in socially anxious versus non-socially anxious individuals. The usual hypothesis is that there will be greater performance differences in threatening versus non-threatening faces for individuals with social anxiety than individuals without social anxiety. Several studies using methods other than binocular rivalry demonstrate these performance differences for individuals with social anxiety disorder (43–46). Similar findings are also available for autistics. For example, in an emotion recognition task using electroencephalography, autistic boys displayed significantly reduced neural responses to negatively valenced (angry and fearful) faces compared to neurotypical controls (47). Another study, in which participants identified whether facial expressions were congruent or incongruent with an image's body language, found that while autistics had shorter viewing times than controls overall, they were especially avoidant of images depicting fear (48). Interestingly, in this and other congruency paradigms, autistic participants were also less accurate than controls at differentiating fearful from angry faces (48–50).

While binocular rivalry studies in general anxiety have found that participants reporting higher levels of anxiousness experience accelerated switch rates (38), binocular rivalry studies in individuals with social anxiety are less common. These studies primarily focus on initial percepts, or the first rivalrous image a participant reports seeing, rather than ongoing switching rates. They indicate that binocular rivalry may be sensitive to social threat, with individuals with social anxiety seeing the threatening face first more often than individuals without social anxiety (51, 52).

The overall aim of this study was to utilize binocular rivalry paradigms to examine similarities and differences in switch rates in response to various stimulus conditions among three groups of adults: adults with a diagnosis of autism or high levels of autistic traits, adults with a diagnosis of SAD or high levels of socially anxious traits (both without an autism diagnosis), and non-anxious neurotypical adults. Given our focus on social anxiousness, we also integrated novel facial stimuli. Our specific hypotheses, based on the results from previous studies (31, 37, 38, 42), were as follows:

1. Across groups, switch rates would be different for different facial valences
2. Switch rates would predict diagnostic group assignment
   a. Higher levels of socially anxious traits would predict faster switch rates.
   b. Higher levels of autistic traits would predict slower switch rates.
3. Predictions for Hypotheses 2a and 2b would be more clearly observed in facial vs. geometric stimuli

Materials and methods

Participants

This study combined data from three studies conducted at Brigham Young University that utilized the same binocular rivalry task and recruited participants for traits related to autism or social anxiety as well as non-anxious neurotypical controls. All studies were approved by the sponsoring institution's IRB (F19260, F2020-242, and IRB2020-429) and funded through internal seed grants and family foundations.

The clinical groups were recruited as a follow-up to previous studies of mental health in women who find social situations confusing or exhausting (53, 54). This sample included women diagnosed with autism who were recruited from existing research databases, local assessment clinics, and via word-of-mouth, and socially anxious women who were recruited from local university and community counseling clinics and via word-of-mouth. All participants were paid for their time or were invited via the university research recruitment system where students were given course credit for participating.

In all, 223 adults (M Age = 21.9 years ±3.44, R = 18–44 years, Table 1) participated in the binocular rivalry tasks, with 47 representing clinically significant autistic traits. We focused on adults given previous studies' significant observations in this age group (31, 37, 38, 42) as opposed to contradictory findings in pediatric cohorts (41). In order to maximize spectra of symptom presentation, we did not match participants based on age, but instead controlled for age in secondary analyses (see Supplementary Table S4). Approximately half of these participants were identified by clinical diagnosis outside of the study (n = 6), internal clinician judgment (n = 4), or clinician administration of the *Autism Diagnostic Observation Schedule-2nd Edition (ADOS-2), Module 4* (55) (n = 14). In order to account for a wide range of symptom presentations, we included all participants

TABLE 1 Participants by diagnostic group.

	N	Age	Sex F/M (%F)	Psychotropic Medication Y/N (%Y)
ASC	47	23.72 ± 5.14 [18–44]	39/7 (84.8%)	17/25 (40.5%)
SA	25	22.16 ± 2.04 [19–27]	21/4 (84.0%)	19/3 (86.4%)
NT	151	21.21 ± 2.57 [18–35]	98/49 (66.7%)	1/33 (2.9%)
Total	223	21.9 ± 3.44 [18–44]	158/60 (72.5%)	37/61 (37.8%)

As we combined data from several studies, screening questions varied slightly between recruitment groups. The number of participants that provided responses for each variable are as follows: (1) Age: N = 203, (2) Sex: N = 218, (3) Psychotropic Medication: N = 98.

with moderate or high ADOS-2 evidence of autism in the autistic group. We used the lower part of that threshold (total score of 5) for females since previous studies have suggested they may score lower on the ADOS-2 even when experiencing symptoms at similar severity levels to males (56, 57). All participating males assigned to the autism group had a total score of 6 or higher.

An additional 23 participants who were not clinically tested were also included in the autistic group due to self-report of clinically relevant symptoms at or near established cutoffs for the *Autism Spectrum Quotient (AQ)* (58) ($n = 19$) (≥ 26) or the *Ritvo Autism Asperger Diagnostic Scale-Revised (RAADS-R)* (59) ($n = 4$) (≥ 65). Twenty-five participants exhibited clinically significant socially anxious traits according to clinician evaluation of the *Mini International Neuropsychiatric Interview (MINI)* interview (60) and below-threshold ADOS-2 scores, and 151 demonstrated neurotypical or subclinical levels of these traits according to each study's measures.

As one of the studies included here specifically included only women, our sample was primarily female (72.5%), even within the high autistic trait group (84.8%), where women have been historically underrepresented (61, 62). Across the 158 participants who reported their ethnicity, 87.3% identified as white, 12.7% identified as Hispanic or Latino, 4.4% identified as Asian, 1.3% identified as African American or Black, and 5.1% identified as Pacific Islander, Native American, or other.

Descriptives

No demographic factors, measure scores, or switch rates exhibited significant skew. We removed outliers above or below 1.5 times the interquartile range for each measure and switch rate condition (Supplementary Table S1). Using the consistency definition of intraclass correlation (ICC) and a 95% confidence interval, we found good reliability between the switch rates measured in sessions 1 and 2 (Spin ICC = 0.806, $F[188, 188] = 5.153$, $p < 0.001$; Neutral ICC = 0.845, $F[187, 187] = 6.464$, $p < 0.001$; Emotional ICC = 0.877, $F[183,183] = 8.133$, $p < 0.001$; see Figure 1).

Depending on their assigned study, some participants took the AQ more than once, in which case scores for both administrations were averaged. One participant's data was omitted from analysis entirely due to a variance of 32 points in AQ score between sessions and only one trial of binocular rivalry having codable time stamps.

As we combined binocular rivalry data from three studies, participants completed several measures of autistic and socially anxious traits. Table 2 describes participant group scores for the behavioral trait measures. The average AQ score in the autism group was above the threshold of 26 for clinical referral. The social anxiety group did not exhibit clinically significant AQ scores ($M = 21.90$, $SD = 6.33$). While many participants met standard criteria for social anxiety and also exhibited clinically significant total LSAS scores, the average total LSAS score for all groups was below the clinical threshold of 90 (ASC $M = 63.1 \pm 12.04$, SA $M = 72.5 \pm 11.27$), which may suggest a comprehensive range of symptom severities recruited in each group and effective subclinical representation. Average total LSAS scores in the neurotypical group were approximately half that of those in the autism and social anxiety groups ($M = 32.28 \pm 7.58$).

Binocular rivalry equipment setup and task

All three studies utilized the same Binocular Rivalry task. To measure the binocular rivalry switch rate, we used a 7,140–79 LEEDS Luxury Virtual Reality Headset, which holds a smartphone inside (Figure 2A). We displayed three images to each participant, each representing a different binocular rivalry condition (Figures 2B–D). The first rivalrous image subjects viewed included two monocular images adapted from stimuli used in Sandberg et al. (63): a red circular patch of square wave gratings presented to the left eye and a blue circular patch of square wave gratings presented to the right eye (spatial frequency = 3 cycles/degree, contrast = 100%). Due to difficulties with achieving stable vergence and minimizing piecemeal rivalry while viewing this stimulus with the virtual reality headset, both patches were made to rotate continuously in a clockwise direction at a rate of 0.33 rotations/s so that the gratings on the red circular patch were always perpendicular to the gratings on the blue circular patch (64, 65).

We also displayed a composite image of a face with an emotional facial expression (angry; presented to the left eye) and an image of a

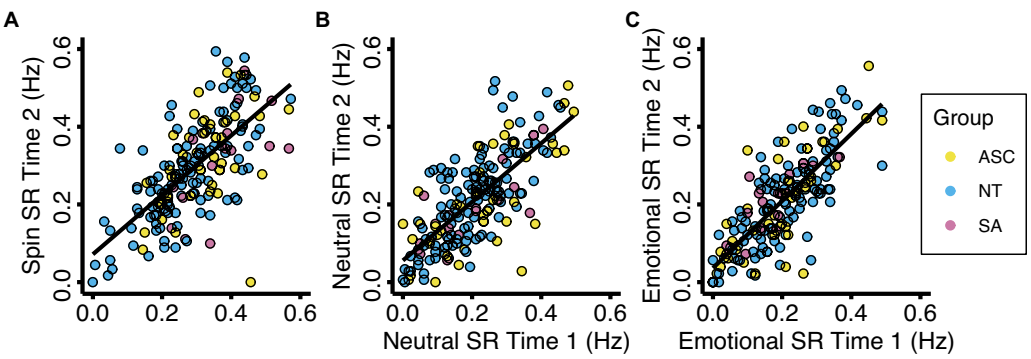

FIGURE 1
Test-retest reliability for the three experimental conditions. Each data point represents the mean binocular rivalry switch rate for one participant on two study visits during each experimental condition. Results show a significant correlation for **(A)** the spin condition (ICC = 0.806, F(188, 189) = 5.178, $p < 0.001$), **(B)** the neutral condition (ICC = 0.846, F(188, 188) = 6.483, $p < 0.001$), and **(C)** the emotional condition (ICC = 0.867, F(183, 184) = 8.073, $p < 0.001$). Abbreviations: ASC, autism spectrum condition; NT, neurotypical; SA, social anxiety; SR, switch rate.

TABLE 2 Psychometric scores.

	ASC	SA	NT	Total
AQ	30.4 ± 6.13	21.90 ± 6.33	14.90 ± 4.77	18.80 ± 8.14 [6–40]
RAADS-R	120.73 ± 37.30	--	30.64 ± 11.16	90.67 ± 53.02 [15–178]
TCI-HA	76.04 ± 17.7	--	54.22 ± 13.82	57.95 ± 17.00 [30–94]
LSAS-Fear	36.80 ± 13.31	42.50 ± 13.27	17.14 ± 7.60	32.67 ± 15.85 [2–62]
LSAS-Avoidance	26.30 ± 10.77	30.00 ± 9.26	15.14 ± 7.56	24.10 ± 11.11 [2–45.5]
LSAS-Total	63.10 ± 23.80	71.53 ± 22.73	31.19 ± 15.95	56.10 ± 27.08 [4–108]

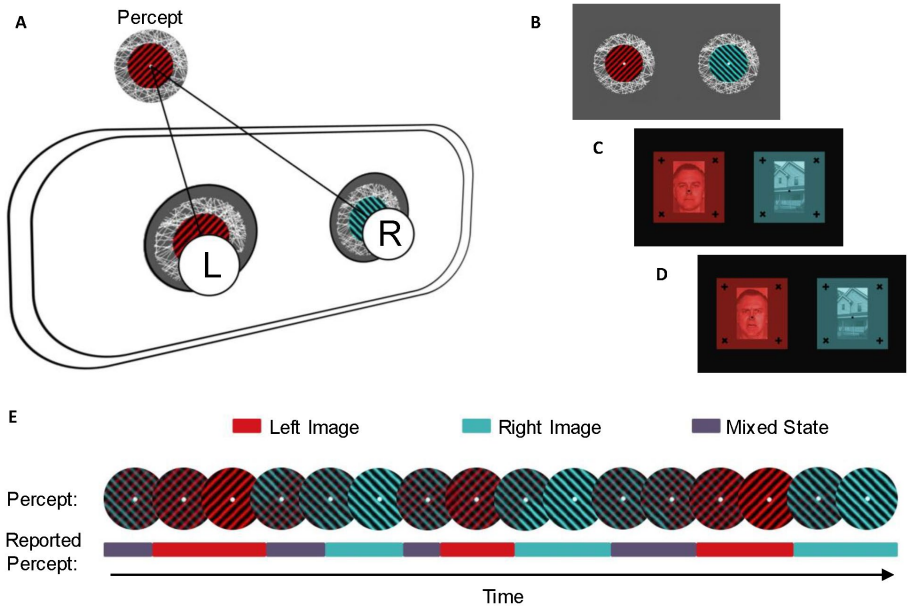

FIGURE 2
Experimental setup and stimuli. **(A)** Stimuli were presented dichoptically through a virtual reality headset. The left eye (L) and right eye (R) were simultaneously presented with distinct images that were visually aligned using centered fixation points, so the left and the right image would be seen as a single percept. **(B)** Stimuli for the spin condition. Each stimulus was presented with an identical fixation point and textured border and animated to rotate clockwise to enhance stable vergence. The colored grating on the left stimulus was aligned perpendicular to the colored grating on the right stimulus. Stimuli for the neutral **(C)** and emotional **(D)** conditions were presented with identical fixation points and solid frames. The left stimulus was a red monochrome image of a person with an emotionless or emotional facial expression, while the right stimulus was a blue monochrome image of a house. **(E)** Example of perceptual switches and reported percepts during the binocular rivalry task. During binocular rivalry, the dominant percept alternates between the dominant perception of the left image (red), the dominant perception of the right image (blue), and a mixed percept (purple). Participants reported perceptual switches in real-time using keypresses.

house (presented to the right eye). The third image composite was an image of a face with a neutral facial expression (presented to the left eye) and an image of a house (presented to the right eye). We selected these facial valences based on previous research which compared response to threatening (angry and/or fearful) faces with neutral faces (66). In particular, a metanalysis of visual paradigms found that increased anxiety is linked with more frequent orientation to threatening images as compared with neutral ones (67). In binocular rivalry tasks, emotional faces have been shown to predominate over neutral ones (68). In an autistic sample, Van der Donck et al. (47) had also identified similar neural stimulation in happy, sad, and neutral facial conditions (47). In order to maximize potential effects when pairing faces with a neutral object in the classic face-house design (69), we opted to use one neutral face and one angry face, theorizing that a neutral face would be most affectively congruent with the neutral house, and a face depicting an angry valence well-established to be interpreted as threatening would be least congruent. Face images were obtained from the Pictures of Facial Affect collection by the Paul Ekman Group (70). All images included a fixation point and a textured background or nonius lines to maintain stable vergence (64). Participants used a LabView program on a desktop computer and the arrow keys on a keyboard to record when their perception changed from seeing one image as dominant to the other.

Participants were presented with up to 10 versions of each image set to determine which version allowed for the best visual alignment. Each version contained identical images from the respective stimulus condition with varying distances between central fixation points. After the six trial runs for the first image set were complete, participants were instructed to remove the goggles to begin the fitting procedure for the following image.

Participants were shown one of the three image sets for six 30-s intervals. During each interval, participants were instructed to

self-report perceptual switches between the image presented to the left eye, the image presented to the right eye, or a mixed percept (defined as less than 80% dominance) using arrow keys on a keyboard (Figure 2E). After the 30 s were finished, subjects were told to close their eyes and rest for 15 s, after which they would open their eyes again and continue the next 30-s reporting period. This process was repeated for each participant for the other two image sets.

In order to ensure the accuracy of keyboard reporting and to account for changes in focus upon ocular relaxation, participants were given two practice rounds before the first geometric image set (spin) and one practice round before each subsequent set (emotional or neutral). After each practice run, the researcher vocally confirmed with the participant that the image remained clear and comfortable to view.

If participants completed both the first and second binocular rivalry appointments in 1 day, they were required to rest for at least 10 min between segments one and two, during which time they were encouraged to relax their eyes by looking at least 5 feet ahead.

Behavioral trait measures

Several self-report surveys and diagnostic measures were acquired, although not all participants completed every measure. There were slightly different combinations of behavioral measures; the total *n* collected for each measure is identified in the description. All surveys were administered via the Qualtrics online software platform (Qualtrics, Provo, UT).

Autism symptoms

Autism spectrum quotient (AQ; *n*=217)

This 50-question survey (58) is frequently used to quantify autism-associated traits in clinical and neurotypical cohorts. Previous studies have found it to have internal reliability above 0.7 (71) and high test–retest reliability (72).

Autism diagnostic observation schedule-2nd edition, module 4 (ADOS-2, *n*=35, Mod 4)

This diagnostic assessment (55) was completed by 35 individuals in the sub-study with the highest concentration of autism traits. Together with the MINI, it was used to differentiate between participants with social anxiousness related to autism or that which was more reflective of an independent social anxiety disorder. Many researchers and clinicians consider the ADOS-2 (55) the gold standard for observing traits of autism. It involves targeted conversation and activities to press for reciprocal social interaction. It was administered by trained clinical researchers.

Anxiety symptoms

Temperament and character inventory, harm avoidance scale (TCI-HA; *n*=152)

The TCI-HA (73) was given to assess anxious traits, which may conflate autism and social or generalized anxiety diagnosis and possibly affect binocular rivalry switch rates. This measure of anxiety is of particular interest since it is used to assess traits of many severities, including subclinical levels of anxiety which are significant but may be overlooked by more strictly clinical measures.

Liebowitz social anxiety scale (LSAS; *n*=57)

This survey (74) is used in the assessment of SAD symptoms. It correlates with the Social Phobia Scale and the Social Interaction Anxiety Scale (75) and scores are also associated with overall fear levels (76). In the first half, participants use a Likert scale of 0–3 to rank the fear they would feel if engaged in various social situations or interactions. Then, they rank the same scenarios based on how much they would avoid such an encounter. Its ability to capture both internal reactions and external behaviors is valuable to understanding potential masking of anxiety symptoms.

Additional measures

Demographics questions

These varied across study and included questions about age (*n*=203), biological sex (*n*=228), race and ethnicity (*n*=157), handedness (*n*=91), and psychotropic medication usage (*n*=98). We also collected information on adverse childhood experiences, PTSD symptoms, suicidality, sleep, health concerns, diet, and exercise that were part of a more extensive study and not intended for this analysis of binocular rivalry data.

Data analysis

To calculate binocular rivalry switch rates, we counted the number of times participants indicated a shift between left-dominant and right-dominant perceptions and divided this count by the 30 s in which keypresses were collected during each trial in order to find the number of switches per second. We did not count partial switches (mixed percepts), which were reported via an up arrow key press.

Initially, we measured the test–retest reliability of our binocular rivalry protocol by calculating intraclass correlation coefficients for each subject's average perceptual switch rate for each condition (spin, neutral, and emotional) in session one and that of the same condition as measured during session two (Figure 1). Once reliability was confirmed, corresponding switch rates from the two repeated sessions were averaged before analysis.

To examine our first hypothesis regarding the effect of stimulus conditions (spin, neutral, or emotional) on switch rate, we used a one-way ANOVA to compare switch rates between image valences. Then, based on that test's significance, we completed post-hoc t-tests to isolate which stimulus conditions were driving the effect. Each compared the effect of two of the three stimulus conditions (spin and neutral, spin and emotional, or neutral and emotional) on switch rate.

Next, we examined our second hypothesis, namely, whether any image condition(s) could predict diagnostic group assignment. We used a similar omnibus ANOVA to examine our second hypothesis regarding whether any image condition(s) could predict diagnostic group assignment. Since the stimulus condition effect could potentially overshadow the diagnostic group effect in the omnibus test, we repeated the ANOVA model three times, once for each image valence (spin, neutral, or emotional), to compare the effect of the diagnostic group on switch rates for each condition. Finally, in order

to assess differences in performance in autism, social anxiety, and neurotypical groups within any significant image condition(s), if applicable, we planned to conduct three additional pairwise regressions with switch rate data from two diagnostic groups within one image valence at a time (Spin ASC vs. Spin NT, Spin ASC vs. Spin SA, or Spin SA vs. Spin NT).

Due to unequal sample sizes and potential unequal variance between diagnostic groups, we also used the non-parametric Kruskal–Wallis test to further assess diagnostic group differences. As in our previous ANOVA model, since any stimulus condition effects identified for Hypothesis 1 could potentially overshadow any diagnostic group effect in the omnibus test for Hypothesis 2, we also compared the effect of diagnostic group on switch rates for each condition by repeating the Kruskal–Wallis test three times with data from only one image valence (spin, neutral, or emotional) in each iteration. In parallel form, we also planned to compare differences in performance in autism, social anxiety, and neurotypical groups within image condition(s) via three follow-up Brunner-Munzel tests with switch rates from two diagnostic groups within one image valence at a time (Spin ASC vs. Spin NT, Spin ASC vs. Spin SA, or Spin SA vs. Spin NT).

As the availability of demographic information such as age, sex, and psychotropic medication varied according to the study in which subjects participated (Table 1), we removed covariates from our original analyses to maximize power. In order to verify that any observed effects were due to diagnostic group or stimulus condition, we repeated each post-hoc analysis with age, sex, and medication usage included. We also repeated the analyses using only data from participants with clinician-verified ADOS-2 scores (35 participants) or, in the absence of available ADOS-2 scores, report of non-study clinical diagnosis of autism (6 participants) rather than relying on thresholds assigned by self-report measures (AQ, RAADS-R, or TCI). To address potential experimental confounds, we repeated the analyses described above using only participants who had data from both time points, as some were only able to complete one session.

Following our analysis of differences between stimulus types and diagnostic groups, we also examined the effect of more broad symptom presentations on switch rates by performing a series of separate regressions with either AQ, TCI-HA, Liebowitz Total, or ADOS-2 scores as the outcome and with switch rate for one stimulus category, age, sex, and the number of data points as predictors. Each regression for each symptom measure was repeated three times, once with switch rates specific to each stimulus condition, for a total of 15 tests. We corrected for multiple comparisons using the Holm–Bonferroni Sequential Correction for each hypothesis question (77).

Results

Main analysis

The aim of this study was to investigate differences in binocular rivalry dynamics among adults with a diagnosis of autism or high levels of autistic traits, adults with a diagnosis of SAD or high levels of socially anxious traits, and non-anxious neurotypical adults. First, we hypothesized that across groups, binocular rivalry switch rates would be different for the two facial stimuli. In order to discern the possible effects of the image type on switch rate, we conducted a one-way ANOVA. Condition was a significant predictor of switch rate ($F[2, 652] = 28.152$, $p < 0.001$). We completed three follow-up paired t-tests to isolate which experiment conditions drove the effect and investigate whether any effects were most prominent within the facial conditions. Image condition was predictive of switch rate for neutral versus spin ($F[1, 437] = 66.75$, $p' < 0.001$) and emotional versus spin ($F[1, 434] = 76.92$, $p' < 0.001$), but not for emotional versus neutral ($F[1, 433] = 0.344$, $p' = 0.558$). Therefore, the spin condition drove the effect of condition rather than differences in facial valence.

Second, we predicted that switch rates would be predictive of diagnostic group, in that an increasing number of socially anxious traits would positively correlate with switch rate and an increasing number of autistic traits would negatively correlate with switch rate. Although diagnostic group assignments aligned with established dimensional measures of autism and social anxiousness, the range of our observed switch rates remained largely consistent between groups. This more narrow range of switch rates also bore out between image conditions. While the spin condition had a slightly wider range of observed switch rates compared to the neutral or emotional facial conditions (Table 3), those measured in all image conditions and diagnostic groups showed as few as no oscillations per second and no greater than 0.564 oscillations per second. To examine whether there were diagnostic group differences in switch rates, we initially repeated the previous omnibus ANOVA but used the diagnostic group, rather than condition, as the predictor. While this was not significant ($F[2, 652] = 0.445$, $p = 0.641$), to ensure any effects of the diagnostic group were not overshadowed by the condition effect present due to including switch rates from all conditions in the model and to continue to explore our third hypothesis regarding whether effects were different between geometric and facial valences, we performed three planned pairwise regressions with each model examining possible group effects of switch rate within one stimulus condition. There were no significant group differences in switch rate by diagnostic group in any trial type (Spin: $F[2, 217] = 2.43$, $p' = 0.271$; Neutral: $F[2, 216] = 0.183$, $p' = 1.00$; Emotional: $F[2, 213] = 0.155$, $p' = 1.00$; see Figure 3).

In order to account for unequal sample sizes and unequal variance between controls and socially anxious participants within the spin condition, we performed a Kruskal–Wallis test with average switch rates for all conditions as the outcome and diagnostic group as the predictor. While this was not significant (X^2 $[2, N = 652] = 1.03$, $p' = 0.597$), in similar fashion to our previous model, we performed three follow-up Kruskal–Wallis tests with each examining possible diagnostic group effects on switch rates within one stimulus condition. Once more, for all stimulus conditions, there were no significant

TABLE 3 Average binocular rivalry switch rates (switches/s) by diagnostic group and condition.

	ASC	SA	NT	Total
Spin	0.316 ± 0.094 [0.114–0.506]	0.343 ± 0.095 [0.183–0.492]	0.287 ± 0.117 [0–0.564]	0.299 ± 0.111 [0–0.564]
Neutral	0.219 ± 0.122 [0.011–0.492]	0.216 ± 0.093 [0.061–0.400]	0.212 ± 0.105 [0.003–0.464]	0.214 ± 0.107 [0.003–0.492]
Emotional	0.202 ± 0.113 [0–0.453]	0.208 ± 0.092 [0.056–0.439]	0.210 ± 0.106 [0–0.464]	0.208 ± 0.106 [0–0.464]

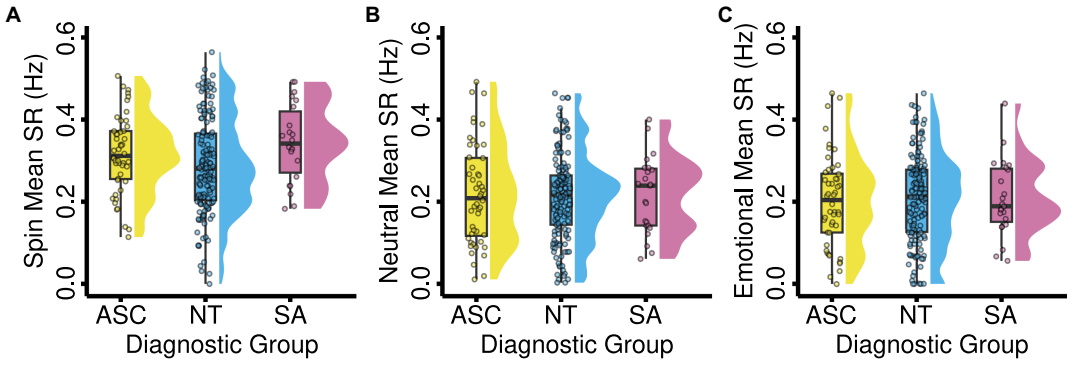

FIGURE 3
Mean binocular rivalry switch rate by diagnostic group. Mean switch rates for ASC, NT, and SA diagnostic groups for **(A)** the spin condition, **(B)** the neutral condition, and **(C)** the emotional condition. Abbreviations: ASC, autism spectrum condition; NT, neurotypical; SA, social anxiety; SR, switch rate.

differences in switch rates according to diagnostic group (Spin: X^2 [2, $N = 652$] = 5.24, $p' = 0.218$; Neutral: X^2 [2, $N = 652$] = 0.21, $p' = 1.00$; Emotional: X^2 [2, $N = 652$] = 0.27, $p' = 1.00$; see Figure 3). Additionally, after correcting for multiple comparisons, follow-up Brunner–Munzel tests revealed no significant differences in switch rates between diagnostic groups (Supplementary Table S2), with no nonparametric findings diverging from those of the original parametric models.

We also used multiple regression analyses to explore whether average binocular rivalry switch rates in any image condition were predictive of self-report measures of autistic or anxious traits. We controlled for age, sex, and the total number of trails administered. AQ, TCI, and Total LSAS scores were not significantly predictive of switch rate in spin, neutral, or emotional image valences (Figure 4; Supplementary Table S3).

Post hoc analyses

Since this analysis was based on data collected through several different projects and some survey measures varied between them, we did not have handedness, age, or medication data for a significant number of our participants. Given that effect sizes of binocular rivalry switch rate differences may be small, in order to maximize power by maintaining maximum sample size, we did not include these factors in our original models. However, since other researchers have suggested that they may also influence binocular rivalry switch rates, we repeated our initial ANOVA models with these factors as well as sex included and found no significant differences in the overlying trends. Although age emerged as a consistent positive predictor across diagnostic groups and stimulus conditions (F[1, 287] = 17.419, $p < 0.001$), stimulus condition was still only predictive of switch rate when comparing geometric stimulus to facial stimuli, but not between facial valences (Emotional vs. Neutral: F[1, 191] = 0.206, $p' = 1.00$; Emotional vs. Spin: F[2, 216] = 0.183, $p' = 1.00$; Neutral vs. Spin: F[2, 213] = 0.155, $p' = 1.00$). (For a complete statistical report, see Supplementary Table S4).

We also repeated our original analyses of diagnostic group differences with only those participants whose group assignment had clinical confirmation (as opposed to using suggested cutoffs for self-report measures alone), which again did not reveal any significant differences in switch rate between ASC, NT, or SA participants (F[2, 547] = 0.197, $p < 0.821$; Supplementary Table S5).

Finally, we also added the number of trials each participant completed for each condition as a predictor since a small percentage of participants did not complete all 12 iterations due to visual fatigue or study attrition, but this was not significantly predictive in any model (F[1, 651] = 0.101, $p < 0.751$; Supplementary Table S6).

Discussion

We did not replicate previously reported significant switch rate differences in autism, social anxiety, and neurotypical populations. First, we examined whether switch rates varied according to image type and found that while participants of all three groups responded differently to geometric as opposed to facial images, there were no significant differences in switch rates for angry versus neutral facial expressions. We also did not find significant differences in switch rate according to diagnostic group classification. Similarly, no switch rates observed during any image conditions were predictive of measures of social anxiousness and autistic traits.

While our results vary from that of Nagamine et al. (38) and Robertson et al. (31, 37), and Spiegal et al. (42) whose designs we modeled, they are in line with the lack of autism-associated changes in switch rates noted by Said et al. (40), Karaminis et al. (41), and Wykes et al. (39) (Object Stimuli). While binocular rivalry is still an emerging area of biomarker research, given that findings around slower switch rates in autism are the most robust of the three diagnostic groups we examined, we are particularly interested in our lack of effect for this cohort. As high rates of comorbid social anxiety are reflective of the autistic community at large, if anxiety supersedes foundational brain differences seen in autism or if symptoms of social anxiousness are representative of the same cognitive processes in both autistic and non-autistic socially anxious groups, our focus on socially anxious autistic individuals may have led to an overshadowing of previously observed binocular rivalry effects. Namely, anxiety's proposed tendency to increase switch rates might counteract or overcome the slower switching associated with autism alone.

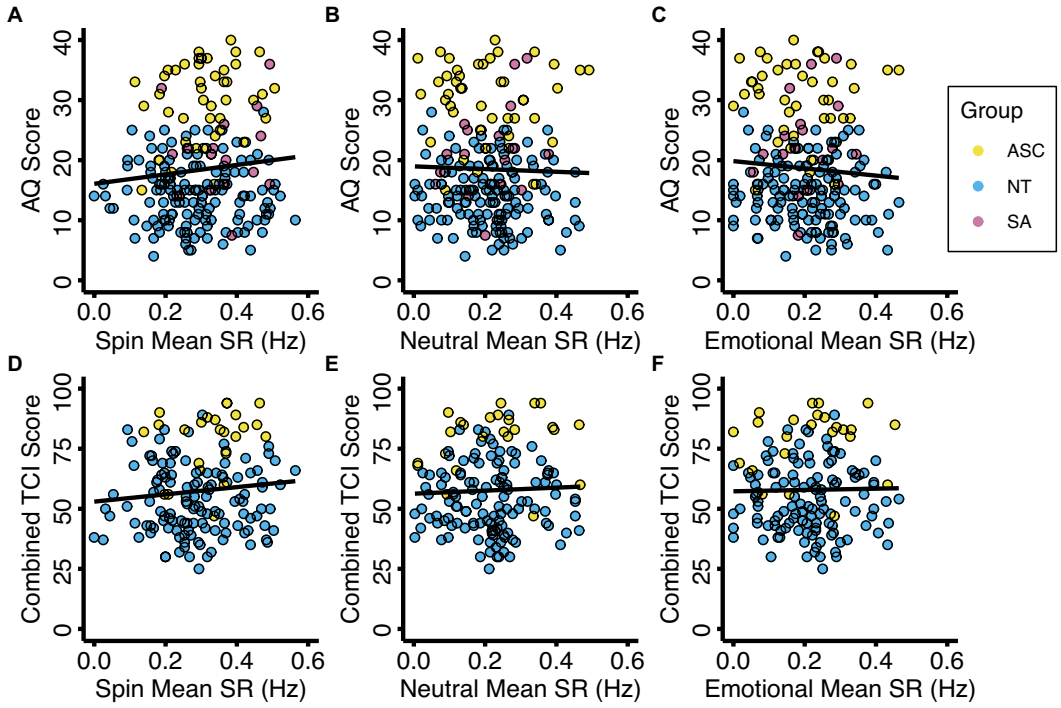

FIGURE 4
Binocular rivalry switch rate with autistic traits and anxious traits. Diagnostic groups are represented by color. Relationships between mean switch rates and autistic traits **(A–C)** and anxious traits **(D–F)** for the three experimental conditions. Abbreviations: ASC, autism spectrum condition; AQ, Autism Spectrum Quotient; NT, neurotypical; SA, social anxiety; SR, switch rate; TCI, Temperament and Character Inventory, Harm Avoidance Scale.

Furthermore, sensory sensitivity has been suggested as a cause of heightened anxiety in autism, meaning that some autistic participants may experience exceptionally high anxiety levels during binocular rivalry tasks regardless of what stimuli are presented, which may illuminate the absence of effect of differing facial valances in this group (78).

Beyond the implications of potential comorbidity, our participant pool also had a significant female majority, even within the autism group. Since prior studies of autism utilizing binocular rivalry used primarily male samples and some researchers theorize that autism may be related to biological sex and gender differences in cognition, particularly as explained via the extreme male brain theory of autism and the female protective effect (19, 79), our inability to replicate the switch rate slowing previously observed in autistic groups may be related to emerging sex differences rather than a broader lack of autism-associated effects. It is also possible that, regardless of sex, the neural mechanisms behind social anxiousness in SAD and autism are so similar that differences are not measurable via binocular rivalry tasks. Finally, the associations between higher levels of sensory sensitivity and anxiety and masking or the effects of camouflaging abilities are not yet fully understood in autistic females, which warrants further exploration.

Concerning our lack of observed differences in social anxiety, 23 of our participants with SAD and 18 with autism were recruited through a more extensive examination of suicidality which is increasingly recognized as especially prevalent in autistics (80) and is also associated with depression. It has recently been shown that depression may slow switch rates (81). If binocular rivalry phenomena are less condition-specific than previously theorized, it is possible that a similar sort of slowing occurred among socially anxious participants in our sample who also experience depressive symptoms, with any social anxiety-associated increases in switch rate (38) being counteracted by comorbid depression's associated decrease.

We also hypothesize that the lack of significant differences in switch rate between facial valences may be related to our choice of a neutral face as a control for the emotional one, which depicted anger. It is possible that individuals with social anxiety, especially those with autism, may subconsciously recognize neutral faces as threatening and, therefore, experience switch rates similar to those observed when viewing the angry expression more widely associated with threat bias. For example, in the still face paradigm, infants with a high genetic likelihood of having autism exhibit fewer prosocial behaviors when interacting with an unresponsive, neutral-faced caregiver, and these decreases in social bids corresponded to greater difficulties with emotional regulation later on in life (82). While this decrease in outreach could reflect a lack of interest, given that the high-likelihood infants still exhibited other signs of distress and frustration at similar levels to the typically developing group, it has been theorized that this withdrawal is a stress/freeze response resulting from heightened emotional and sensory sensitivity to the ambiguous response (82). This idea also aligns with Tottenham et al.'s (83) findings that autistic participants' visual avoidance of neutral faces corresponded to the perceived threat level for each image (83). The same study also used functional magnetic resonance imaging to observe that while autistic individuals experienced differential amygdala activation for all facial

valances, the effect was most strong for neutral stimuli. A similar study also found that during exposure to neutral faces, right amygdala activation was heightened in those with social anxiety disorder but not in controls (11). This observation may suggest a similar condition-associated tendency to assign negative valences to images that neurotypical participants process as non-threatening. Therefore, we suggest that future studies of binocular rivalry in socially anxious populations, especially those with a high prevalence of autism, incorporate a wider variety of facial expressions or utilize a less emotionally ambiguous facial affect such as happiness for baseline comparisons.

We identified three primary limitations in the present study. First, data collection relied on participant self-report of perceptual switches. Although participants were trained to respond to the task consistently and test–retest reliability was sound, the precise instance of a perceptual switch during binocular rivalry is ambiguous by nature. Additionally, the experimental paradigm did not account for potential individual differences in the onset of binocular rivalry (84). Third, our study did not explore associations between neural activity and self-reported switch rate, although prior evidence strongly suggests self-report accuracy in neurotypical and autistic individuals (42).

Conclusion

Although we did not replicate the significant switch rate differences related to anxiety and autism that were observed in prior studies (31, 37–39, 42, 85), we did replicate the absence of a significant effect observed by other teams (39–41) and speculate that this lack of effect may be due to similar cognitive processes involved with social anxiousness in autism and social anxiety alike. We also investigated the external validity of previously observed binocular rivalry trends by incorporating a larger participant group than had been accessible during prior investigations and by representing a more comprehensive range of clinical and subclinical levels of social anxiousness and autistic traits. More broadly, we developed and verified a replicable binocular rivalry protocol utilizing virtual reality goggles in a sensory-sensitive group.

Our absence of observed visual processing differences according to facial emotional valence, as was previously measured with eye-tracking and congruency tasks, might illuminate future discussions of binocular rivalry as a measure of threat detection in socially anxious groups, particularly as binocular rivalry may represent higher or lower stages of visual processing than other measures. Furthermore, our lack of observed effects may imply that the binocular rivalry differences seen in more severe, independent instances of either condition are not generalizable to comorbid or subclinical cases, which are potentially even more common and should not be overlooked during screening or intervention. Similarly, the lack of observable differences in switch rates between clinical, subclinical, and neurotypical participants suggests the need for further investigations of neural similarities and distinctions between social anxiousness in autism and social anxiety.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Brigham Young University Institutional Review Board F19260, F2020-242, and IRB2020-429. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JO, JM, BB, and JN developed stimulus and experiment design. SK, JO, JM, and HB scheduled participants and administered protocol. HB, JM, JO, and SK processed the data and verified the inter-rater reliability. RL and SK conducted initial literature review and wrote introduction. SK, JO, and HB described methods and materials. SK, JO, and JN developed the analysis script in R and wrote results and conclusions. SK and JN developed script for statistical figures. JO finalized designs, created original methods illustrations, wrote all image captions, and prepared the data files and analysis scripts for sharing on the Open Science Framework. SK and JO wrote the discussion and conclusion. TG and MS verified clinical interpretation of results and provided insight into potential sex differences. RL and JN supervised the manuscript. All authors participated in reviewing, editing, and revising the manuscript.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1181797/full#supplementary-material

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Linehan's biosocial model applied to emotion dysregulation in autism: a narrative review of the literature and an illustrative case conceptualization

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Emotion dysregulation (ED) is a transdiagnostic difficulty prevalent in autism spectrum condition (ASC). Importantly, recent research has suggested that ED is involved in self-harm and suicidality. Pre-existing models on the etiology of ED in ASC focus mainly on biological factors to ASC features, such as sensory sensitivities, poor flexibility, and sensitivity to change. However, although psychosocial factors seem to play a role in the emergence of ED in ASC as well (e.g., childhood maltreatment and camouflaging), there is a lack of a comprehensive model conceptualizing biosocial factors involved in ED in autistic people. Linehan's biosocial model (1993) is one of the leading etiological models of ED in borderline personality disorder (BPD). It conceptualizes ED as emerging from transactions between a pre-existing emotional vulnerability in the child and an invalidating developmental environment. Beyond its clinical relevance, Linehan's model has gathered empirical evidence supporting its pertinence in BPD and in other psychiatric disorders. Although ASC and BPD are two distinct diagnoses, because they may share ED, Linehan's biosocial model might be useful for understanding the development of ED in ASC. Hence, this article aims to provide an application and extension of Linehan's model to conceptualize ED in ASC. To do so, we conducted a narrative review of the literature on ED and its underlying factors in ASC from a developmental perspective. To investigate the pertinence of the biosocial model applied to ED in autistic people, we were interested on data on (i) ED and its behavioral correlates in ASC, in relation to the biosocial model, (ii) the potential biological and psychosocial correlates of ED in ASC and (iii) the overlapping difficulties in ASC and BPD. Finally, to assess the pertinence of the model, we applied it to the case of an autistic woman presenting with ED and suicidal behaviors. Our review and application to the case of an autistic woman suggest that ED in ASC encompasses factors related to both biological and psychosocial risk factors as conceptualized in the BPD framework, although in both domains ASC-specific factors might be involved.

KEYWORDS

autism spectrum condition, emotion dysregulation, self-harm, suicidality, Linehan's biosocial model, etiology

Introduction

Emotion dysregulation (ED) refers to emotional experience and/or expression that interferes with appropriate goal-directed behavior (1). ED has been widely studied in borderline personality disorder [BPD; (2, 3)]. Linehan's biosocial theory (1993), one of the leading etiological models of BPD, places ED at the core of the disorder. Linehan's theory conceptualizes ED as emerging from transactions between emotional vulnerability and an invalidating developmental environment (4, 5). Emotional vulnerability refers to biological factors with a genetic basis evidenced by disruptions in the emotional system involving different brain areas (e.g., prefrontal regions and amygdala) (6). Linehan's theory has subsequently added temperamental impulsivity as an additional risk factor for BPD (4). Emotional vulnerability results in dysfunctions in three dimensions: (a) emotional hypersensitivity (i.e., low threshold for emotional reactions), (b) hyperreactivity (i.e., increased change in emotional intensity and extreme reactions), and (c) a slow return to emotional baseline (i.e., long-lasting emotional reactions) (6, 7). Invalidation, on the other hand, refers to the inadequate responses of the environment to the emotional needs of the child (5). It may occur through the neglect, minimization or punishment of the child's emotional experience, but also through physical and sexual abuse (4, 8). According to Linehan's theory, in people presenting with emotional vulnerability, early invalidation may result in maladaptive coping (i.e., self-harm with or without suicidal intent) when they are faced with difficult emotions (9, 10). An important corollary of this biosocial perspective is that, during their development, people with BPD did not learn the adaptive skills to regulate their emotions effectively. Hence, they may display rigid and pervasive dysfunctional strategies that were involuntarily targets of operant conditioning (e.g., "mom listens to me and is nice when I cut myself"; "dad says that it is stupid to cry") or modeling (5). Therefore, as adults, people with BPD lack the skills to regulate their emotions, as they were taught that emotional reactions are not to be trusted (i.e., they self-invalidate) and that emotions are dangerous and should be escaped or avoided (e.g., using crisis behaviors or emotional avoidance) (5). Importantly, Linehan developed dialectical behavior therapy (DBT), the treatment targeting ED with the most empirical support, based on this model (11, 12).

Some empirical studies have tested Linehan's model in BPD [e.g., (13, 14)]. Although it is not consensual, the model has amassed considerable evidence in its support. For instance, Reeves et al. (14) found that emotional vulnerability and ED were substantially associated with BPD symptoms, with ED mediating the relationship between emotional vulnerability and BPD symptoms. In addition, Carpenter and Trull (2) gathered findings supporting the role of biological factors such as emotion sensitivity and lability in the emergence of BPD. Interestingly, studies have supported the role of emotional hypersensitivity and slow return to baseline but not hyperreactivity in the emotional vulnerability found in people with BPD (6, 7). Regarding invalidation, Reeves et al. (14) found that parental invalidation in childhood does not predict BPD, while other findings have come to opposite conclusions (15–17), particularly concerning the involvement of maternal invalidation (18). Beyond the association between parental invalidation and BPD, cultural and intra-individual factors seem to be involved in the emergence of BPD. For instance, Keng and Soh (18) found that the association between self-reported maternal invalidation and BPD was moderated by two cultural factors: self-construal (i.e., the extent to which the self is defined independently of others or interdependently with others) and conformity to norms (18). In addition, Keng and Wong (16) showed that low levels of self-compassion were associated with BPD independently of parental invalidation. Finally, regarding the transaction between emotional vulnerability and invalidation, some studies support the transaction (4, 19) while others do not (13).

ED is strongly associated with BPD (3). However, several recent findings suggest that ED is a transdiagnostic mechanism of psychopathology (20–24). Although Linehan's model has not been directly studied outside BPD, findings support the involvement of biological vulnerability and invalidation in the emergence of ED in various psychiatric disorders (25), including trait impulsivity (26), and childhood maltreatment (linked to invalidation) (27–29).

In autism spectrum condition (ASC),[1] there has been a growing interest in overlapping difficulties with BPD, including ED (32, 33). Indeed, there is a considerable overlap in the diagnostic criteria for ASC and BPD (e.g., difficulties in social interactions) (34), which increases the risk of misdiagnosis, especially in women (35, 36). The high prevalence of ED in autistic individuals [e.g., between 50 and 60% in autistic youth; (37–39)] and its association with self-harm and suicidal behaviours (40, 41) may be an additional source of misdiagnosis with BPD (42). Indeed, autistic people presenting with ED and self-harm are reported to be at greater risk of being misdiagnosed with BPD since these difficulties are strongly associated with BPD (36, 42). It should also be noted that ASC and BPD can co-occur (34), with the co-occurrence being linked to higher suicidality than in BPD or ASC alone (43–45).

Few studies have investigated the etiological factors involved in ED in ASC, and most have focused exclusively on the role of ASC-related factors [e.g., (38, 39, 46)]. Thus, to our knowledge, no studies have attempted to conceptualize ED in ASC in relation to Linehan's model. This is of special relevance given the emerging interest in DBT to treat ED in ASC (47, 48). Indeed, recently, DBT has been found to be feasible and acceptable in autistic adults without intellectual disability (49, 50). In those with self-harm and suicidal behaviours, initial evidence suggests that DBT is effective in reducing ED (49). Nevertheless, to improve the pertinence of DBT to autistic individuals, it is of the utmost importance to provide treatments that consider the specific features potentially involved in ED in this population (51).

Case formulation is central to effectively implement behavioral treatments (52). Linehan's biosocial model provides a theoretical framework to inform case formulation when treating clients with BPD. However, it is still unknown whether it might also apply to

1 Note on terminology:
Throughout the manuscript, we use the term "autistic people" (identity-first), rather than "people with autism" or "people with autism spectrum disorder," as this was the terminology explicitly favoured by the majority of the autistic participants of a large-scale survey (30). We also use "autism spectrum condition" instead of the DSM-5 term of "autism spectrum disorder (ASD)" to be respectful to those on the spectrum who feel that the term "disorder" is stigmatising, whereas the term "condition" acknowledges both the difficulties and the differences and strengths in autistic people (31).

autistic adults. This is crucial since DBT is in its early stages in ASC and that ED in autistic people is still poorly understood (32).

This article aims to provide an application of Linehan's model to conceptualize ED in ASC. To do so, we conducted a narrative review of the literature on ED and its underlying factors in ASC across the lifespan. Indeed, narrative reviews are well suited to address research questions with a broad scope to draw conclusions and generate areas for future research questions (53, 54). To investigate the pertinence of the biosocial model applied to the ED found in autistic people, we were interested on data on (i) ED and its behavioral correlates in ASC, in relation to the biosocial model, (ii) the potential biological and psychosocial correlates of ED in ASC and (iii) the overlapping difficulties in ASC and BPD. Finally, to assess the pertinence of the model, we applied it to the case of an autistic woman presenting with ED and suicidal behaviours.

Our review was conducted using PubMed, Medline Ovid SP and PsycINFO search engines. Articles had to meet the following inclusion criteria: (a) articles published after 2000, (b) articles in English, (c) articles published in a peer-reviewed journal (d) articles interested in autistic individuals without intellectual disability and/or individuals with BPD. Given that our approach was developmental, we included articles on ED and its correlates in both youth and adults with these diagnoses. Hence, we specify throughout our review whether the findings relate to youth or adults. Our articles research paired keywords were the following ones: "Emotion dysregulation," "Emotion regulation," "Emotion," "Emotional reactivity," "Autism," "Adults," "Children," "Youth," "Adolescents," "Borderline personality disorder," "Impulsivity," "Impulsiveness," "Self-harm," "Non-suicidal self-injury," "Suicidality," "Suicide," "Linehan's biosocial model,"" Linehan theory," "Emotional vulnerability," "Invalidation," "Trauma," "Adverse events," "Bullying," "Autistic camouflaging," "Emotional scaffolding," "Predictors," "Correlates," "Aetiology," "Etiology." To ensure the quality of our narrative review, we referred to the six criteria listed in the Scale for the Assessment of Narrative Review Articles [SANRA; (55)].

For the illustrative case conceptualization, we used the client's quantitative and qualitative data. The client provided informed consent for the use of her data and participated in building and writing the case conceptualization. The use of personal data was approved by the University of Strasbourg research ethics board (Reference: CE-2022-138).

Emotion dysregulation in ASC

Recent research suggests that autistic people are more likely to develop ED than the general population (32, 33, 39). In fact, studies have shown fewer emotion regulation abilities and greater maladaptive strategies (e.g., rumination, avoidance) in autistic youth compared to their non-autistic peers (32, 56). Although ED has been mostly studied in autistic youth, it also concerns adults (57). Similar to findings in the general population (58), autistic women appear to present with greater ED than autistic men (59–61).

ED is not a diagnostic criterion for ASC (62), but given its high prevalence in autistic people, some researchers have questioned whether it should be added to ASC core features (39, 40, 63). Indeed, ED has been found to be highly associated with autistic core features (39, 51). Among them, restricted and repetitive behaviours (RRBs) in particular have been found to be the strongest ED predictor in autistic people (39, 64), suggesting that RRBs might contribute to ED, possibly through inhibitory dyscontrol (i.e., executive dysfunction) (39). Indeed, effective emotion regulation relies on inhibitory control and cognitive flexibility, which enables the use of context-dependent strategies (65). This is especially the case for emotion regulation skills that require increased adaptability, such as problem solving and cognitive reappraisal (65). Executive dysfunction might thus interfere with this ability (32, 51, 66), and lead to the increased use of maladaptive emotion regulation strategies (e.g., rumination, avoidance, suppression) but also RRBs (38). However, other findings indicate that RRBs rather stem from ED (39, 64, 67), since one quarter of these behaviours appear in reaction to emotional triggers (67). Irrespective of the direction of the relationship between ED and RRBs, recent data suggest that self-harming behaviours in ASC are similar to those seen in the general population (68). Therefore, contrary to past research suggesting that self-harming behaviours are part of RRBs in autistic people (69, 70), self-harming behaviours might actually be distinct from RRBs. Indeed, recent studies suggest that self-harming behaviours are used by autistic people to regulate painful emotions, particularly low-energy affective states like sadness and high-energy affective states like anger and anxiety (41, 71). By contrast, unlike self-harming behaviours, RRBs may serve the function of sensory stimulation and are primarily characterized by their automatic and stereotyped nature (62).

There is a lack of consensus on whether ED is a core problem in ASC or whether it is stems from co-occurring disorders (38), as co-occurring mental health issues (e.g., anxiety and depression) are prevalent in ASC (72, 73) and that ED is a transdiagnostic difficulty (23). However, a growing number of studies suggest that co-occurring disorders result from preexisting ED in ASC, suggesting that ED predisposes to the emergence of psychiatric disorders especially in adults (40, 57, 74). Given that few studies with a longitudinal design have focused on ED in ASC [e.g., (64)], the direction of the relationship between ED and psychiatric disorders in ASC has not been yet been fully elucidated.

In ASC, ED has been associated with dysregulated behaviours (e.g., meltdowns, outbursts) (38, 75). Similar to BPD (76), recent studies suggest that ED is involved in self-harm with or without suicidal intent in ASC (40, 41, 71, 77). However, only recently research has started to highlight the high prevalence of self-harm (71, 78, 79) and suicidality in ASC (80, 81). A meta-analysis revealed a prevalence of 42% of self-harm in autistic people, irrespective of age and the presence of intellectual disability (79). Some findings suggest that the characteristics of these behaviours are similar to those found in the general population (68) and might be used by autistic people to regulate painful emotions, particularly low-energy affective states like sadness and high-energy affective states like anger and anxiety (41, 71). Moseley et al. (41) suggest that self-harm in ASC may also have other functions: i.e., self-punishment, deterrence from suicide, sensory stimulation and/or social communication.

Regarding suicidality, reviews have reported prevalence rates in ASC between 10 and 50% (82, 83). High suicidality rates have been reported in both autistic youth (84) and adults (77, 85), with adults without intellectual disability, especially women, being at the highest risk of dying by suicide among the autistic population (85–88). In relation to ED, Conner et al. (40) found that elevated ED was associated with increased suicidal behaviours in autistic youth. Some findings support a strong association between self-harm and

suicidality, suggesting that autistic adults may develop capability for suicide through self-harm (78, 89).

Few studies have investigated factors contributing to the heightened rates of ED and suicidality in autistic women relative to autistic men (59, 61). In addition to an increased anxiety (59), recent findings point to an increased use of camouflaging in autistic women contributing to elevated distress and risk of suicidality (90, 91). In addition, autistic women, especially those without intellectual disability, are at higher risk of late diagnosis than men (92), which increases their exposure to invalidation and the pressure of exhibiting socially appropriate behavior (93). Although autistic women might be more likely to mask their social difficulties, these difficulties (e.g., identifying others' intentions) persist even though they are less visible to others, making them more vulnerable to the societal invalidation toward women, particularly sexual violence (94, 95). These findings suggest the need to pay special attention to mental health in autistic women, especially regarding ED and suicidality.

As in BPD (96), Conner et al. (33) pointed to ED as a risk factor for the use of psychotropic medication, emergency services and psychiatric hospitalizations among autistic people. ED also contributes to impairments in adaptive functioning in ASC in childhood (97, 98) and adulthood (38).

Overall, findings support the implication of both emotional vulnerability and invalidating experiences in the development of ED in ASC [e.g., (40, 99–101)]. However, to our knowledge, no studies investigated the transactional relationship between the two components in this context.

Biological correlates of ED in ASC

Biological vulnerability to ED

Numerous studies have linked autistic features, including peculiarities found at the emotional level, to the atypical brain development in ASC (38, 102). Indeed, neuroimaging findings show an atypical neural functioning underlying impaired emotion regulation in ASC (101, 103–105). For instance, in autistic adults without intellectual disability, Richey et al. (101) reported a hyporegulation of key brain regions involved in effortful emotion regulation (i.e., decreased ability to enhance the nucleus accumbens' activation and to lower the amygdala's activation) while engaging in cognitive reappraisal compared to non-autistic adults (101). Autistic adults also showed decreased dorsolateral prefrontal cortex activation (dlPFC) during the task, another brain region involved in goal-directed processes (101). By contrast, some previous findings showed a hyperactivation in this region in ASC, suggesting a potential compensatory activation to overcome cortical inefficiency during effortful emotion regulation (106). Moreover, using functional magnetic resonance imaging (fMRI), Mazefsky et al. (103) found a longer lasting brain activity in areas involved in sustained emotional information processing (i.e., insula, pulvinar and dlPFC), akin to rumination, in autistic youth compared to non-autistic peers. These regions have been shown to be involved in ED in conditions other than ASC (107, 108). This suggests an atypical neural activity behind the tendency to ruminate in ASC, which is a maladaptive emotion regulation strategy prevalent in autistic people (103).

Despite the paucity of studies, some findings support the involvement of the three dimensions of emotional vulnerability (i.e., hypersensitivity, hyperreactivity and slow return to emotional baseline) in ASC. For instance, Lassalle et al. (109) found that autistic individuals were hypersensitive to fear stimuli with a significantly higher activation of the amygdala than non-autistic individuals. Sensory hypersensitivities have also been linked to increased psychophysiological arousal and increased anxiety in autistic people (40, 110, 111). Regarding hyperreactivity, the majority of findings have reported an increased physiological response to emotional stimuli in autistic individuals compared to non-autistic individuals [e.g., (105, 112)]. However, few other studies have rather supported equivalent physiological arousal to emotional triggers between autistic and non-autistic individuals (39, 113). It is noteworthy that discrepant results have also been reported in BPD regarding physiological hyperreactivity (6, 7). Finally, there are findings in support of the long-lasting nature of emotional arousal in autistic children, evidenced by the prolonged duration of cortisol secretion following a stressor compared to non-autistic peers (114).

Challenges related to ASC core features that contribute to ED

A growing body of evidence suggests a link between core ASC features and ED, with the higher the autistic traits, the higher the ED (39, 51, 71, 115). Relatedly, Samson et al. (39) found that interventions enhancing emotion regulation skills in autistic children improved not only ED but also difficulties related to ASC features, which indirectly supports the link between ED and autistic traits.

Effortful emotion regulation is a deliberate process of self-regulation (116). Thus, due to the additional daily challenges linked to ASC-related difficulties (e.g., executive dysfunction, social interaction difficulties) and subsequent anxiety and fatigue, it is crucial to acknowledge that emotion regulation may come with increased cost for autistic people (39, 51, 117, 118). Beyond this increased load, ASC-related difficulties might directly interfere with effective emotion regulation (39, 51). Therefore, the "emotional vulnerability" component of the biosocial model that we propose includes the contribution of ASC-features previously acknowledged in Mazefsky and White's model (2014) and integrates recent findings (Figure 1).

Effortful emotion regulation requires accurate identification of key aspects of the situation to use appropriate strategies (65). However, difficulties with social skills in ASC (62), particularly due to theory of mind (ToM) peculiarities, may interfere with effective emotion regulation (51, 119). However, it is important to highlight that the ToM peculiarities are neither specific to nor systematic in ASC (120). Additionally, effortful emotion regulation requires identifying one's emotional experience to be able to modulate it (121). Yet, alexithymia, which refers to the difficulty in identifying and expressing one's emotions, is common in ASC (122), limiting insight into one's own emotions and thus preventing their deliberate modulation (38, 51). In autistic adults, alexithymia has been found to predict self-harm, particularly when experiencing high-energy states (i.e., anger, anxiety) (41). In autistic women in particular, alexithymia has been found to be related to ED, irrespective of BPD traits (123). Together, these difficulties could explain why autistic people may react impulsively to emotional triggers with a lack of goal-directedness (38).

Furthermore, effective emotion regulation relies on cognitive flexibility, which enables the use of context-dependent strategies (65). This is especially the case for skills that require increased adaptability, such as problem solving and cognitive reappraisal (65), and unfamiliar situations that also trigger the change-related anxiety common in ASC (51, 62). Poor cognitive flexibility might thus

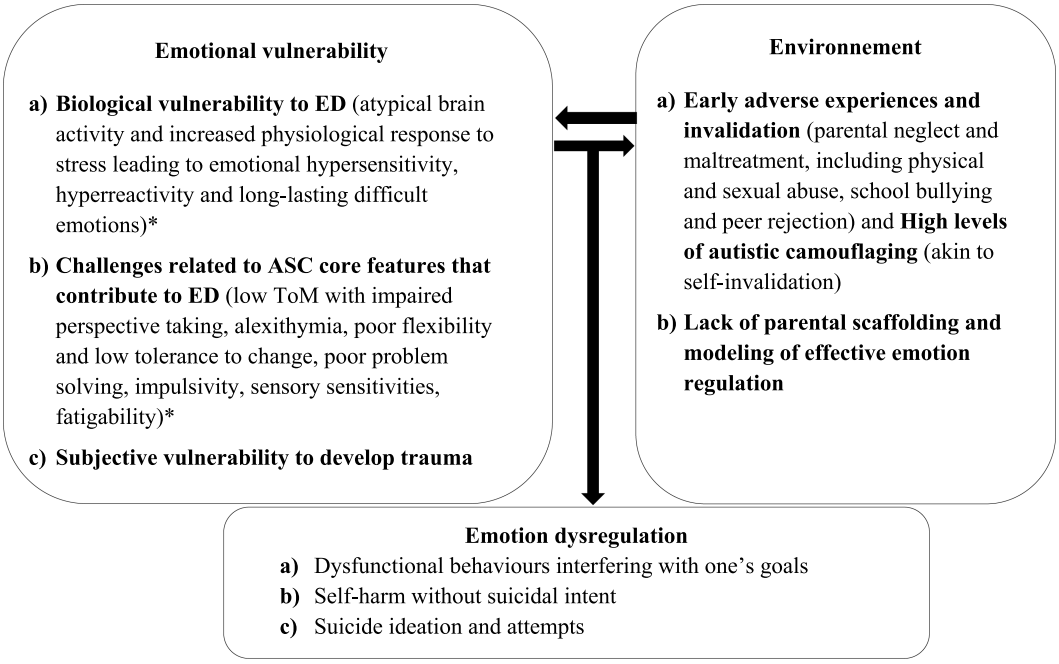

FIGURE 1
Linehan's model application to ED in ASC. * Factors included in Mazefsky and White's model (2014).

interfere with this ability in autistic people (32, 51, 66), and lead to the overuse of maladaptive emotion regulation strategies (e.g., rumination) or to the rigid use of adaptive emotion regulation strategies that do not fit the ongoing situation (e.g., distress tolerance skills) (38, 124). Consistent with this view, Aldao and Nolen-Hoeksema (125) suggested that individuals might develop a 'default' regulatory approach that interferes with the ability to use new and more adaptive strategies, such as reappraisal. This might be particularly true for autistic people, due to cognitive flexibility difficulties and change-related anxiety. Moreover, RRBs have been found to be the strongest predictor of ED in ASC (39), with one quarter of them appearing in reaction to emotional triggers (67). This points to the difficulty in inhibiting automatic behaviors in ASC, which also interferes with goal-directed behaviors and flexible emotion regulation (38, 39). Interestingly, emotional vulnerability, particularly the increased and sustained physiological activation following emotional triggers, possibly interfere with both cognitive and behavioral control in ASC (126). Thus, increased emotional vulnerability might promote automatic emotional responses in autistic individuals, which interferes with effortful emotion regulation (126). Moreover, it is noteworthy that ADHD, characterized in its hyperactive dimension by impulsivity, frequently co-occurs with ASC, including in adults (e.g., (127) found a prevalence of 33.3%). Therefore, if present, ADHD co-occurring features are likely to contribute to emotional difficulties (128).

Sensory sensitivities, which are common in autistic people (62), have also been reported to be significantly related to ED in ASC (39–41, 51). In a sample of autistic adults without intellectual disability, Moseley et al. (41) found that sensory sensitivities were a strong predictor of self-harming behaviors along with alexithymia, anxiety and depression (41). Importantly, in autistic youth, some studies have suggested that sensory sensitivities were the strongest and single predictor of self-harm (129). This association may be due to the distress reported by autistic people when experiencing intense sensory discomfort (130).

Psychosocial risk factors contributing to ED in ASC

Early adverse experiences and invalidation

Autistic people are at heightened risk of experiencing adverse childhood events (131–133), particularly autistic girls (134, 135). This increased exposure to adverse experiences can be understood through the double-empathy theory, which highlights difficulties of reciprocity and mutuality between autistic and non-autistic people due to a lack of mutual understanding of each other's subjective experience (136, 137). Hence, on the one hand, autistic individuals may face challenges in understanding and fitting into a "non-autistic" environment due to their particularities, and, on the other hand, the environment around them may contribute to their exclusion by failing to understand their atypical functioning and needs (138). As a result, from childhood onwards, autistic people are more likely to be rejected and maltreated, both within the family and in the wider community.

Moreover, some studies also highlight an increased vulnerability to be detrimentally affected by adverse events in ASC, with a wider range of events acting as possible catalysts for trauma (e.g., "sensory trauma" and major changes) (139, 140), supporting the hypothesis of a transactional relationship between biological and social factors in the emergence and maintenance of ED in autistic people. Adverse experiences in autistic children are associated with co-occurring disorders and/or the worsening of ASC-related difficulties in childhood (133, 141) and in adulthood (e.g., mood and anxiety disorders, PTSD) (131).

Autistic children may experience different forms of adverse events. First, autistic children, including those without intellectual disability, are at heightened risk of maltreatment, particularly physical neglect, and abuse (99, 100, 135), including sexual abuse (95). In fact, parents of autistic children are more likely to be emotionally and physically punitive at the child's behavior (e.g., non-responsiveness and rigid adherence to routines) as they may perceive it as oppositional (142). Maltreatment is associated with increased dysregulated behaviors in autistic children (e.g., aggression and self-harm) (100), with those who have been abused being at greater risk of engaging in dysregulated behaviors, including suicide attempts (99). For instance, Taylor and Gotham (133) found that 90% of their sample of autistic children with high mood symptoms had experienced at least one traumatic event. Importantly, heightened exposure to trauma may predispose autistic children to develop a co-occurring BPD given that early traumatic experiences are a key risk factor for the disorder (143).

Additionally, autistic children have a 4-fold increased risk of being bullied at school compared to their non-autistic peers (144, 145) due to the misunderstanding of their atypical functioning and social difficulties (144), with those without intellectual disability being at higher risk (100). Importantly, repeated adverse experiences, including school bullying, have been shown to be associated with higher levels of distress and altered physiological arousal in adulthood (146). Recent findings by Camodeca & Nava (147) add to these results by showing that victimization strongly predicts increased physiological arousal to emotional triggers in non-autistic adults. Interestingly, this association has also been found in the case of exposure to bullying perpetrated to others (i.e., witnessing bullying without intervening) (147).

Furthermore, the heightened exposure of autistic people to adverse experiences persists in adulthood (140, 148). Indeed, autistic adults report more emotional bullying and greater sexual victimization compared to the general population (148, 149), particularly women (94, 95). Additionally, autistic adults, especially those who were diagnosed in adulthood, may suffer from a lack of social support, including from relatives who reject or misunderstand their diagnosis (150–152).

Given that chronic invalidation may be widespread in ASC (i.e., family members, school, society), autistic adults may present with high levels of internalized stigma related to their ASC diagnosis [e.g., (153, 154)], which may, in turn, contribute to high levels of autistic camouflaging, i.e., efforts of masking and/or compensating for autistic traits to 'fit in' in society (155, 156). Recent findings show that autistic camouflaging negatively affects mental health (e.g., depression and anxiety) (91, 93) and is associated with lifetime suicidality in autistic adults without intellectual disability (157, 158), especially autistic women (90, 91). Interestingly, autistic camouflaging is akin to self-invalidation in Linehan's model in many ways. First, both are the consequence of invalidation in childhood (159). Second, both teach one to mistrust one's internal states and to rely on the environment for clues on how to respond. Third, the tendency to look for external validation in both cases interferes with developing a sense of self (156). Fourth, both might be of adaptive value to avoid negative reactions such as violence and bullying (155).

Lack of parental scaffolding and modeling

Caregivers play a key role in helping the child learn effective emotion regulation, particularly through parental scaffolding, defined as a parent's support of their child's emotion regulation (115, 160). This is especially the case for autistic children, given their vulnerability to develop ED and the increased influence of parental behavior on their social and emotional development (115, 161). In autistic children, effective parental scaffolding has been associated with enhanced emotion regulation, while low parental scaffolding has been associated with ED (115, 160, 162, 163). In addition, some findings show that parents of autistic children may mainly rely on passive co-regulation strategies while providing emotional scaffolding (i.e., following the child's lead), instead of active strategies (i.e., prompting/helping, redirection of attention, physical comfort) (162).

Additionally, studies point to parental ED as a potential contributor to ED in autistic youth (57, 97, 162, 164). Indeed, fewer parental externalizing problems (e.g., aggression, hyperactivity) have been linked to adaptive emotion regulation skills in autistic children (162). This may reflect that providing effective parental scaffolding and modeling for emotional regulation requires the parents to be able to use effective emotion regulation strategies to regulation their own emotions (164-166). For this reason, Flujas-Contreras et al. (165) investigated the impact of a clinical intervention aiming at enhancing the parents' emotion regulation skills (e.g., mindfulness skills, problem solving and strategies for managing their children's behavior and emotional problems) on their autistic children's emotion regulation abilities. Unsurprisingly, both the parents' and the children's emotion regulation abilities improved significantly following the intervention (165). These results bring additional support to the development of parent-based interventions to enhance ER abilities in autistic children (165, 166). These early interventions may be of preventive value in helping to thwart the development of ED in autistic people since childhood.

Illustrative case conceptualization

Mrs. F. is a 37-year-old woman who has a full-time job and lives with her husband and young child. Mrs. F. was diagnosed with ASC without intellectual disability at the age of 35, in addition to previous diagnoses of postpartum depression and PTSD. She was subsequently diagnosed with ADHD. Mrs. F. has experienced daily suicide ideation since childhood. As a child, she frequently reflected on ways to attempt suicide and tried once to die by stopping to eat. In adulthood, she attempted suicide twice by medication overdose. Both suicide attempts required hospitalizations in an intensive care unit. Mrs. F. does not exhibit self-harm without suicidal intent. She underwent a comprehensive psychiatric evaluation as part of her ASC diagnostic assessment, including the Mini-International Neuropsychiatric Interview (M.I.N.I.; (168, 169), for the French version). No co-occurring BPD was identified. No one else in Mrs. F.'s family is known to have received an ASC diagnosis. Mrs. F's case formulation using our application of the biosocial model to ASC is in Figure 2 and her scores on self-reported scales measuring dimensions related to the components of the model are shown in Table 1.

Emotional vulnerability

Mrs. F. reports that several ordinary events can trigger distress and intense reactions (e.g., bursting into tears), resulting in a wide range of situations as potential crisis triggers (e.g., «I do not understand why I can get so distressed over something that is not really important»).

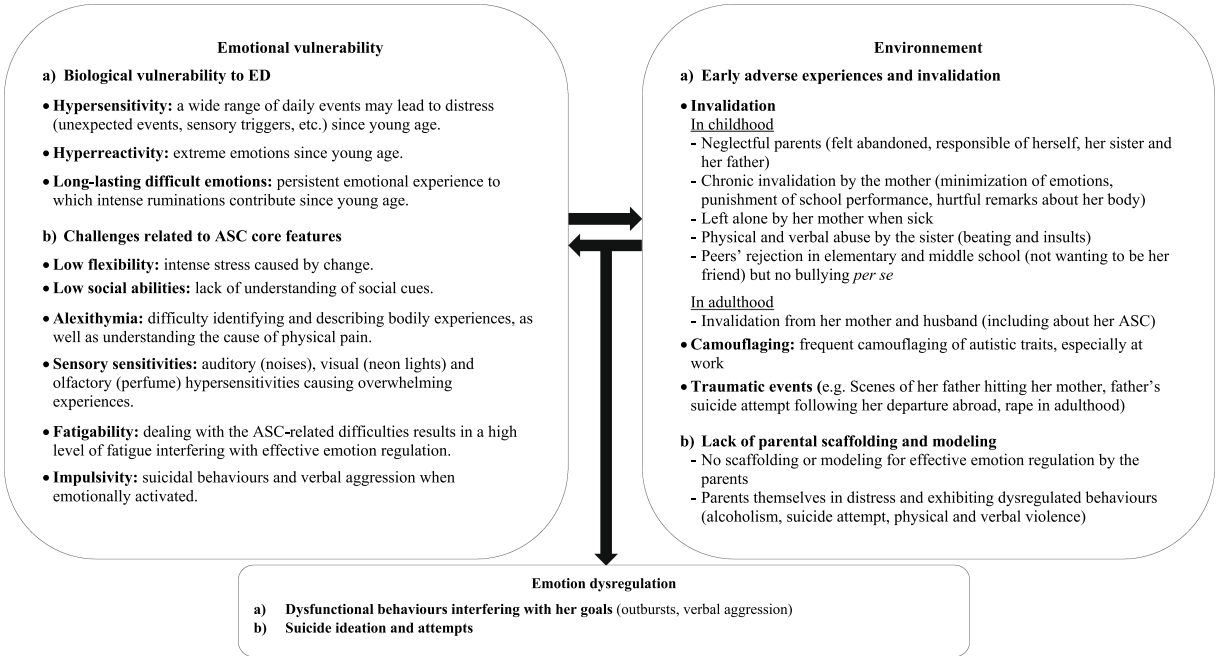

FIGURE 2
Case conceptualization of Mrs. F. based on our application of Linehan's model to ED in ASC.

TABLE 1 Mrs. F.'s scores on a battery of scales measuring the components of Linehan's model applied to ASC.

Scale	Assessed dimension	Mrs. F.'s score	Reference value*	Maximum score
Autism Spectrum Quotient [AQ; (170)]	Autistic traits	44[a]	32	50
Beck Anxiety Inventory [BAI; (171)]	Anxiety	33[a]	30	63
Beck Depression Inventory-Second Edition [BDI-II; (172)]	Depression	44[a]	29	63
Difficulties in Emotion Regulation Scale [DERS; (173)]	Emotion dysregulation	124[a]	96	175
Beck Scale for Suicide Ideation [BSS; (171)]	Suicide ideation	27[a]	26	38
Eight-item General Alexithymia Factor Score [GAFS-8; (174)]	Alexithymia	51	60	40
Camouflaging of Autistic Traits Questionnaire [CAT-Q; (175)]	Autistic camouflaging	108 [a]	100	175
Sensory Processing Sensitivity Questionnaire – Sensory Sensitivity Subscale [SPSQ; (176)]	Sensory sensitivities	7.75 [a]	5.2	10
Emotional Vulnerability-Child Scale [EV-Child; (177)]	Emotional vulnerability in childhood	119 [a]	62	132
The Childhood Trauma Questionnaire—Short Form [CTQ-SF; (178)]	Childhood trauma			
	Emotional abuse	20 [a]	13	25
	Physical abuse	5	10	25
	Sexual abuse	5	8	25
	Emotional neglect	17 [a]	15	25
	Physical neglect	12 [a]	10	25

AQ: clinical cut-off (170); BAI: cut-off for severe anxiety (171); BDI: cut-off for severe depression (172); DERS: cut-off for severe ED suggested by Neacsiu et al. (179); BSS: cut-off used by van Spijker et al. (180); GAFS-8: cut-off for high to very high alexithymia in a sample from the general population (174); CAT-Q: cut-off used by Cook et al. (181); SPSQ: mean score in a sample of women from the general population (182); EV-Child: mean score in a sample of female students (177); CTQ-SF: cut-off scores for moderate to severe from Bernstein and Fink (183). [a]Score above the reference value.

This is akin to hypersensitivity to emotional cues relative to Linehan's model (1993). She also describes feeling intense and long-lasting emotions fueled by ruminations (e.g., «It [the emotion] feels like a geyser», «It [the emotion] stays there for a long time […] stagnant», «It goes round and round in my head»). This is supportive of the two additional facets relative to emotional vulnerability in Linehan's model (1993): i.e., emotional hyperreactivity and slow return to baseline when facing difficult emotions. Mrs. F. reports dealing with these emotional difficulties since a very young age. These elements along with Mrs. F.'s self-reported problems in understanding her emotions (i.e.,

alexithymia) indicated that it was crucial to include these elements into the psychoeducation on the biological vulnerability component of the model. Indeed, these elements, along with the ASC-related difficulties highlighted below, probably contribute to the high level of distress Mrs. F. experiences on a daily basis. This understanding is essential to increase emotional awareness and decrease self-invalidation (e.g., «I do not understand why I can get so distressed over something that is not really important») and shame, which are, respectively, a prerequisite for effective emotion regulation and a motivational factor.

Regarding ASC-related factors associated with ED included in our application of Linehan's biosocial model to ED in ASC, Mrs. F. reports that, due to her need for sameness, last-minute changes provoke intense anxiety. Becoming a mother at the age of 32 has been a major additional source of stress, as her child's changing needs and reactions are a source of unrelenting unexpected events and sensory discomfort (e.g., her child's crying). Difficulties in reading social cues are a major source anxiety, as they are associated with doubts over how to interpret and react to others' behavior. In addition, Mrs. F. has auditory (noises), visual (neon lights) and olfactory (perfume) hypersensitivities that cause overwhelming sensory experiences (e.g., «It is an invasion [...] it can cause extreme discomfort», «I struggle to put it [the sensory stimulation] aside and be available for the rest of the things»). Mrs. F. also describes having difficulties identifying and describing her bodily experiences, as well as understanding what causes her physical pain. This is especially the case when she is in an emotional crisis (e.g., «When I am overwhelmed, there is no access to anything [in her body and mind], I am just in survival mode»). In extreme cases, Mrs. F.'s impulsivity can lead to verbal aggression or unplanned suicidal behaviors, which was the case in her first suicide attempt. Dealing with the ASC-related difficulties and camouflaging them result in a high level of fatigue. This interferes with her ability to regulate her emotions effectively (e.g., «Compensating for sensory overload, camouflaging, social interactions and, also, managing my emotions… it is exhausting! »). Camouflaging in particular is described as extremely costly and exhausting (e.g., «I do it deliberately to modify my behavior […] it is there all the time and it is exhausting»). Her responsibilities as a mother also add to the daily fatigue, as she needs to attend to the constantly changing needs of her child. Highlighting the ASC-related difficulties and adding them to the biosocial model allowed to specifically target them, especially in individual sessions. Indeed, as highlighted in a first-person account of an autistic person who benefitted from DBT (184), DBT therapists need to consider the specific needs and motivational factors of autistic clients to increase the pertinence of DBT. Here, this means to be aware of ASC-related features that are likely to contribute to ED, integrate them in the biosocial model, as well as in the targets and goals of the therapy. In addition, therapists' destigmatizing attitudes toward ASC draw upon this conceptualization, as it aids to validate the difficulty to cope with these challenges on a daily basis (e.g., adapt to a non-autistic world), to teach to self-validate instead of self-stigmatize and camouflage, to provide targeted psychoeducation (e.g., on autistic camouflaging and its impact on mental health), to help identify and label emotions, but also problem-solve (e.g., in relation to sensory triggers).

History of invalidation and adverse events

Mrs. F.'s parents had alcohol use disorder. She reports feeling abandoned in her childhood, unable to rely on her parents. During her childhood and adolescence, she witnessed repeated scenes of physical violence perpetrated by her father on her mother, and, at times, by her sister on her mother. Some of these scenes were traumatic. Emotional abuse was frequent, as Mrs. F.'s mother repeatedly told her «no one will love you, you'll end up alone» or «go look in the mirror how ugly you are» while Mrs. F. was crying. She was an excellent student throughout her school years. In response to her high grades, her mother used to say «you could have done better». Mrs. F. reports that her mother did not care for her even when she was sick, always prioritizing work. Mrs. F. also reports that her sister was physically and verbally violent towards her, hitting and insulting her. Her mother's invalidation (e.g., punitive and oversimplifying behaviors) continued into adulthood. She explains that her father was the only person she felt understood by. However, her father attempted suicide after she left home to live abroad. Before her departure, he told her that he would attempt suicide if she left. Mrs. F. reports that she still feels guilty over her father's suicide attempt.

Mrs. F.'s parents exhibited dysregulated behaviors (alcohol use disorder, physical and verbal violence, and suicide attempts) indicative of a great psychological distress and major difficulties to regulate their emotions. Thus, Mrs. F.'s parents were not able to provide her with the necessary emotion regulation scaffolding and modeling. On the contrary, their own difficulties were a source of recurrent invalidation and trauma. In addition to the trauma related to events in her family, Mrs. F. was a victim of rape as a young adult, and subsequently developed a PTSD related to this event.

At school, Mrs. F. reported feeling isolated. Nevertheless, she reported that school was "a safe haven" because it was a structured environment, where she found intellectual fulfillment, and support from the teachers. In middle school, she was the target of bullying from peers. She had difficulty integrating groups of friends (e.g., «I did not have the codes of how things were done») and felt rejected.

In later years, Mrs. F. has experienced high levels of invalidation regarding her ASC diagnosis, both from her family and her husband, e.g., «you are just lazy», leading to increased anger, shame and sadness.

The psychosocial factors highlighted here were key to better understand Mrs. F.'s developmental environment, as well as its potential effects on ED and on her overall mental health. Specifically, they helped to identify predisposing factors that seem to have contributed to self-invalidating behaviors [i.e., a secondary target in DBT involved in ED; (5)] and, more broadly, to ED – e.g., repetitive punitive invalidations and lack of scaffolding and modeling of effective emotion regulation from her parents. Given the transaction between the invalidating environment and her emotionally vulnerable temperament, including her ASC-related difficulties, it is understandable that she felt and reacted the way she did. This knowledge, inherent to the dialectical perspective of the biosocial model (5), was crucial for the therapist to validate the client and to teach her to self-validate. In addition, this allowed the therapist to provide psychoeducation on the possible link between adverse events (e.g., parents' dysregulated behaviors, lack of emotional scaffolding) and current emotional difficulties (in transaction with biological factors), including suicidal behavior. According to the DBT framework and conceptualization (5), Mrs. F. was in stage 1 of DBT, that is, she presented with behavioral dyscontrol (e.g., life-threatening behaviors). It is only in stage 2, once dysregulated behaviors are no longer present, that PTSD and the sequelae of traumatic and invalidating experiences may be directly targeted.

Discussion

This article aimed at applying and extending Linehan's biosocial model (5) to ED in autistic people across the lifespan. This is of particular interest as ED is prevalent in this population (57, 185) and seems to be involved in the high rates of self-harm and suicidality (40, 41). Consequently, DBT is an emerging topic in the field of interventions targeting ED in ASC, with promising preliminary results (50, 51). However, no studies so far had focused on the utility of Linehan's biosocial model, which underlies DBT for BPD, in ASC.

Our review and application to the case of an autistic woman suggest that ED in ASC encompasses factors related to both biological and psychosocial risk factors as conceptualized in the BPD framework, although in both domains ASC-specific factors might be involved. Indeed, in addition to the biological vulnerability similar to BPD (i.e., hypersensitivity, hyperreactivity and slow return to emotional baseline) (105), ToM peculiarities, sensory sensitivities, lack of cognitive flexibility, change-related anxiety and RRBs have been associated with ED in ASC (39, 51). Alexithymia, prevalent in ASC, has also been reported to be linked to ED in autistic adults (41), especially in autistic women (123). It is worth noting that ASC-related difficulties may interfere directly with the ability to self-regulate (32, 39, 51) but also contribute to high levels of anxiety and fatigue making emotion regulation costly for autistic people (39, 51, 117). Such is the case for Mrs. F., whose autistic features (e.g., sensory hypersensitivity, hypervigilance regarding social rules and how to behave in social situations) are both involved in her emotional vulnerability and in the costs of real-life use of adaptive emotion regulation skills. We note, however, that people with BPD might present with autistic-like features, including sensory hypersensitivities (187) and ToM peculiarities (188). Therefore, our findings support the application and extension of Linehan's model to ASC, but it also highlights under-researched topics in BPD. Indeed, it is likely, for example, that sensory particularities may also play a role in ED in people with BPD, as this has been shown to be the case in the general population (189).

Regarding psychosocial risk factors, our review suggests that, similar to BPD and other psychological conditions (4, 28, 29), invalidating experiences seem to contribute to the emergence of ED also in autistic people. In fact, findings report that autistic children are highly exposed to different early stressful and traumatic experiences (e.g., physical and emotional maltreatment from caregivers and school bullying), especially because of their atypical functioning that cause misunderstanding and rejection from others (131, 132, 139, 187). Autistic girls seem to be particularly vulnerable to experience these adverse events (134, 135). Importantly, adverse experiences have been associated with co-occurring psychopathology and/or the worsening of difficulties related to ASC in childhood (133, 141). As in BPD, these experiences have been associated with self-harming behaviors with or without suicidal intent in autistic children (99, 100), particularly in those who have been sexually abused (99). In adulthood, these experiences have been associated with numerous co-occurring disorders such as mood and anxiety disorders, PTSD (131), and BPD (143, 190).

Beyond the impact of adverse experiences, given the potential transactional link between biological and environmental factors of ED in ASC, it is likely that the specific needs of the autistic child might differ from those of the child at risk to develop BPD. For instance, autistic children might need increased parental scaffolding and modeling to learn effective emotion regulation skills than children who will develop BPD (115, 165). The necessary adjustments of the caregivers (e.g., teachers, parents) can be promoted by an early diagnosis of ASC (191) and enhancing the parents' emotion regulation skills (165).

In addition, our review and extension of the biosocial model to ASC includes excessive autistic camouflaging as a form of self-invalidation resulting from internalized invalidation from others (192). In addition to being costly, the self-invalidation associated with autistic camouflaging might be detrimental to the development of adaptive emotion regulation skills as well as to the sense of self and self-acceptance in autistic people (156, 193). Importantly, recent studies found a strong negative association between autistic camouflaging and lifetime suicidality in autistic adults, especially autistic women (90, 91, 157). The latter finding can be explained by several factors. Indeed, autistic women, especially those without intellectual disability, are diagnosed later than men (92). Relatedly, greater expectations for adolescent and adult autistic women to engage in adaptive social communication and behavior are more prominent (91). This may, in turn, be involved in the enhanced use of compensatory behavior to mitigate social challenges and mask autistic traits in autistic females, i.e., camouflaging (91, 192). Therefore, if autistic women, especially those who are undiagnosed, are more likely to mask their mindreading and overall social difficulties, this may promote their social inclusion (194). However, they probably lack the social skills that might make them less vulnerable to societal invalidation towards women in general, including sexual violence (94, 95, 195). Mrs. F.'s case illustrates the impact of late diagnosis (at the age of 35) and the resulting autistic camouflaging to "try to fit in" since childhood. We speculate that an early diagnosis could be beneficial in several ways. For example, it could foster the understanding of one's own functioning, prevent self-invalidation and enhance self-acceptance in autistic people. In autistic women, earlier diagnosis could also be of preventive value in relation to sexual violence, enabling access to targeted sexual education and assertiveness programs (195).

Moreover, regarding the overlap in biosocial correlates of ED between ASC and BPD, it appears crucial to expand our knowledge of ED and its mechanisms in both diagnoses. Thus, we suggest considering the following points of potential differentiation in future studies. First, people with BPD might present with autistic-like features, such as sensory hypersensitivities (187) and ToM peculiarities (188). Thus, comparative studies are needed to investigate the extent to which the ASC-related factors specifically contribute to ED in ASC relative to disorders with ASC-like features such as BPD. We also suggest to further investigate how these factors may interact with each other and contribute to ED. For instance, recent findings suggest an association between high sensory sensitivity (i.e., low sensory threshold and ease of excitation) and alexithymia in non-autistic young adults, with this interaction impacting emotion processing and regulation (196). Second, ED in BPD is significantly involved in interpersonal problems (e.g., conflicts, physical/verbal violence) due to mood swings and chronic fear of abandonment (62, 197). In ASC, relationships are not likely to be affected in the "stormy" way found in BPD, as social difficulties are rather related to poor social abilities that makes it difficult to bond with others (198). It seems therefore relevant to investigate the impact of ED on relationships in both BPD and ASC to potentially highlight distinctions in ED between the two diagnoses.

Third, in BPD, ED is strongly linked to affective instability in interpersonal contexts (199). In ASC, by contrast, ED seems to arise from the interaction between ASC traits and contextual factors (e.g., invasive sensory stimuli, changes in the environment/planning) (38, 39). Thus, it seems relevant to further investigate whether and how ED might be more related to widespread context cues in ASC compared to BPD. Fourth, to date, evidence supports the role of emotional vulnerability and invalidation separately in the development of ED in ASC. Thus, the transaction between the two is yet to be empirically tested in ASC. Fifth, previous findings have reported differences in the development of personality styles between ASC and BPD (200). Hence, it seems relevant to explore whether and how the factors inherent to the development of personality in BPD contribute to ED relative to ASC (201).

Finally, we acknowledge that the paucity of data on ED and its mechanisms in ASC might have limited the potential determinants of our application of Linehan's model. Nevertheless, given the increasing awareness of the impact of ED on autistic individuals' mental health, our application has the advantage of providing a pragmatic model that can inform the delivery of psychological treatments for this population. Additionally, our application of the model to ASC may foster new and much needed research on the biosocial mechanisms of ED in ASC. For instance, as a growing body of research has shown that autistic women are at greater risk for severe ED (61) and suicidality than men (86). Hence, it seems crucial to consider this discrepancy in future studies by systematically exploring cross-gender (including transgender and gender non-conforming individuals) differences in the implication of the determinants of ED in ASC. Moreover, our application might provide clinicians with a comprehensive framework of ED in ASC, enhancing the systematic assessment of traumatic and invalidating experiences in autistic clients. The latter include different layers of invalidation, which might be related to intersectional factors (e.g., gender) involved in family invalidation, peer invalidation but also societal discrimination leading to self-stigma and self-invalidation (94). Finally, our application of the model may inform psychological treatments targeting ED, especially DBT, the psychotherapy that has amassed the most evidence in the treatment of ED in BPD (5, 12). As DBT was developed based on Linehan's biosocial theory (5), applying and extending this theory to ED in ASC may foster the adaptation of DBT to treat ED in autistic people, especially since preliminary data on its feasibility and effectiveness in autistic adults are promising (49, 50). This is of particular importance as evidence-based interventions targeting ED in autistic individuals are lacking, especially for adults (202), and that ED might be associated with self-harm and suicidal behaviors in this population (40, 41), especially autistic adults without intellectual disability (86). Furthermore, our application of the Linehan's biosocial model to ASC might promote specific adaptations to autistic people, increasing the acceptability and efficacy of DBT applied to this population (184). For example, increased scaffolding and modeling from the therapist and the use of a psychoeducational biosocial model that integrates the ASC specificities highlighted here might be particularly valuable to this aim.

Author contributions

DB: conceptualization, methodology, investigation, and writing – original draft. LW: conceptualization, methodology, supervision, and writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Pregnancy in autistic women and social medical considerations: scoping review and meta-synthesis

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Introduction: This article addresses a topic that has been largely overlooked by scientific literature, namely pregnancy in autistic women. Generally, the issue of sexuality in disability, particularly in disabled women, autistic or otherwise, has been underexplored. However, it is necessary to scientifically investigate this topic to propose adequate social and health policies. Therefore, we chose to conduct a scoping review to answer three main questions: "What does it mean for an autistic woman to be pregnant?"; "How do these two conditions coexist?"; "Are health services prepared to receive this population adequately or does autism become a stigma for pregnant women?"

Methods: We conducted a systematic review and qualitative thematic synthesis following the Preferred Reporting Guidelines for Systematic Reviews and Meta-Analyses on autistic women and pregnancy in the last 10 years.

Results: The studies included in our review are 7, extremely diverse in terms of methodologies and sample sizes. Despite the heterogeneity of samples and methodologies, all research tends to highlight the following results. For autistic women during pregnancy, three areas seem to be the most difficult: sensory issues, mood disorders, and relationships with specialists.

Discussion: Our study found that women with ASD face unique challenges during childbirth that differ from those of neurotypical women. Participants often felt belittled, ignored, and uninformed about the care they received, and being placed at the centre of attention was often seen as negative and hindering rather than positive. However, the research shows us how some "expected" results, such as difficulties in breastfeeding, have been disproven.

KEYWORDS

autism, autistic women, social medicine, developmental psychology, neurodivergence

1. Introduction

Fairly little has been written about pregnancy in autistic women, although this topic should be deepened for several reasons. In this article we will consider Autism Spectrum Disorder (ASD) in the light of the latest paradigm-shifting (1), which consider it a different condition, rather than a deficit. It is important to address this issue as the right to health should be ensured for all equally; however, scientific literature has highlighted that autistic people encounter multiple barriers in accessing health services, in many cases they receive ineffective pharmacological treatments, and very often, professionals do not know how to manage problem behaviors or stereotypical behaviors during routine medical examinations (2–4).

Autism is a neurodevelopmental condition with childhood onset (5) (6) that involves difficulties in verbal and non-verbal communication, restricted and repetitive behaviors, sensory peculiarities, different inflammatoryprocesses1 (7) and executive functions ranging from normal to impaired (8). The prevalence estimate of ASD suggests that men appear to receive a diagnosis more frequently compared to women. However, the latest evidence has underlined a trend of underdiagnosis for the autistic condition in women rather than a lower prevalence (9). Therefore, our in-depth analysis of the topic can have multiple intentions and implications: to learn more about autistic women and their experience of pregnancy, and to train health professionals in the culture of neurodiversity and neurodivergence.

Recent literature has paid little attention to how disabled and/or autistic women experience the entire sphere of sexuality. Indeed, reproduction, menstrual cycle, pregnancy, and maternity management still appear taboo. Moreover, as a result social and health services' have limited knowledge about these topics (10). Thus, autistic women struggle to open up when they seek health and social services. However, despite communication and sensory difficulties, high functioning autistic (including those previously diagnosed as Asperger's disorder) often marry or have long-term relationships and sometimes even have children (11). It is not uncommon for some individuals with ASD to become aware of their diagnosis in adulthood (12).

However, while, in the last decades, research on the causes and manifestations of autism has made significant progress, a less explored aspect pertains to the potential interaction between some typical ASD's symptoms, such sensory abnormalities, and pregnancy in women with this condition. Indeed, experiencing heightened or diminished sensory sensitivity during a particularly delicate moment such as pregnancy may have effects on social interactions, predisposition to engage with others, and consequently, on mood, as some studies in this review indicate (10, 13, 14).

Specifically, individuals with autism often experience sensory hyperresponsivity or hyposensitivity, displaying atypical responses to sensory stimuli from the environment (15). These altered sensory sensitivities may involve one or more of the five senses, namely sight, hearing, smell, touch, and taste, and their intensity can vary from person to person (16). Moreover, some studies in recent years are beginning to hypothesize that sensory aspects may underlie the entire autistic symptomatology (17) (18). Therefore, women with autism who desire to become mothers may face unique and complex challenges due to these sensory characteristics.

Pregnancy is a critical period in a woman's life, during which her body undergoes a series of physical, hormonal, and psychological transformations (19). These changes might be perceived differently by women with autism due to their atypical sensory responses. Heightened or diminished sensitivity to environmental stimuli could amplify the physical and emotional experiences typical of pregnancy, thereby impacting the entire process.

Sensory alterations in women with autism may manifest in various ways during pregnancy (20). For instance, increased sensitivity to sound could make it challenging to tolerate common noises associated with daily life or medical visits, raising the risk of stress and anxiety for pregnant mothers. Moreover, heightened sensitivity to light or smells could intensify the occurrence of nausea and early pregnancy-related discomforts (21).

Conversely, some women with autism may experience reduced tactile sensitivity, which could influence the perception of typical physical changes during pregnancy, such as sensations related to fetal movements (22). These altered sensory experiences might also impact the pregnant mother's ability to respond to her body's needs during pregnancy, leading to reduced awareness of physical changes or potential complications (13).

Furthermore, the way women with autism interact with others during pregnancy may be influenced by sensory aspects (23). Difficulties in understanding non-verbal communication nuances and social interactions could complicate social support during this critical period, influencing the emotional well-being of the expectant mother.

Thus, sensory processing can have a significant impact on childbirth-related tasks such as breastfeeding which could represent a very important dimension due to the bodily and sensory dimensions involved (24).

Understanding the impact of sensory aspects related to ASD on pregnancy is crucial for providing adequate support and assistance to women with autism who wish to become mothers. Clearly, in addition to these sensory challenges, autistic women face difficulties related to communication during interactions with healthcare providers, express a lack of information and appropriate support, and experience distress due to a perception of lack of control during childbirth. Each of these stress factors has negative implications for the mental well-being and emotional state of women during pregnancy and childbirth.

It is also known that, in adulthood, autism is often accompanied by other psychopathologies such as anxiety and depression (25) or also personality disorder or psychosis (26). Pregnancy and motherhood are sensitive transitions for all women, and even more for autistic females who have a greater risk of developing psychopathological comorbidities (27) such as postpartum depression.

Increased awareness of these challenges allows healthcare professionals and social workers to tailor their practices to ensure a more positive and satisfying pregnancy experience for these women. Additionally, research in this field can contribute to the development of targeted interventions to address the specific sensory needs of women with autism during pregnancy, thereby improving their overall well-being and that of their children (28).

2. Methods

In this scoping review, we examined the literature covering the issue of autistic women and pregnancy. A scoping review can be a

useful tool to explore the landscape of a developing issue. We conducted a scoping review and qualitative synthesis of themes following Preferred Reporting Guidelines for Systematic Reviews and Meta-Analyses [PRISMA; (29)].

The research team searched three databases – PubMed, Psychinfo, and Web of Science – for scientific literature on autistic women and pregnancy in the last 10 years. The research team considered it necessary and sufficient to search these three databases. The review was conducted following the protocol suggested by Arksey and O'Malley (30), specifically designed for individuals with disabilities or similar conditions.

2.1. Stage 1: identify the research question

The investigation begins with an overview of the issue and any potential complications. Therefore, we pondered if this issue had received enough attention in the scientific community. What does it mean for an autistic woman to be pregnant? The scientific literature highlights a worsening of some symptoms of autism, especially regarding sensorial issues and mood. How do these two variables interact in pregnant autistic women? Are health services ready to adequately accommodate this population, or does autism become a stigma for pregnant women?

2.2. Stage 2: identify relevant studies

To find studies relevant to the given study questions, keywords were used. The following search phrases were used: "Autistic women pregnancy" and "pregnant" or "childbirth." The eligibility criteria included studies published in the English language between 2013 and 2023. Articles were included if: (a) the sample included individuals with a clinical diagnosis of autism, or Asperger's Syndrome (AS); (b) participants were facing or had already faced one or more pregnancies.

2.3. Stage 3: study selection

The search was conducted through three databases: (i) Psychinfo; (ii) Web of Science; (iii) PubMed. A total of 119 articles were identified, 50 records were selected by title and abstract after duplicates removal, 43 records were assessed as full-text eligible articles. At this step, articles were excluded if: (a) based on animal models; (b) based on medical testing; (c) concerned other disabilities and not specifically autism. The non-specificity of various contributions, which have investigated the issue in the vast sea of disability, is a major limitation of this area of research (Figure 1).

2.4. Stage 4: chart the data

The organization of the data from the chosen articles was the fourth stage of the scoping review framework. This stage was carried out using Microsoft Excel. Author(s), title, publication year, the country where the first author's university is affiliated, research setting, purpose, participant demographics, research methods, measures, interventions, important findings, and limitations were the data points that were gathered Table 1.

2.5. Stage 5: collate, summarize, and report results

The final step of the Arksey and O'Malley (30) paradigm involved categorizing the pertinent findings into themes, giving outcomes priority depending on their applicability to the research objectives, and placing a strong emphasis on the type of intervention. Relevant information was provided, such as sample size, participants, procedures, and results. The results section below contains a complete report of all data.

3. Results

Jane Donovan (31) conducted a study in 2020 to describe the childbirth experiences of women with ASD. Twenty-four women between the age of 29 and 65 from different countries around the world, who had given birth to healthy newborns, were interviewed. The interviews took place in a setting of their choice, where they felt comfortable. Some chose their home, while others preferred telephone interviews or video calls via Skype/Facebook. Three main themes emerged from the results obtained: communication difficulties, feeling stressed in an uncertain environment and becoming an autistic mother. In conclusion, participants expressed difficulties in communicating with the nurses Communication problems included difficulties in conveying their needs, alerting nurses when they felt unwell, or not understanding what was communicated to them. This ineffective communication resulted in feelings of anxiety and fear and prevented participants from making further attempts to communicate.

Lewis et al. (14), in 2021, conducted a narrative analysis with online interviews. The women who participated had to be over 18 years old, have at least one birth experience, and a self-diagnosis of autism. In this study, 16 self-identified autistic women took part, and two of them shared multiple birth stories, resulting in a total of 19 birth narratives. Participants ages at the time of the study ranged from 21 to 57 years, while their ages at time of giving birth ranged from 19 and 41 years. The interval since giving birth ranged from 6 months to 26 years. All participants identified as female, and most of them were white. Six participants were from the United States, six from the United Kingdom, and two from New Zealand. Five participants were aware of their autism diagnosis at the time of the survey. The narrative method for data analysis used in this study was based on Burke's (32) dramatistic pentad, which identifies five elements of a story: Act, Scene, Agent, Agency, and Purpose. The most frequent source of trouble (Agency) was an imbalance between a nursing action or a healthcare provider's act and how that action was carried out. Participants felt that their experiences were minimized, their wishes were ignored, and they were denied important education and communication by those involved in their care due to the actions, comments, and tone of the members of the healthcare team, all of which were frequently perceived as lacking compassion. Many participants believed that they were in labor and required hospital admission, or that their labor had progressed, and needed examination. However, participants admitted that their concerns were

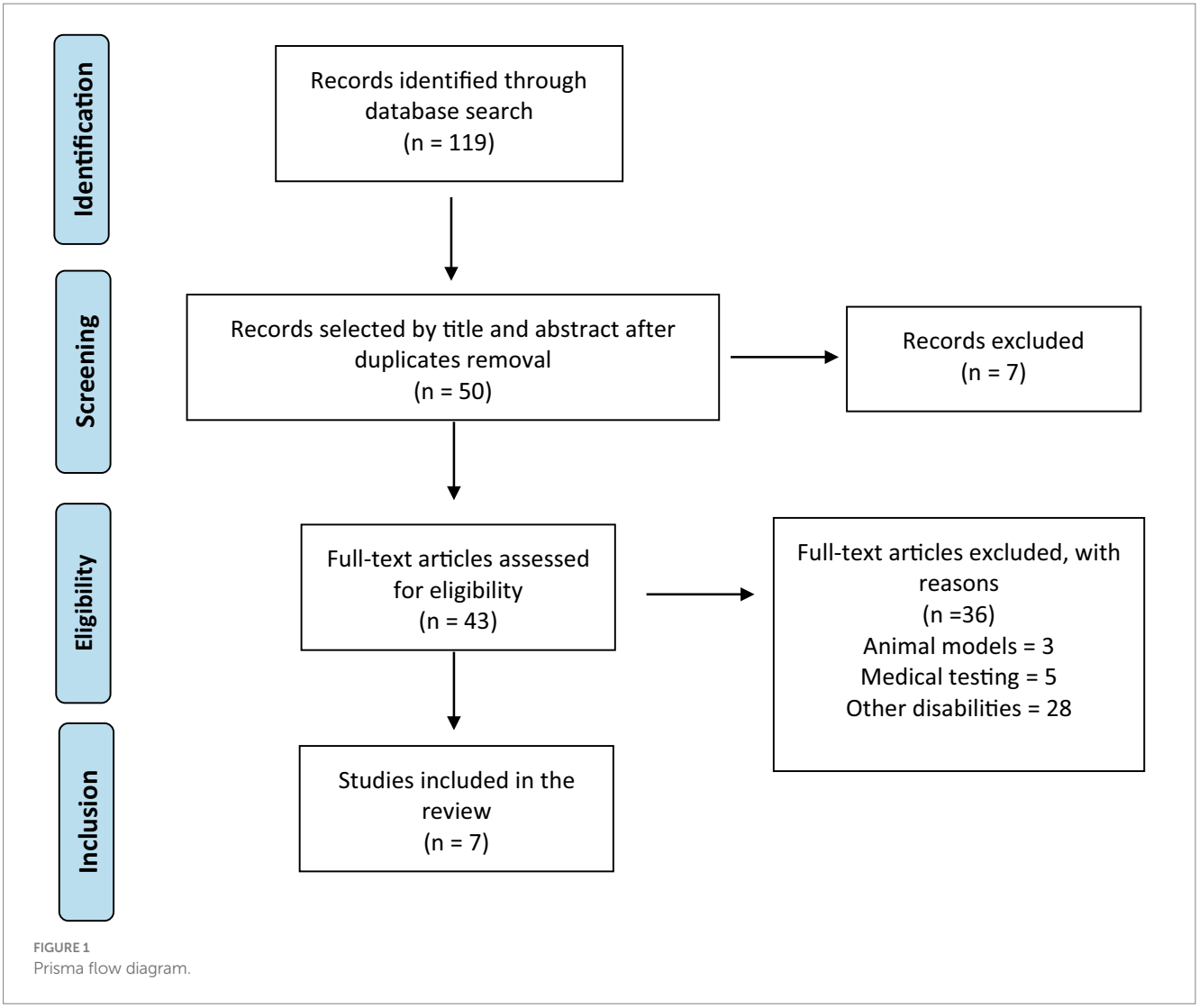

FIGURE 1
Prisma flow diagram.

belittled by the medical staff, which made them feel uncomfortable. The second most frequent reason for the trouble was an imbalance between the qualities of the person giving birth (Agent) and the environment where the delivery took place (Scene); this problem was frequently linked to autistic characteristics. Participants stated that sensory events related to birth, such as sights, sounds, smells, pressure, and temperature, exacerbated their existing sensory hypersensitivities and caused discomfort, dissociation, and trauma. Many participants reported feeling so overstimulated by their senses that they became dissociated throughout labor, significantly impacting their ability to interact with the medical staff and actively participate in labor. Participants indicated that the social and sensory stimuli in the birthing environment (Scene) as well as how they were handled by medical staff members (Agency) had the most influence on shaping their birth stories.

Pohl and collaborators (33) conducted a study, in 2020, on autistic and non-autistic mothers. 410 autistic mothers and 258 non-autistic mothers participated and completed the survey. Mothers with autistic children were then excluded, reducing the number of non-autistic mothers to 132 and autistic mothers to 355. Two- thirds of the sample of autistic mothers had received the diagnosis, while the remaining third had not. Prenatal and postnatal depression were also substantially more common in autistic moms than in non- autistic mothers. Regarding whether they felt the birthing process had been appropriately described to them, autistic moms were more likely to feel this way than non-autistic mothers. There was also a significant difference between the groups in terms of reporting this. Antenatal class attendance, however, did not change significantly between groups. Autistic mothers were more likely than non-autistic mothers to require multitasking in parenting and housework. They were also more likely to create socialization opportunities for the child and perceive themselves as more organized parents than non-autistic mothers. There were no significant differences between autistic and non-autistic mothers in their ability to put their child's needs ahead of their own or seek ways to boost their child's self-confidence. Within the group of mothers with autism, the majority (61%) felt they should have been provided with additional support because of their diagnosis, and 41% of mothers received inadequate support from institutional sources such as hospitals or clinics.

Hampton and collaborators (34) conducted a study on the last trimester of pregnancy involving 24 autistic and 21 non-autistic women. Semi-structured interviews lasting 20 to 60 min were conducted midway through the third trimester of pregnancy. The interviews discussed the bodily and sensory experiences of pregnancy,

TABLE 1 Provides a summary of the authors, participants, measurements, and conclusions.

References	*N*	Methodology	Demographics	Primary findings
Gardner et al. (13)	8	Secondary analysis of a qualitative data set that evolved during the process of developing a research questionnaire to assess childbearing experiences of women with Asperger syndrome.	Eight women (Asperger Syndrome) with average age of 39 years (range, 27–52 years).	Results are presented according to the traditional three stages of pregnancy – the prenatal period, intrapartum period, and postpartum period – which is the model that most clinicians use when providing care. Additionally, women have suggested some potential ideas that may be helpful for clinicians when caring for this population of women.
Rogers (10)	1	Emails correspondence during pregnancy and after. One interview after childbirth.	Melanie, 26 years old.	Melanie's experience reveals communication difficulties with professionals, and a perception of hospital very "heavy" of sensory elements: noises, shouting, touching and being touched represented a strong stressor for Melanie during visits.
Donovan (31)	24	Interviews conducted using a semi structured interview guide.	Twenty-four women ages 29–65 years from the United States, United Kingdom, and Australia, all of whom gave birth to healthy new-borns in an acute care setting.	Study participants expressed communication difficulties with nurses in a variety of ways. Including trouble conveying needs, alerting nurses when they felt ill, or not understanding what was said to them. Ineffective communication with nurses resulted in feelings of anxiety and being scared and inhibited participants in further attempts at communication.
Phol et al. (33)	487	Online survey and an analysis of the answer using Chi-squared analysis.	Autistic mothers ($n = 355$), and non-autistic mothers ($n = 132$), each of whom had at least one autistic child, were included in our final analysis.	Autistic mothers face unique challenges and the stigma associated with autism may further exacerbate communication difficulties. Greater understanding and acceptance amongst individuals who interact with autistic mothers is needed, and autistic mothers would benefit from additional and better-tailored support.
Lewis et al. (14)	16	Online interviews.	16 autistic women shared 19 birth stories.	Nurses need to provide thorough and nonjudgmental education about the birth process to ensure that autistic women feel safe and in control and do not withdraw from care.
Dugdale et al. (35)	9	Semi-structured interview and narrative analysis.	9 autistic mothers with at least one child between the ages of 5 and 15.	Four themes emerged: 1. *Autism fundamentally impacts parenting*; 2. *Battle for the right support*; 3. *Development and acceptance*; and 4. *The ups and downs of parenting*. The majority of participants' kids either had an autism diagnosis or were undergoing testing. Subjects also discussed their social and communication problems, such as finding it difficult to socialize, feeling different or having sensory demands.
Hampton et al. (34)	45	Interviews conducted using a semi structured interview guide.	24 autistic and 21 non-autistic women during the third trimester of pregnancy.	The study's findings suggest that prenatal healthcare for autistic individuals can be improved by adjusting sensory and communication needs. To ensure that autistic individuals receive appropriate support, prenatal healthcare professionals need to receive more comprehensive training related to autism.

as well as encounters with medical experts. Nine subthemes were grouped into three main themes: "The physical and psychological impact of pregnancy," "The influence of official and informal assistance," and "Fears and hopes of parenthood."

While the non-autistic group reported only sensory changes related to smell and taste, the autistic group frequently mentioned changes in sound, lighting, and touch. The participants in the autistic group also reported feeling more anxious and depressed with some of them connecting these changes to hormonal factors. Both groups discussed physical exhaustion, but several members of the autistic group also discussed mental exhaustion and related issues. Furthermore, the group of autistic women clearly expressed their preference for specialist-patient communication in writing or by telephone. Furthermore, autistic women expressed concern about the hospital environment, which they considered inadequate and lacking in training to accommodate autistic women. They also expressed concerns about the executive functions required for parenthood.

Dugdale and collaborators (35) conducted research on 9 autistic mothers with at least one child between the ages of 5 and 15. The women were asked to complete a semi-structured interview which was subsequently analyzed from a narrative point of view. Four main themes emerged: (i) Autism fundamentally impacts parenting; (ii) Battle for the right support; (iii) Development and acceptance; and (iv) The ups and downs of parenting. Most participants' children either had an autism diagnosis or were undergoing testing. The participants also discussed their social and communication challenges, such as finding it difficult to "socialize with other parents," feeling different or having sensory demands. Shared diagnoses helped participants feel closer and more connected to their children. Another frequent challenge was managing sensory sensitivity while parenting, particularly during pregnancy. Participants described difficulties in seeking help for themselves or their children because they felt misunderstood, judged, or disregarded. Participants discussed how having an autistic trait was often associated with being misunderstood. All the participants received an autism diagnosis after becoming parents. Some interviewees reported feeling "guilty" before receiving a diagnosis. Before their diagnosis, some participants spoke of feeling "sorry" for their struggles and how they affected their children. After receiving a diagnosis, participants' experiences were positively "re-process[ed]." Many found that this lessened their sense of guilt, improved their self-acceptance, and provided an explanation that was consistent with who they were. The "hardest thing" about parenting, according to many, was dealing with their children's autism or other special needs. Some participants believed this was because their child was "different," and they felt they did not belong in "the usual mom's club."

Rogers and collaborators (10) conducted a case study and shared the findings obtained from the stories of Melanie, a girl with Asperger. Melanie's story was elicited through emails—pre and post birth, and through one interview (post birth). She was very eager to participate with the researchers and to share her story. The interview was audio recorded, transcribed, and verified by the participant. Three themes emerged from the thematic analysis of Melanie's narrative, the interview, and the content of her emails. The main theme related to the communication and services issues she encountered with healthcare professionals. Sensory issues were also very prominent in her narrative, and the challenges of parenting were quite evident. Melanie first contacted the researchers by email when she was 6 months' pregnant. Her narrative began with a concise description of her childhood. At 25 weeks, Melanie started to make more frequent visits to the hospital where her sensory stress became more pronounced. The girl described some of these experiences in detail. Melanie's account reveals her perceptions of how ASD affected her perinatal experience, as well as her belief that ASD influenced the way her midwives and doctors conducted their medical assessments. Furthermore, the young woman highlighted how even the hospital and its staff were too very "heavy" sensory elements: noises, shouting, touching and being touched represented a strong stressor for Melanie.

Marcia Gardner and collaborators (13) conducted a study on the pregnancy experience of women with Asperger's syndrome (ASD). This qualitative study describes the childbearing experiences of eight women with Asperger syndrome. Four major themes emerged: Processing Sensations, Needing to Have Control, Walking in the Dark, and Motherhood on My Own Terms. Most women commented about difficulties in processing sensations associated with pregnancy and heightened sensitivities to touch, light, sounds, and interaction. Additionally, several women felt they had less control over their actions and environment. Deciphering the child's behavior was also a challenging task, and the women received help from their mothers. The feeling of judgment and expectations toward them came from the medical-health environment and the professionals they met.

4. Discussion

The selected studies in this review appear to share some results and limitations, the latter primarily related to heterogeneous methodologies and samples.

The diagnosis of autism in adulthood still appears to be one of the major clinical challenges to overcome, and it seems to be even more difficult if requested by a woman. Much has been discussed about the camouflage effect of autism in autistic women, which means a greater cognitive ability of women to hide the signs and symptoms of autism. Therefore, many women participating in autism research have not received a formal diagnosis, but have self-diagnosis, leading them to the awareness of being on the autism spectrum. Currently, researchers are forced to accept self-diagnoses of autism; otherwise, there would be a risk of not having enough subjects to be involved. However, this limitation must be taken into consideration.

Regarding our review goals, the consulted research has led us to highlight the following results:

Regarding aspects related to the sensory sphere, the results have shown that pregnancy for autistic women represents a moment with more sensory challenges compared to non-autistic women. In fact, while sensory changes in the non-autistic group were limited to smell and taste, the autistic group commonly reported changes involving sound, light, and touch, making everyday life more difficult. Therefore, aspects related to abnormal sensory perception were inevitably linked to both relational and emotional difficulties (14, 34).

From an emotional perspective, it emerged that the group of autistic women showed an increase in anxiety and low mood (31). Additionally, both groups stated that being pregnant attracted social attention, and for neurotypical women, this situation tended to be pleasant, while autistic women found it difficult to manage an increase in conversations and being the center of attention (35).

Finally, in line with our hypotheses, the different way in which people with autism perceive stimuli determines not only different sensory experiences but also distinct emotional experiences, which medical specialists (e.g., gynecologists and midwives) often struggle to understand and effectively respond to the needs and requests of their patients during that time (10). Our studies have highlighted that, autistic mothers experience greater difficulty in interacting with professionals during their pregnancy; they prefer to communicate with professionals via a phone call rather than in person. Moreover, for many women, discussing their autism during pregnancy represents more of a stigma than a source of support. In fact, the prevailing belief among women is that revealing their autism would lead specialists to treat them worse, which also highlights a certain fear of being judged by others.

Therefore, the examined studies have found that women with ASD face unique challenges during childbirth that differ from those of neurotypical women. It emerged that the participants often felt belittled, ignored, and uninformed about the care they received, also experiencing being at the center of attention as something negative and hindering, rather than positive. On the other hand, the research shows us how some "expected" results, such as difficulties in

breastfeeding, have been contradicted (autistic women may experience slightly more discomfort in breastfeeding but still prefer it because it is considered "better" for the child). Meanwhile, there seems to be an urgent need to refine specific identification and intervention protocols for autism in adulthood. The current situation presents us with professionals who are not prepared to handle the specific communicative, physical, emotional, and sensory needs of autistic women, thereby they are unable to provide adequate assistance.

One of the limitations of this review is certainly related to the scarcity of articles in the literature on the topic of pregnancy among autistic women, indicating the limited attention given to this topic and the consequent availability of knowledge in clinical settings.

5. Conclusion

Pregnancy can be a challenging experience for any woman, bringing both joy and a multitude of physical and physiological changes. However, for autistic women, the changes that come with pregnancy can be particularly overwhelming and confusing. During pregnancy, in fact, autistic women may experience difficulties with sensory processing, depression, anxiety, and fatigue, making it challenging to carry out the day-by-day activities required for a healthy pregnancy. To address these challenges, a medical and social approach could be adopted to provide support for autistic women during this delicate time. On the other hand, professionals should be trained on autism to address the impact of Autism during pregnancy. The deepening of this topic could also contribute to that movement of increasingly in-depth analysis of the autistic phenotype and its various expressions (36).

In this regard, the National Autistic Society has proposed the use of a "Health Passport" to help autistic individuals communicate their needs to healthcare professionals, including doctors and nurses. Widespread use of this tool, along with extensive training for healthcare personnel on managing the needs of pregnant autistic women, with a focus on communication and sensory aspects, could be particularly beneficial. In summary, identifying the unique challenges faced by pregnant autistic women and providing appropriate support could go a long way in ensuring their well-being during this critical period. Services for ASD should propose programs for ASD individuals and caregivers concerning social skill training to improve abilities in relationships and affective-sexual training programs.

To address this issue in our Adult Autism Center, we propose a specific sexual education program for people with autism in adulthood. The aim is to improve knowledge of the body and enhance social skills to form relationships. The program has three different levels, related to the same level of ASD described in DSM 5 (6). The teaching team is composed of psychologists, psychiatrists, urologists, and gynecologists. All the teachers are also specialized in autism and disability. The course is gender-mixed, involving males and females in the same group. In the ASD level-1 course, only ASD individuals are admitted. In the ASD level-2 course, ASD individuals may be supported during the lessons by their social coach, who usually assists them in daily activities. The ASD level-3 course is directed to patients' caregivers. Topics taught include body anatomy, contraception, coitus, and pregnancy. In a separate program, a social-skill training program is focused on improving social abilities. ASD individuals should be prepared for these issues.

Data availability statement

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

Author contributions

RF, PR, and GC contributed to the conception and design of the study. RF wrote the first draft of the manuscript. LR and FD organized the database and performed the statistical analysis. RK and RS reviewed all the papers. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Psychosocial therapeutic approaches for high-functioning autistic adults

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Autism spectrum disorder (ASD) is characterized by impaired social interaction and communication skills, repetitive behaviors, restricted interests, and specific sensory processing. Particularly, adults with high-functioning ASD often remain unrecognized, presumably due to their high compensatory skills, but at the cost of high stress, which is often linked to anxiety and depression. This may further explain the significantly high suicide rates and reduced life expectancy among individuals with ASD. Thus, providing support to high-functioning autistic adults in managing core symptoms, as well as co-occurring anxiety and depression, appears essential. To date, only a limited number of evidence-based psychosocial therapeutic options are available, and very few of them have undergone rigorous evaluation in a clinical context. To obtain a comprehensive understanding, a systematic literature search was conducted according to the PRISMA checklist, and only studies demonstrating robust methodological quality were included and discussed in this review article. Although promising initial key factors and methods have been identified, additional evidence-based studies are imperative to ascertain the optimal treatment and evaluate the long-term outcomes for adults with high-functioning ASD.

KEYWORDS

autism, high-functioning, adults, interventions, therapy, treatment, psychosocial, cognitive-behavioral

Introduction

Autism spectrum disorder (ASD) comprises a heterogeneous group of neurodevelopmental disorders characterized by impaired social interaction and communication skills, restricted patterns of behaviors and interests, and specific sensory processing. Within this spectrum, adults with high-functioning autism, characterized by quite normal language use and no intellectual impairment, are often overlooked, even by healthcare professionals, due to their less severe core symptoms. Instead, they may predominantly present co-occurring symptoms, such as anxiety or depression, along with secondary issues like frequent work changes or unemployment (1). However, it is imperative to recognize that these individuals frequently experience significant impairment, which they may compensate for at the cost of enduring elevated stress. The phenomenon of "masking" or "social camouflaging" is prevalent, often leading to a state known as "autistic burnout" (2, 3) and complicating the process of receiving an ASD diagnosis (4). As a result, adults with high-functioning autism often seek

psychotherapy to address challenges related to depression, anxiety, difficulties in social interaction and communication, as well as coping with everyday life and stress regulation (5, 6).

Despite the evident need for therapeutic support in this clinical population, their access to appropriate healthcare services remains insufficient. In contrast to the availability of specialized treatments for children and adolescents, few tailored options exist for adults with high-functioning ASD. Additionally, even when in contact with the healthcare system, they often receive less adequate treatment (5, 7). Furthermore, research concerning treatments for autism predominantly focuses on children and adolescents, with limited investigations addressing interventions for adults with ASD. These studies examining treatments for adults with high-functioning autism frequently suffer from small sample sizes, biased samples, absence of control conditions, and lack of randomization. Moreover, the diversity in intervention content, procedures, assessment methods, and outcomes across studies makes it challenging to summarize the findings. Consequently, there remains very limited evidence regarding interventions for high-functioning autistic adults. Nonetheless, both the current National Institute for Health and Clinical Excellence (NICE) (8) and German (6) guidelines advocate psychosocial interventions for autistic adults, particularly regarding the management of core symptoms, co-occurring mental health conditions, daily life skills, and stress.

The most promising psychosocial approaches, to date, are based on Cognitive Behavioral Therapy (CBT), which emphasizes thoughts and beliefs to understand and modify behavior and emotional experiences. The structured nature of CBT, combined with the provision of information about ASD and the therapeutic methods, goal-setting, and home assignments, is well-suited for individuals with autism, corresponding with their need for predictability and information. In addition, the training of specific skills, also in daily situations, might support the translation from specific to more general skills and the generalization across different situations, which is specifically challenging for ASD individuals. Moreover, Mindfulness-Based Interventions, as a more recently developed CBT approach, complement the traditional approaches by focusing on present thoughts, emotions, and perceptions with acceptance and without evaluation. Mindfulness-Based Interventions aim to increase psychological flexibility and potentially reduce anxiety and depression symptoms.

This review aims to systematically outline the current evidence-based psychosocial approaches for treating the most prominent core and associated symptoms in high-functioning autistic adults. Focusing only on well-designed research studies that investigate these interventions with a high level of methodological validity, a systematic search and analysis was conducted according to the PRISMA schema to present, summarize, and discuss the relevant literature on this topic.

Methods

A targeted literature search was conducted in January 2023 using the databases MEDLINE, PsycINFO, and PsycARTICLES via the EBSCO interface by combining all of the following search terms: (a) "autism spectrum disorder," "autism," "autistic" or "ASD," AND (b) "high-functioning," "Asperger," or "without intellectual impairment," AND (c) "therapy," "intervention," or "treatment." Only original articles written in English and from peer-reviewed journals were considered, supplemented by a search in current national guidelines (e.g., NICE). Additionally, the reference lists of the included articles were screened. Studies targeting adult patient samples (> 18 years) with an IQ > 70 were included, while those with younger or mixed age samples and with an IQ < 70, as well as studies without a description of age or IQ, were excluded. The inclusion of articles was first determined through an evaluation of the title/abstract and, subsequently, the full publication. The literature search was performed by one clinical expert rater.

To evaluate exclusively the evidence-based therapeutic approaches for autistic adults, only quantitative and controlled trials/studies were included. To ensure the minimum degree of statistical power, only studies with a sample size of $N > 16$ were considered, as this is the minimal sample size for detecting a potential large effect between groups (within-between interaction effect of $f = 0.4$, repeated measure ANOVA, power $(1\text{-}\beta) = 0.80$, α-level $= 0.05$, one-tailed testing). For the detection of median or small effects, even larger sample sizes would be necessary. With a focus on psychosocial interventions, only interventions targeting core or co-occurring anxiety and depression symptoms of ASD were included, while interventions targeting other comorbid specific disorders (e.g., OCD) or subgroups (e.g., only unemployed individuals) in ASD samples, as well as biological (e.g., TMS) or somatic (e.g., biofeedback, dance therapy) interventions, were excluded. Furthermore, only psychosocial interventions targeting various domains of social functioning were included, while interventions targeting only one specific skill (e.g., emotional face recognition) and/or only very specific skills (e.g., training of one strategy for better reading) or settings (e.g., only employment/academic) were excluded (for an overview of the selection process, see Figure 1, based on the PRISMA schema).

Results

The keyword search via the EBSCO interface revealed 607 articles, with 528 written in English and 422 published in peer-reviewed journals. After filtering for adult samples (>18 years), 123 articles remained. Further narrowing to quantitative studies revealed 106 articles. After excluding articles related to diagnostics or observational studies, samples containing individuals with intellectual impairment or other intervention populations (e.g., parents of ASD individuals), 68 articles remained, related to interventions for high-functioning autistic adults. After further exclusion of articles with no psychosocial intervention for ASD core, anxiety or depression symptoms (e.g., targeting OCD; biological/somatic interventions), no control condition, sample sizes of N < 16, or interventions targeting only one, very specific skill or area (academic/employment context), or due to methodical concerns, nine articles remained, constituting the basis for synthesis and narrative integration (for an overview, see Figure 1). From these studies, information regarding the design, sample size, aims, interventions (including content, methods, and adaptations to ASD), control conditions, setting, and results were systematically extracted. The results of this review were synthesized and incorporated with the clinical experience of the authors (for an overview of the integrated studies and treatment programs, see Table 1).

Interventions targeting ASD core symptoms

Interventions targeting ASD core symptoms primarily focus on social functioning in group settings to facilitate interactions and

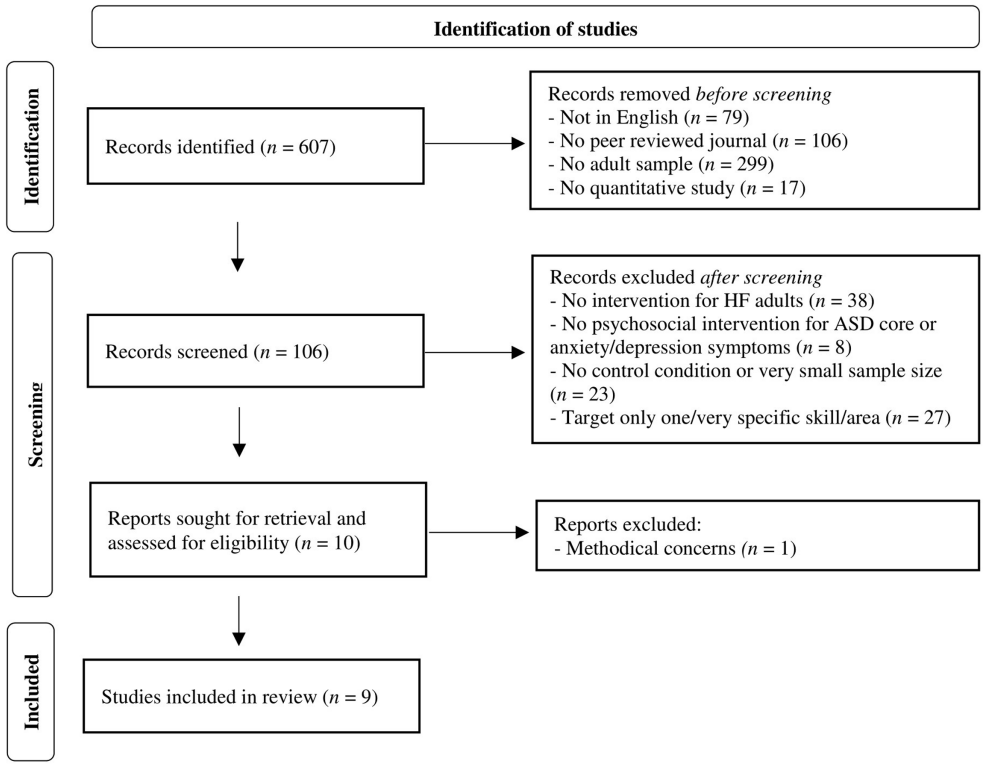

FIGURE 1
Flowchart of the literature search and selection process.

shared experiences. In this context, five studies could be identified, with three of them investigating the same program (PEERS-YA).

The Program for the Education and Enrichment of Relationship Skills for Young Adults (PEERS YA) (9–11) is manualized and aimed at supporting friendships and the development of autonomy through social skills training. It covers etiquette for games, sports, dating, verbal and digital conversational skills, perspective-taking skills, conflict resolution, and responding to teasing and bullying. The structured sessions follow a fixed order, starting with psychoeducation, followed by exploration of social rules through Socratic dialogue, modeling, and training of various social interactions through role plays, and perspective-taking tasks. Skills practice is conducted through behavioral rehearsals with feedback and homework. Caregivers of the young adults also receive psychoeducation and didactic instructions for supporting the participants with training and applying skills. Three RCT studies demonstrated that the PEERS YA program significantly increased social skills knowledge, overall social skills, social skills behavior and responsiveness, social engagement and empathy, and decreased social anxiety and loneliness, with some effects maintained after 4 months.

The Acquiring Career, Coping, Executive Control, Social Skills program (ACCESS) is another CBT-based social functioning intervention, aiming to increase skills and beliefs for adult functioning (12). It includes three main modules: (1) stress and anxiety coping skills, (2) self-determination skills, and (3) adaptive and social skills (regarding friendships and social etiquette at work). The program involves structured sessions, psychoeducation, learning to detect and change negative emotional states (e.g., through cognitive restructuring and reappraisal), modeling of behavior (e.g., through role plays), and training of social skills. Additionally, self-talk strategies related to self-determination (e.g., goal setting, planning and execution, decision-making, problem-solving, self-advocacy) are explored and trained. Caregivers of the young adults also receive psychoeducation and didactic instructions to support the participants in applying skills in daily life and increasing their autonomy. As additional part of the intervention, participants engage in a vocational activity for 3 h per week. Results showed significantly increased coping self-efficacy related to a stronger belief in the ability to access social support in coping with stressors, as well as increased adaptive and self-determination skills according to caregiver reports.

To investigate if a manualized structured social skills training is more effective than a non-structured social interaction group, another RCT study was conducted in autistic high-functioning adults by Ashman et al. (13). Both interventions covered themes like communication and language, emotion recognition and responding, family and friendships, employment, and dating. While the social skills training was highly structured and used role plays, discussions, multimedia exercises, and homework to foster social learning, the social group primarily discussed these themes but included also some role plays and regular homework. Results showed equal improvement regarding visual social cognition, social responsiveness, and functional impairment with no significant difference between groups. However, participants seemed to appreciate the higher structured approach in the social skills training, as indicated by higher attendance rates.

Summarizing all described treatments targeting social dysfunction as a core symptom of ASD, both the PEERS and ACCESS program are

TABLE 1 Overview of the integrated studies and treatment programs.

Treatment concept	Study description	Primary outcome targets	Design	Sample size	Duration	Setting	Intervention elements	Results
Interventions targeting ASD core symptoms								
PEERS YA	Social skills Program for the Education and Enrichment of Relationship Skills for Young Adults (PEERS YA; age: 18–23 years) vs. wait list CC (9)	Social skills and knowledge, perspective taking skills	RCT	$N = 22$ $n = 12$ IC, 10 CC	14 weeks	- Group intervention - 9–10 participants - 90 min sessions weekly - 2 therapists - Caregiver support group	- Psychoeducation - Socratic dialogue - Social behavior/rules modelling and interaction tasks (e.g., role plays) - Perspective taking tasks - Structured skills practice by behavioral rehearsals - Performance feedback - Homework	- Increased overall social skills, social skills knowledge, social responsiveness, empathy, get-together frequency - Decreased loneliness after intervention
PEERS YA	Social skills Program for the Education and Enrichment of Relationship Skills for Young Adults (PEERS YA; age: 18–23 years) vs. wait list CC (10)	Social skills and knowledge, perspective taking skills	RCT	$N = 22$ $n = 12$ IC, 10 CC	16 weeks	- Group intervention - 10 participants - 90 min sessions weekly - 2 therapists - Caregiver support group	See Gantman et al. (9)	- Increased overall social skills, social skills knowledge, and social engagement - Reduced ASD symptoms related to social responsiveness after intervention
PEERS YA	Social skills Program for the Education and Enrichment of Relationship Skills for Young Adults (PEERS YA; age: 18–23 years) vs. wait list CC (11)	Social skills and knowledge, perspective taking skills	RCT	$N = 52$ $n = 29$ IC, 23CC	16 weeks	- Group intervention - until 10 participants - 90 min sessions weekly - 2 therapists - Caregiver support group	See Gantman et al. (9)	- Increased social skills knowledge, social behavior and responsiveness, empathy - Decreased social anxiety after intervention
ACCESS	Acquiring Career, Coping, Executive Control, Social Skills program (ACCESS; age: 18–38 years) vs. waitlist CC (12)	- Stress and anxiety coping skills - Self-determination skills - Adaptive and social skills	RCT	$N = 44$ $n = 29$ IC, 15 CC	19 weeks	- Group intervention - 14 participants - 90 min sessions and 3 h vocational activity weekly - 1 therapist - Caregiver support group	- Psychoeducation - Emotion recognition/ regulation (e.g., cognitive restructuring, reappraisal) - Behavior modelling (e.g., role plays) - Social skills training - Self-talk strategies regarding self-determination (e.g., goal setting, planning/ execution, decision-making, problem-solving, self-advocacy) - Homework	Increased coping self-efficacy, adaptive and self-determination skills after intervention
Structured social skills training	Structured social skills training vs. non-specific social interaction CC (13)	Social skills	RCT	$N = 19$ $n = 10$ IC, 9 CC	16 weeks	- Group intervention - 10 participants - 60 min sessions weekly - 1 therapist	- Emotion recognition and responding - Discussions/exercises regarding social situations (e.g., role plays) - Homework	Increased social cognition and responsiveness, functional impairment after both interventions
Interventions targeting ASD co-occurring symptoms and quality of life								
CBT	Cognitive behavior therapy (CBT) vs. recreational activity CC (14)	Co-occurring mental health-related symptoms	RCT	$N = 75$ $n = 35$ IC, 40 CC	36 weeks	- Group intervention - 6-8 participants - 180 min sessions weekly - 2 therapists	- Psychoeducation - Social skills training (e.g., role-plays) - Goal setting - Behavior analysis - Identification/ Reappraisal of dysfunctional thoughts - Exposure exercises - Homework	- Increased quality of life after both interventions ($d = 0.31$) - No chance in sense of coherence, self-esteem, psychiatric symptoms - Lower drop-out rates and higher subjective improvement, wellbeing, understanding of difficulties, ability to express needs after CBT

(Continued)

TABLE 1 (Continued)

Treatment concept	Study description	Primary outcome targets	Design	Sample size	Duration	Setting	Intervention elements	Results
MBT	ASD adapted Mindfulness Based Therapy (MBT) vs. wait list CC (15)	Co-occurring anxiety and depression symptoms	RCT	$N = 42$ $n = 21$ IC, 21 CC	9 weeks	- Group intervention - 10-11 participants - 150 min sessions and 4–6 h meditation practice weekly - 2 therapists	- Psychoeducation - Mindfulness-based tasks (e.g., body scan, meditation) - Mindfulness-based Coping - Future planning - Homework	- Reduced anxiety ($d = 0.76$), depression ($d = 0.78$), rumination ($d = 1.25$) - Increased positive affect ($d = 0.79$) after intervention
CBT/MBSR	Cognitive behavior therapy (CBT) vs. Mindfulness Based Stress Reduction (MBSR) intervention (16)	Co-occurring anxiety and depression symptoms	Controlled, not randomized trial	$N = 59$ $n = 27$ CBT, 32 MBSR	13 weeks	- Group intervention - 9-11 participants - 90 min sessions weekly - Number of therapists is not mentioned	CBT: - Psychoeducation - Problem definitions - Emotion regulation/Coping - Challenge of dysfunctional thoughts - Plan/execution of tasks - Future planning - Homework MBSR: See Spek et al. (15)	- Reduced anxiety, depression, rumination, autistic symptoms - Increased global mood after both interventions
Online CBT/ Online MBT	Online Cognitive behavior therapy (CBT) vs. Mindfulness Based therapy (MBT) vs. waitlist CC (17)	Co-occurring anxiety symptoms	RCT	$N = 54$ $n = 16$ CBT, 19 MBT, 19 CC	6–8 weeks	- Individual intervention - Self-guided online courses	MBT: - Awareness - Non-judgment attitude by instructed exercises CBT: - Psychoeducation - Anxiety management by instructed exercises	- Reduced anxiety symptoms after both interventions (vs. CC) - No Change in depressive symptoms, daily functioning, wellbeing

IC, intervention condition; CC, control condition.

specifically designed to facilitate the transition to adulthood in young high-functioning autistic adults. The included studies demonstrate significant improvements in social functioning related to social skills knowledge and application, social interactions and engagement, empathy, social anxiety and loneliness (9–11), social responsiveness (9–11, 13), and social cognition (13), with a maintenance effect regarding social skills knowledge and application, social engagement and symptoms related to social responsiveness at 4-month follow-up (10). Furthermore, findings showed improved functional impairment, coping self-efficacy and adaptive and self-determination skills (12). However, a non-structured social interaction group, was found to be equally effective in improving social cognition, responsiveness, and functional impairment (13). The duration of the final versions of the interventions ranged from 16 to 19 weeks, with weekly 60–90-min sessions for 10–14 participants per group and, in part, a caregiver-group, in parallel (10–12). The ACCESS program additionally implemented 3 h of vocational activity per week for the participants. While the PEERS program was led by two facilitators (10, 11), the other interventions were led by only one facilitator (12, 13). Adaptations to the needs of autistic adults were integrated by providing a small group format, concrete rules and steps, context and structured practice with feedback, and themes conceptualized according to the needs of young autistic adults (9–11). The ACCESS program was adapted with a focus on high structure, multimodal teaching methods, and concrete activities to ground abstract concepts (12). For the intervention investigated by Ashman, no adaptions were reported (13). To promote generalization, all of the social functioning interventions described include homework tasks (9–13), while both transition-to-adulthood interventions involve caregiver support in the application and training of skills (9–12). While the PEERS program includes further CBT elements, such as frequent practice of skills through role plays and behavioral rehearsals in various contexts (9–11), the ACCESS program addresses the issue of generalizability by providing training in various situations and incorporating a vocational activity for 3 h per week (12).

Interventions targeting ASD co-occurring symptoms and quality of life

Interventions targeting frequently co-occurring anxiety and depression symptoms in ASD adapt established and well-assessed general CBT approaches to the needs of autistic adults. In this context, four studies could be identified.

One study by Hesselmark et al. (14) compared a CBT intervention with a recreational activity control group on mental health-related symptoms in autistic adults. Both conditions were implemented in highly structured sessions. The manualized CBT intervention contains three modules: (a) self-esteem and ASD awareness, (b) social contacts and handling everyday life, and (c) psychological and physical health, while the recreational condition includes conducting collective recreational activities. Accordingly, the CBT condition involves psychoeducation, training of social skills (e.g., through role plays), goal setting, behavior analysis, identification and reappraisal of dysfunctional thoughts, and related exposure exercises. Results revealed improved quality of life after both conditions and no

significant intervention effect for sense of coherence, self-esteem, and psychiatric symptoms. However, CBT was related to lower drop-out rates, higher subjective improvement after intervention, increased wellbeing, understanding of their difficulties, and ability to express needs at follow-up.

Another study by Spek et al. (15) compared Mindfulness-Based Therapy (MBT) with a waitlist control group regarding co-occurring symptoms of anxiety and depression in autistic adults. The intervention aiming to increase own perception and foster acceptance through mindfulness-based tasks, partly related to stress and coping. It involves psychoeducation, practicing body scan, mindful breathing, movement and eating exercises, meditation, evaluation of experiences and training of mindfulness coping strategies, exercise planning, and homework. Results demonstrate a significant decline in anxiety, depression, and rumination, as well as increased positive affect after intervention.

Another study aiming to primarily treat co-occurring symptoms of anxiety and depression compared Mindfulness-Based Stress Reduction (MBSR) and CBT interventions in autistic adults by Sizoo and Kuiper (16). The same MBSR protocol (with minor adaptions) was used as in the study from Spek et al. (15). The CBT intervention covers themes like processing styles, relationships and interactions between thoughts, feelings, and behavior, the cognitive model, and dysfunctional thoughts. Additionally, individual problems, social interaction, signs of stress, coping with stress and negative emotions, and future plans with possible obstacles were addressed. The means of choice were providing information and psychoeducation, problem definitions, reflection, and discussions. Additionally, challenging thoughts, detecting stress, training to cope with stress/negative emotions and of social interaction, reflecting on obstacles for future plans and homework were utilized in a highly structured setting. Results showed equally effective interventions, with significantly reduced anxiety, depression, rumination, and autistic symptoms, as well as increased global mood after both interventions, maintained at the 3-month follow-up.

In a more recent study, conducted by Gaigg et al. (17), CBT and MBT were compared to a neutral control condition regarding anxiety in an online setting (without a therapist) in autistic adults. The MBT intervention included awareness of the present moment and a non-judgmental attitude regarding thoughts and feelings through instructed exercises, while the CBT intervention contained psychoeducation regarding anxiety and anxiety management through instructed exercises. Results showed significantly reduced anxiety after the online MBT and CBT interventions vs. the control condition, as well as maintenance effects at 3- and partly at 6-month follow-up. No intervention effect was found regarding depressive symptoms, daily functioning, and wellbeing.

Summarizing all the described treatments targeting co-occurring ASD symptoms, the integrated studies demonstrated significant improvements in quality of life after a CBT and recreational activity intervention (14). CBT was additionally associated with higher subjective improvement, wellbeing, understanding of difficulties, ability to express needs, and lower drop-out rates. Furthermore, a MBT intervention (15) led to reduced anxiety, depressiveness, and rumination, as well as increased positive affect compared to a control condition. Likewise, a MBSR and CBT intervention (16) showed equal improvements regarding anxiety, depression, rumination, autistic symptoms, and global mood, with a maintaining effect. Regarding online interventions (17), both CBT and MBT led to less anxiety compared to a control condition, even over time, but no intervention effect was found for depressive symptoms, daily functioning, and wellbeing. A maintaining intervention effect was observed for anxiety symptoms at 3-month (16, 17) and somewhat attenuated at 6-month follow-up (17) and for depressive symptoms, only in one study, at 3-month follow-up (16). The duration of the on-site group interventions ranged from 9 to 36 weeks, with weekly 90–180-min sessions for 6–10 participants per group. Notably, one mindfulness-based intervention (15) integrated additionally 4–6 h of weekly meditation practice as homework. All on-site intervention groups were led by two therapists. The self-guided MBT/CBT online courses (17) was implemented with a duration of 6–8 weeks. In one CBT intervention (14) the settings were tailored and included more limit setting/rules and fewer exposure tasks, while in one mindfulness-based intervention (15) breathing exercises and the program duration were extended, cognitive elements were omitted, and supported homework planning were included. All on-site interventions were adapted to the needs of autistic adults by implementing clear language use, including avoiding metaphors (14–16) and, in part, ambiguous or imagination-related language (15). In the on-site CBT vs. mindfulness-based intervention (16) study, both protocols were specifically designed for autistic adults, including features such as a slower pace, descriptions of autism from other autistic adults, instructed repetitions, and supported homework planning. For the self-guided MBT and CBT online courses (17), no specific adaptions to autistic needs were reported. All on-site group-interventions included elements to promote generalization by including homework tasks (14–16) and, in part, supported planning of mindfulness-based exercises in daily life (15, 16), conceptualizing future plans and reflecting on possible obstacles (16).

Discussion

The present review offers a concise examination and description of the current state of the very few evidence-based psychosocial interventions for high-functioning autistic adults, with a particular focus on CBT approaches including MBT. The findings from the integrated studies provide valuable insights into possible key elements of the interventions and reveal promising preliminary evidence for CBT-based approaches in treating social functioning and co-occurring symptoms of anxiety and depression, as well as enhancing quality of life in autistic adults. The review further supports the importance of adapting interventions to the needs of autistic adults. However, the discussion also underscores the need for further research and improvements in study designs to advance the field of interventions for autistic adults.

Interventions targeting ASD core symptoms

One of the key findings from the reviewed studies is the significant improvement in social functioning, including social skills, interactions, responsiveness, and empathy (9–11, 13), after CBT-based interventions. These findings highlight the potential of CBT-based approaches to enhance dealing with social interactions by

incorporating concrete activities to ground abstract concepts and improve the understanding of social rules and interaction for autistic adults. Additionally, CBT interventions showed positive effects on social cognition, further emphasizing their relevance in addressing core symptoms of ASD. Most of these gains were maintained after the interventions, indicating potential sustainability (10). The CBT interventions also proved effective in reducing social anxiety and feelings of loneliness (9–11), potentially alleviating some of the social challenges commonly experienced by individuals with autism. Moreover, these interventions led to a significant increase in functional abilities and adaptive behaviors (12), which may directly impacts individuals' ability to navigate daily life and engage in various activities effectively. The increase in coping self-efficacy suggests that participants felt more confident in managing challenges and stressors, contributing to better resilience and overall wellbeing. While these positive outcomes may primarily be attributed to the implemented themes and methods, a higher degree of structure appears to be conducive for attendance in the interventions (13).

Particularly, the PEERS YA program stands out, as to date the best evaluated and effective CBT-based intervention in this regard (9–11). Additionally, the ACCESS program showed promising results (12). Both interventions used a CBT multimodal and high structured approach and implemented themes and methods that might be crucial for their effectiveness. Likewise, adaptations were made according to the needs of autistic adults, incorporating a concrete, highly structured approach and elements that facilitate generalization by enhancing skills application in real-life situations. These adaptations are in accordance with current NICE and German AWMF guidelines recommendations (6, 18, 19). However, further studies are needed to identify the specific elements that lead to the improvements in social functioning and determine the most effective degree of structure (13).

Interventions targeting co-occurring symptoms and quality of life

Furthermore, the integrated interventions targeting co-occurring symptoms of anxiety and depression and quality of life in high-functional autistic adults showed positive outcomes, indicating the potential value in alleviating these symptoms in this population. The integrated interventions provided preliminary evidence for CBT-based approaches with significant improvements in symptoms of anxiety (15–17) and depression (15, 16) as well as health related factors (14–16). Thus, autistic adults can benefit from both interventions. Both, CBT and MB-based interventions demonstrated similar effectiveness in treating co-occurring symptoms of anxiety (16, 17), mainly with a maintaining effect (16, 17). The results regarding interventions targeting co-occurring depressive symptoms appeared less consistent, but showing also comparable effectiveness in reducing depressive symptoms for CBT and MB-based interventions, with only in part a maintaining effect (14, 16, 17). In the study comparing an CBT and MB-based intervention (16), including an additional passive control condition may have helped ascertain that the improvements were indeed the result of the intervention, rather than being influenced by other factors (even if previous studies have already made that comparison). Furthermore, this study would have benefited from a randomized allocation and/or matching regarding important characteristics, even if participants' allocation seemed to have happened in an unbiased manner. To date, further well-designed RCTs are needed to elucidate more specifically the relationship between the integrated intervention elements and their effects and further optimize the interventions.

Moreover, the included CBT and MB-based interventions led to decreased rumination and increased positive affect/global mood (15, 16), which are important mental health-related outcomes itself as well as potentially mediating factors for anxiety and depression symptoms. Additionally, findings from the integrated studies demonstrated that quality of life, were comparable positively impacted by CBT and a recreational activity group intervention (14). However, the CBT intervention showed additional benefits, including higher subjective improvement, increased wellbeing, improved understanding of difficulties and ability to express needs, and lower drop-out rates, suggesting CBT may be more effective in addressing the specific needs and challenges faced by individuals with autism. The similar improvement in quality of life might be explained by the broadly similar elements of the highly structured group setting and the resources-oriented and activating content in both conditions. Thus, future studies will have to elucidate, which elements are effective and in what way.

Based on the findings of the reviewed studies, online interventions showed promise in addressing co-occurring symptoms in high-functioning autistic adults. Notably, both CBT and MBT interventions delivered in a cost-effective online setting (17), resulted in reduced anxiety levels in comparison to the control condition. However, neither intervention demonstrated a discernible effect on depressive symptoms, daily functioning, or overall wellbeing. The maintaining effect observed for anxiety symptoms at the two follow-ups underscores the potential enduring benefits of these interventions in mitigating anxiety-related symptoms in high-functioning autistic adults, in an easily accessible and cost-effective online setting. Nonetheless, these preliminary findings should be interpreted with caution due to variations in baseline anxiety levels before intervention, which may impede direct comparison of subsequent changes brought about by the interventions. While these outcomes hold promise, it is imperative for future studies to validate this result through ensuring comparable anxiety levels in all conditions prior to the intervention as well as to compare on-site vs. online interventions and explore the currently lacking research on single versus group-based interventions.

All described on-site treatments targeting co-occurring ASD symptoms showed a similar structure as well as longer duration compared to the online intervention. Potentially, incorporating extended practice might be beneficial to enhance treatment outcomes. Notably, all on-site interventions incorporated a clear language use and elements supporting generalization to cater to the needs of autistic adults. The adoptions made in the reviewed studies are in accordance with the current NICE and German AWMF guidelines (6, 8). However, it is essential to acknowledge that the guidelines are also based on the limited existing studies and expert consensus. Therefore, further research is still needed to strengthen the evidence base.

Overall assessment of the current evidence base

The present review provides preliminary evidence for CBT-based approaches in addressing social functioning and co-occurring

symptoms in high-functioning autistic adults. However, it is important to acknowledge the limitations and gaps in the existing literature. Despite the integrated studies, there remains a shortage of rigorously conducted RCTs with too small sample sizes. Hence, besides the integrated evidence-based studies, future research should focus on rigorously conducting well-controlled RCTs with larger and more diverse samples to establish stronger evidence and provide a more comprehensive understanding for intervention effectiveness. This is particularly crucial considering that the prevalence of ASD is comparable to that of other mental disorders, such as eating or panic disorders, for which multiple well-investigated treatments already exist.

Although the integrated studies have the highest level of evidence-base to date, some minor methodological limitations were identified that should be discussed and addressed in future research. The main limitation of the design of the review is the applied high methodological rigor criteria, narrowing the inclusion of otherwise potentially promising studies. However, these rigorous inclusion criteria are also a strength, ensuring to include only high quality studies. Even if we have carefully chosen the search interface, including international databases of medicine, psychiatry and psychology, using additional databases and including also publications in other languages than English, might have revealed further studies.

A major part of the excluded studies suffer from the lack of control conditions and small sample sizes. While the sample sizes of the included studies were larger compared to most of the existing studies, thus ensuring the detection of large effects, the importance of larger sample sizes for identifying potential medium or small effects, which may still hold clinical relevance, cannot be overstated. To detect the full range of potential effects, the need for larger sample sizes in future studies targeting interventions for autistic adults becomes apparent. By enhancing the sample sizes in future studies, we can gain a more valid understanding of the intervention effects and improve the precision of the findings, ultimately contributing to the advancement of evidence-based treatments for autistic adults.

Furthermore, most of the integrated studies (9, 11–15) relied solely on pre-post measures, with only a few studies including additional follow-up assessments (10, 16, 17) with rather short time frames. Hence, our review emphasizes the importance of investigating the sustainability of intervention effects over longer time periods in future research.

While the inclusion criteria of this review focused on studies with a control group design and mainly integrated RCTs, some methodological limitations still persisted. Studies utilizing solely passive control conditions (9–12, 15) may underestimate the inherent impact of any active component, whereas studies employing solely active control conditions (13, 14, 16) might limit the ability to distinguish specific intervention effects, particularly if the inserted contents and methods are similar (13, 14, 16). By examining both types of control condition (17), a deeper understanding of intervention effectiveness can be gained, facilitating the identification of impactful components and their application in designing more effective and cost-efficient treatments. Such knowledge seems pivotal in tailoring interventions to the specific needs of individuals with autism, where some may benefit from more general factors, like a structured environment and social interaction, while others may require more targeted therapeutic approaches. This may also result in cost reductions for the healthcare system and increase the range of available interventions for autistic adults.

In line with the general research situation, the integrated studies demonstrated a gender imbalance, with a greater proportion of male participants in the included studies. Additionally, many interventions focused primarily on young adult samples (9–12) or individuals of younger or middle-aged age groups. Consequently, the generalizability of the findings to female autistic adults or older age groups is limited. Therefore, future studies should strive to include more diverse samples and address the needs of middle-aged or older autistic adults, especially in the context of social functioning interventions.

Another critical point in the current research situation, which is partly also applicable to the integrated studies, is that the integration of multiple intervention components and outcomes, as well as the utilization of diverse methods, hampers the ability to compare the interventions or summarize their effects. Future research studies could benefit by initially identifying the effective components responsible for intervention effects and subsequently using the same standardized treatment manuals based on these components for implementation. This approach may enhance the consistency and replicability of interventions in future studies.

Regarding the setting, the reviewed studies highlighted the potential of online-based interventions to increase accessibility and reduce barriers to treatment for autistic adults. This is especially important in regions with limited access to services or during times of pandemics, as online interventions may provide a cost-effective and convenient alternative. Particularly, individuals with ASD are often overwhelmed by the demands of daily life, making online-based treatments potentially less stressful and more adaptable to their schedules. Additionally, their high affinity for digital tools may increase the acceptance of online interventions. However, it is imperative to conduct further investigations to validate the efficacy of online interventions and understand their specific benefits and limitations.

As research progresses, there is a growing interest in targeting mental health-related outcomes, such as quality of life, and examining potential mediating factors, such as emotion regulation and coping with negative emotions and stress. The significance of supporting autistic adults in managing daily life stress cannot be underestimated, as it is linked to their social functioning (5, 20, 21). Moreover, addressing dysfunctional coping strategies and emotion dysregulation can have far-reaching implications for quality of life (22), social functioning (23), and co-occurring symptoms (24). Consequently, interventions focusing on emotion regulation and stress management are emerging as essential to improve the quality of life in high-functional autistic adults. Several RCTs are already underway to further investigate these mental health-related factors using CBT approaches in high-functioning autistic adults (25, 26).

As there is a pressing need for well-controlled studies with larger sample sizes to address the specific challenges faced by high-functioning autistic adults and more online-based investigations are needed, our research team is currently evaluating an online group-based social functioning vs. a social cognition training intervention vs. TAU condition in a RCT with a total sample size of $N = 360$ (27). To our knowledge this is currently the world's largest well-controlled

psychotherapy trial in adult ASD. Both interventions are manualized and underwent initial evaluations regarding their feasibility and efficacy. The group intervention comprises modules such as psychoeducation, stress management, and social communication training (article is in the process of publishing), while the computer-based training (28) target social cognition by multimedia materials depicting emotional expressions and complex real-life social situations. Through this rigorous and well-powered RCT trial, we are confident that our research will contribute valuable evidence-based findings toward establishing effective psychosocial interventions for high-functioning autistic adults. The comparison of these two promising interventions may shed light on their relative merits, offering valuable insights into best practices for supporting this population in their social functioning and cognitive skills. Furthermore, this research addresses the growing need for online-based interventions, which may offer increased accessibility and flexibility for individuals with autism.

However, besides addressing only individual factors in autistic adults, it is crucial to consider the adaptation of their environment to better meet their specific needs. Modifications in the sensory, physical, and social surroundings can play a significant role in improving the overall wellbeing and functioning of individuals with autism. This approach aligns with the social model of disability (29), which posits that disability arises from a mismatch between an individual's needs and the support provided by their environment. To enhance the accessibility and effectiveness of services for autistic adults, adjustments should also be implemented within the healthcare system. Current research recommends creating low-stimulus environments and ensuring communication in the preferred style of autistic adults. Moreover, it is essential to enhance healthcare providers' knowledge and experience regarding autism and ASD interventions (30). By cultivating a deeper understanding of autism-related challenges and needs, healthcare professionals can better serve and support individuals with autism. Autistic adults themselves have expressed preferences in how they wish to be treated by therapists: They value adjusted communication and expect therapists to possess a profound understanding of autism-specific issues, in addition to demonstrating attentiveness, kindness, and acceptance (6). Integrating these perspectives into research and interventions can lead to more effective and tailored support for individuals with autism, empowering them to achieve their full potential. In conclusion, addressing the environmental factors and accommodating the unique needs of autistic adults alongside individual-focused interventions can significantly contribute to their overall wellbeing and quality of life. By adopting a person-centered approach and aligning with the preferences and perspectives of individuals with autism, we can foster a more inclusive and supportive environment, leading to better outcomes in clinical practice and research endeavors.

Conclusion

In conclusion, this review serves as a foundation for advancing interventions for high-functioning autistic adults, highlighting the potential of evidence-based CBT-based psychosocial interventions, as well as the need for further research and adaptations to cater to the unique needs of this population. By continuing to address methodological limitations and focusing on evidence-based practices, researchers can contribute to support high-functioning autistic adults. The results of this review highlight the necessity for additional research aimed at developing and validating psychosocial interventions tailored to high-functioning autistic adults, addressing core symptoms as well as co-occurring conditions, while also emphasizing procedures that promote generalization and long-term effectiveness. Specifically, methodologically rigorous randomized controlled trials (RCTs) with sufficient sample sizes are required to further investigate the comparative effectiveness and acceptability of ASD-adapted CBT-based approaches. These investigations should also identify the necessary adaptations of standard procedures from established CBT interventions for treating anxiety and depression symptoms that are most effective and beneficial for the autistic needs. The results of this review indicate a pressing need for more evidence-based interventions to cater to this underserved population effectively. By addressing these research gaps, we can contribute significantly to the improvement of mental health and quality of life in high-functioning autistic adults, ultimately fostering a more inclusive and understanding society.

Data availability statement

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

Author contributions

TS: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. DE: Supervision, Writing – review & editing. ID: Supervision, Writing – review & editing. LT: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

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

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Presence and correlates of autistic traits among patients with social anxiety disorder

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Introduction: Due to their similar behavioral presentation, it can sometimes be challenging to distinguish between a social anxiety disorder (SAD) and the social avoidance that is frequently described in autism spectrum disorder (ASD). Moreover, a growing body of evidences is reporting that a significant proportion of subjects with ASD also meet the requirements for SAD and, vice versa, subjects with SAD tend to exhibit a higher prevalence of autistic traits.

Aim: In this framework, the current study aims to evaluate prevalence and correlates of autistic traits in a sample of adult subjects diagnosed with SAD and healthy controls (HC), also evaluating which autism spectrum dimensions may statistically predict higher SAD symptoms.

Methods: 56 subjects with a clinical diagnosis of SAD and 56 gender and age matched HC were recruited from the Psychiatric Clinic of the University of Pisa. Subjects were assessed with the SCID-5, the Social Anxiety Spectrum – Short Version (SHY- SV) and the Adult Autism Subthreshold Spectrum (AdAS Spectrum).

Results: SAD group scored significantly higher in all AdAS Spectrum and SHY-SV domains and total score compared to the HC group with no significant gender difference. SHY-SV total and domain scores, were strongly and positively and strongly correlated with all AdAS Spectrum domains and total score. AdAS Spectrum total score and *Childhood/Adolescence, Non-Verbal Communication, Empathy* and *Restricted interests and Rumination* domain scores score were significant predictors of higher SHY-SV score.

Conclusion: Our results confirm the link between SAD and autistic traits also in adult population, describing not only high levels of autistic traits in SAD adults, but also significant correlations between many core features of the two disorders and a predictive role of autistic traits on higher SAD symptoms.

KEYWORDS

social anxiety disorder, social anxiety spectrum, autism spectrum disorder, subthreshold autism spectrum, autistic traits

1 Introduction

Social anxiety disorder (SAD), with a reported lifetime prevalence up to 13% (1, 2) is one of the most prevalent mental illnesses and a topic of significant interest for researchers, although being frequently neglected in clinical settings. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition – Text Revision (DSM-5-TR), SAD is a

syndrome characterized by elevated fear and anxiety that manifest before or during social settings, worries about being poorly perceived, and a propensity to avoid interactions (3). The feelings of fear and anxiety experienced by the patients typically cover a wide range of scenarios: some patients only experience mild symptoms occurring exclusively in specific contexts, while others experience more severe symptoms that interfere with almost all social interactions (e.g., having a conversation or meeting new people, being watched while eating or drinking, performing in front of others) (3, 4). Typically, SAD has an early onset and a chronic course, frequently lasting lifelong (5–7). In most cases, symptoms begin throughout adolescence and last for several years before assistance is sought (8), rising significantly the chances of dropping out of school, failing exams (9), and failing to graduate (10, 11). Moreover, SAD is linked to severe functional disability and noticeably diminished quality of life (9), raising the likelihood of developing another major comorbid disorder such as anxiety and mood disorders and substance or alcohol use disorders throughout the course of the lifespan (12–15).

Furthermore, while SAD can progress and worsen with the development of paranoic delusion, on the other social anxiety has also been reported as a major component in patients with schizophrenia, influencing its treatment, progression and prognosis (16, 17). In particular, the risk of developing depression, is significantly increased by SAD and, in this case, linked to a worse prognosis and a higher chance of suicide attempts (18, 19). In this context, one of the most common co-occurrent disorder reported with SAD is autism spectrum disorder (ASD) (20).

One of the primary concerns in the field of SAD since its conceptualization, has been the establishment of a diagnostic threshold (21). Many researchers indicated that SAD should be categorized as spectrum of severity rather than a discrete condition based on subjectively selected thresholds (22), and that the borders of SAD should be established by severity rather than qualitative traits (23, 24). In this framework, the most recent editions of the DSM introduced some adjustments to the chapter on SAD, reflecting a new and improved knowledge of the disorder in various social contexts (3, 24). Following this idea, some research postulated that SAD should be better classified as a dimensional continuum (22). According to such researches, a spectrum model of psychopathology can help identify the wide range of sub-threshold manifestations that may coexist with the primary mental condition (25). The term "spectrum" is used in this context to characterize mental health illnesses that include a variety of symptoms and behavioral patterns linked to a recognized DSM or ICD construct (25). While the spectrum of symptoms and traits includes the primary symptoms of the current DSM diagnostic categories, it also includes sub-clinical and atypical manifestations, as well as temperamental and/or personality traits and isolated signs and symptoms, symptom clusters, and behavioral patterns (26–32). According to this viewpoint, spectrum symptomatology is similar to the hidden section of an iceberg beneath the water's surface, whereas full-blown diagnostic criterion symptoms represent only the visible portion (25). Following this model, the "Social Phobia Spectrum Self-report" (SHY-SR) instrument was developed and validated in the early 2000s as part of the "spectrum project," an international collaboration aimed at shedding light on the validity of a dimensional approach to psychopathology (25–32). The SHY-SR was designed to measure not only the prototypic symptoms of SAD, but also atypical presentations, temperamental features, and other notable clinical and sub-clinical aspects associated with the primary symptoms (33, 34). The questionnaire had a high internal consistency, strong inter-rater reliability, and discriminant validity and throughout the years it has been employed in a variety of clinical contexts throughout the last few decades (7, 33, 35, 36). However, due to the excessively long time for its compilation and some outmoded and superfluous items, recently its application in routine clinical practice has been difficult; for this reason, the same authors recently proposed a shortened and renewed version, the Social Anxiety Spectrum – Short Version (SHY-SV) (37).

ASD is a frequent neurodevelopmental disorder that affect at least 1% of the population (38). The core characteristics of ASD are impaired social communication skills, repetitive and restricted interests and behaviors, and hypo-and hyper-reactivity to sensory stimuli (3). The more recent conceptualization of ASD depicts it as a heterogeneous disorder whose symptoms lie across a continuum that ranges from the milder presentations to most severe ones. In the recent years, research on ASD has emphasized the need to examine milder, sub-clinical manifestations of the autism spectrum as well as the full-blown clinical forms, which appear to be distributed along a continuum from the general to the clinical population (31, 39–42). First-degree relatives of people with ASD were firstly studied for sub-threshold autistic features, which are referred to as "broad autism phenotype" (43, 44); however, additional research has discovered other groups of people that are more likely to exhibit autistic features, from students of scientific courses to psychiatric patients with different types of disorders (44–53). In particular, subthreshold autistic traits are of interest because they exert a negative impact on quality of life and to represent a major risk factor for the emergence of various psychiatric disorders, as well as suicidal thoughts and behaviors (54–57). However, considering that autism spectrum is still a condition mainly associated to child healthcare due to its early onset, subthreshold autistic traits, or even milder clinical forms of ASD may easily remain under-recognized and undertreated during adulthood, silently worsening the trajectory of other comorbid disorders (58).

Due to their similar behavioral presentation, it can sometimes be challenging to distinguish between SAD and the social avoidance that is frequently described in ASD (59, 60). To this date, many researches have demonstrated that the symptoms of SAD and ASD significantly overlap in many fields. The key areas where most of the symptomatologic overlap happens are those of social interaction and social skills (61); for example, the two disorders share the difficulties in talking in front of others (62) and the avoidance of eye contact as well as paying little attention to the area around an interlocutor's eyes (63). In particular, atypicalities in social attention have been linked to both SAD and ASD. In the first the avoidance of social clues like faces with direct gaze can make it harder for the subject to reappraise or get used to the perceived threat, thus contributing to the maintenance of SAD symptoms (64). In the latter, atypical social attentiveness has been observed to precede clinical signs in ASD (65, 66). A growing body of evidences highlighted that a significant proportion of subjects with ASD also meet the requirements for SAD (67–69), while, in a similar way, subjects with SAD tend to exhibit a higher prevalence of autistic traits (67, 70). In this context, in light due to the relevance of autistic traits even in non-ASD clinical samples, some authors proposed the idea that various psychiatric illnesses might arise as a result of a neurodevelopmental alteration comparable to the one connected to ASD (38, 58, 71, 72), where the vast range of ASD

presentations ought to be viewed as the tip of a larger iceberg that contains a number of clinical and non-clinical phenotypes (31, 73).

Accordingly, the recent literature has stressed the necessity to consider disorders like SAD and ASD as extremes along natural continuums phenotypes of traits that are typically distributed throughout the general population, implying the absence of clear-cut borderlines between having no symptoms, increased sub-clinical traits and a formal diagnosis, while even in the latter there are significant individual variances in symptom strength (74–78). Moreover, given the heterogeneity of social competence among the general population, it is plausible that difficulties in social competence functions may link autism spectrum symptoms to increased social anxiety even in non-clinical individuals (79, 80).

In this framework, the aim of the present study was to evaluate prevalence and symptomatologic correlates of autistic traits in a sample of adult subjects diagnosed with SAD and healthy controls (HC), by using two self-report questionnaires, the SHY-SV and the AdAS Spetrum, validated to assess not only the typical symptoms of the two disorders as described by DSM-5-TR criteria, but also the full spectrum of signs and symptoms (so-called atypical as long as they are not included in the diagnostic criteria of the DSM), temperamental traits, and behavioral manifestations of SAD and ASD. Possible autism spectrum dimensions statistically predictive of higher SAD symptoms were also evaluated.

2 Methods

Data have been collected between September 2022 and March 2023 at the Psychiatric clinic of the University of Pisa.

2.1 Study sample and procedure

The total sample was made of 112 subjects belonging to two diagnostic groups, the SAD group and the HC group, which both counted 56 subjects each. The subjects in the SAD group were recruited from out-patients afferent at the Psychiatric Clinic of the University of Pisa, while subjects in the HC group belonged to health care and paramedical personnel; the recruitment of the latter was carried following a sex-and gender-matched criteria. All subjects had to be between the ages of 18 and 70 and be prepared to sign an informed consent in order to be recruited. The diagnoses of SAD, as well as the lack of mental disorders among HC individuals, were confirmed using the Structured Clinical Interview for DSM-5, Research Version (SCID-5-RV) (81). Exclusion criteria included an age under 18 or over 70, language or intellectual impairment that made the examinations difficult to complete mental disabilities, lack of collaboration skills, and persistent psychotic symptoms.

The presence of BD or Major Depressive Disorder was excluded through the use of the SCID-5-RV and clinical and anamnestic evaluation at the time of recruitment. However, a small number of participants were contemplated to be experiencing a depressive episode as long as the depression symptoms were not as severe as those of the category disorder. Similarly, the existence of other anxiety disorders was acknowledged as long as their symptoms were noticeably less severe than the ones of the SAD.

The study was conducted in accordance with the Declaration of Helsinki. The study was fully explained to the eligible individuals, who then gave their written informed permission after having a chance to ask any questions. The subjects received no compensation for taking part.

2.2 Measures

Assessment procedures included the SCID-5-RV (81), the Social Anxiety Spectrum – Short Version questionnaire (SHY-SV) and the Adult Autism Subthreshold Spectrum (AdAS Spectrum). Questionnaire evaluations were carried by psychiatrists, who were trained and certified in the use of the study instruments.

2.2.1 Social anxiety spectrum – short version questionnaire

The SHY-SV consists in 139 items organized in 5 domains (*Interpersonal sensitivity, Behavioral inhibition, Performance, Social situations* and *Substance Abuse*) and an appendix (*Childhood and adolescence*). The answers to the various items are coded in a dichotomous way (yes/no) and the scores relating to the single domains and appendices are obtained by counting the number of positive answers. The SHY-SV was developed by Dell'Osso et al. (37); the validation study reported strong internal consistency, great test–retest reliability and convergent validity with other dimensional measures of SAD.

2.2.2 Adult autism subthreshold spectrum

AdAS Spectrum is a self-report questionnaire designed to assess the wide range of autism spectrum manifestations in adults who do not have language or *intellectual disabilities*. The questionnaire consists of 160 organized into seven domains: *Childhood and adolescence, Verbal communication, Nonverbal communication, Empathy, Inflexibility and Adherence to Routine, Restricted interests and rumination* and *Hyper-and Hyporeactivity to Sensory Input.* The answers to the various items are coded in a dichotomous way (yes/no) and the scores relating to the single domains and appendices are obtained by counting the number of positive answers. The AdAS Spectrum was developed by Dell'Osso et al. (32); the validation study reported a high internal consistency, excellent test–retest reliability (Kunder-Richiardson coeffi-cient = 0.964, ICC = 0.976) and convergent validity with other dimensional measures of autism spectrum (31). The validity and reliability of the questionnaire was confirmed by further studies (39, 40) and a diagnostic threshold was defined at the score of 70.

2.3 Statistical analysis

Student' *t*-test and Chi-square tests were used for comparing socio-demographic variables among group. Student' *t*-test was used to compare the scores obtained by the two diagnostic groups on the SHY-SV and AdAS questionnaires as well as to compare the scores obtained in the two questionnaires in the SAD group divided by gender. Pearson's correlation coefficient was used for evaluating the pattern of correlations among the scores reported on the two psychometric instruments within the SAD, and HC subjects. Subsequently, in order to evaluate which AdAS Spectrum domains were statistically predictive of SHY-SV score in the sample, linear

regression analyses were performed with SHY-SV scores as the dependent variable and AdAS Spectrum total (first regression) and domain scores (second regression) as independent variables. All statistical analyses were performed with SPSS version 26.0 (82).

3 Results

The SAD sample reported a mean age of 39.57 years (±12.56) and consisted of 29 (51.8%) males and 27 (48.2%) females. The HC group reported a mean age of 38.52 years (±13.05) and consisted of 25 (44.6%) males and 31 (55.4%) females (see Table 1). Regarding the educational level, 14 (12.5%) subjects reported to have a master degree, 39 (38.4%) subjects reported to have a degree, 47 (42%) subjects referred to have graduated, 10 (8.9%) subjects had a middle school certificate, 1 (0.9) subject did not finish the elementary school and 1 subject preferred not to disclose. Regarding the occupational role, 23 (20.5%) subjects were students, 19 (17%) subjects were unoccupied, 19 (17%) subjects were housewives, 35 (31.3%) subjects were employed, 1 (0.9%) subject was retired and 15 (13.4%) subjects preferred not to disclose. Regarding the marital status 13 (11.6) subjects referred to live with their parents, 19 (17%) subjects were married, 29 (25.9%) subjects were unmarried, 6 (5.4%) subjects were divorced, 1 (0.9%) subject was a widower and 44 (39.2%) subjects preferred not to disclose.

TABLE 1 Age and sex in the overall sample and comparison between diagnostic groups.

	SAD	HC		
	mean ± SD	mean ± SD	*t*	*p*
Age	39.57 ± 12.56	38.52 ± 13.05	0.435	0.664

		n (%)	*n* (%)	Chi-square	*p*
Sex	M	29 (51.8) [a]	25 (44.6) [a]	0.449	0.285
	F	27 (48.2) [a]	31 (55.4) [a]		

Each subscript letter denotes a subset of categories whose column proportions do not differ significantly from each other at the 0.05 level.

Student *t*-test results showed that SAD group scored significantly higher in all AdAS Spectrum and SHY-SV domains as well as in their total compared to the HC group (see Tables 2, 3).

Moreover, results from the comparison between gender in the SAD group highlighted no significative difference in the scores obtained on the AdAS Spectrum (see Table 4).

According to the correlation analysis, in the total sample, the total SHY-SV scores, as well as all SHY-SV domains scores, were significantly and positively correlated with all AdAS Spectrum domain and AdAS total score. All correlation coefficients were strong, with the exception of those reported for the SHY-SV domain Substance abuse, which were medium or weak (see Table 5).

Lastly, results from linear regression analysis showed that AdAS Spectrum total score was a significant predictor of a higher SHY-SV score (beta = 0.88; $t = 19.92$; $p < 0.001$) (see Table 6). A further linear regression highlighted the AdAS Spectrum *Childhood/Adolescence* (beta = 0.12; $t = 2.19$; $p = 0.031$), *Non Verbal Communication* (beta = 0.35; $t = 4.28$; $p < 0.001$), *Empathy* (beta = 0.26; $t = 4.54$; $p < 0.001$), *Restricted interests and Rumination* (beta = 0.21; $t = 3.10$; $p = 0.002$) domain scores as significant positive predictors of high SHY-SV total scores (see Table 7).

TABLE 2 Comparison of SHY-SV scores among the diagnostic groups.

SHY-SV scores	SAD group mean ± SD	HC group mean ± SD	*t*	*p*
Interpersonal sensitivity	14.59 ± 4.60	1.66 ± 2.87	17.83	<0.001
Behavioral inhibition	6.70 ± 2.82	0.73 ± 1.29	14.39	<0.001
Social situations	21.39 ± 5.50	2.03 ± 2.06	24.65	<0.001
Aubstance abuse	1.41 ± 1.42	0.21 ± 0.45	5.99	<0.001
Performance	14.78 ± 5.58	1.32 ± 1.86	17.13	<0.001
Total	58.87 ± 12.35	5.96 ± 6.99	27.90	<0.001

TABLE 3 Comparison of SHY-SV scores among the diagnostic groups.

AdAS spectrum scores	SAD group mean ± SD	HC group mean ± SD	*t*	*p*
Childhood/Adolescence	10.43 ± 8.24	0.66 ± 1.12	8.79	<0.001
Verbal communication	7.70 ± 4.19	0.46 ± 0.60	12.80	<0.001
Non-verbal communication	11.68 ± 5.90	1.00 ± 1.17	13.28	<0.001
Empathy	4.96 ± 3.01	0.20 ± 0.48	11.71	<0.001
Inflexibility and adherence to routine	11.75 ± 6.10	1.45 ± 1.65	12.20	<0.001
Restricted interest and rumination	5.91 ± 3.77	0.86 ± 1.34	9.46	<0.001
Hyper– and hyporeactivity to sensory input	3.80 ± 4.32	0.30 ± 0.57	6.01	<0.001
Total Score	56.23 ± 19.89	4.93 ± 4.25	18.87	<0.001

TABLE 4 Comparison of AdAS spectrum scores between males and females in the SAD group.

AdAS scores	*M* mean ± SD	*F* mean ± SD	*t*	*p*
Child./Adolesc.	9.14 ± 3.85	11.81 ± 11.13	−1.186	0.245
Verb. comm.	8.45 ± 3.54	6.89 ± 4.72	1.405	0.166
Non Verb. comm.	12.21 ± 4.12	11.11 ± 7.40	0.678	0.502
Empathy	4.31 ± 2.04	5.67 ± 3.70	−1.682	0.100
Inflex. & routine	10.96 ± 4.99	12.59 ± 7.11	−0.997	0.323
Restrict. interest & rum.	5.07 ± 3.00	6.81 ± 4.32	−1.766	0.083
Hyper-hyporeact.	3.59 ± 4.43	4.04 ± 4.27	−0.387	0.700
Total	53.72 ± 13.63	58.92 ± 24.94	−0.959	0.344

TABLE 5 Pearson's correlations coefficients (*r*) among SHY-SV domains score and AdAS spectrum scores in the total sample.

	Child./ Adolesc.	Verb. comm.	Non-verb. Comm.	Empathy	Inflex. & routine	Restrict. interest & rum.	Hyper-hyporeact.	Tot. score
Interpers. sens.	0.592*	0.762*	0.702*	0.657*	0.697*	0.641*	0.581*	0.823*
Behav. inhib.	0.609*	0.690*	0.702*	0.612*	0.623*	0.508*	0.621*	0.781*
Social sit.	0.623*	0.760*	0.815*	0.783*	0.734*	0.684*	0.513*	0.876*
Subst. abuse	0.191*	0.625*	0.566*	0.435*	0.343*	0.347*	0.217*	0.478*
Performance	0.526*	0.711*	0.763*	0.634*	0.655*	0.716*	0.341*	0.780*
Tot. score	0.624*	0.801*	0.819*	0.741*	0.737*	0.706*	0.531*	0.885*

* Significant correlation for $p < 0.05$.

TABLE 6 Linear regression analysis with SHY-SV total score as a dependent variable and AdAS Spectrum total score as independent variables in the total sample.

	b (SE)	BETA	*t*	*p*	CI 95%	
					Lower bound	Upper bound
constant	6.36 (1.81)		3.507	0.001	2.766	9.954
AdAS spectrum total score	0.85 (0.04)	0.885	19.917	<0.001*	0.767	0.937

R square = 0.783; Adjusted R square = 0.781. *= statistically significant value ($p < 0.05$).

TABLE 7 Linear regression analysis with SHY-SV total score as a dependent variable and AdAS spectrum domains as independent variables in the total sample.

	b (SE)	BETA	*t*	*p*	CI 95%	
					Lower bound	Upper bound
constant	5.77 (1.66)	–	3.479	0.001	2.483	9.063
Child./Adolesc.	0.56 (0.21)	0.124	2.193	0.031*	0.044	0.876
Verb. comm.	0.90 (0.49)	0.149	1.853	0.067	−0.064	1.871
Non Verb. comm.	1.46 (0.34)	0.351	4.279	<0.001*	0.782	2.132
Empathy	2.28 (0.50)	0.259	4.543	<0.001*	1.287	3.281
Inflex. & routine	−0.27 (0.35)	−0.065	−0.770	0.443	−0.960	0.423
Restrict. interest & rum.	1.60 (0.51)	0.214	3.104	0.002*	0.578	2.622
Hyper-hyporeact.	0.798 (0.41)	0.099	1.937	0.055	−0.019	1.615

R square = 0.832; Adjusted R square = 0.820. *= statistically significant value ($p < 0.05$).

4 Discussion

According to our results, the group of subjects diagnosed with SAD not only scored, as expected, significantly higher in the SHY-SV questionnaire than the HC group, but also reported a higher prevalence of positive answers in all AdAS Spectrum domains as well as in the questionnaire's total score with no significant difference when compared by gender. Moreover, we globally found significant and strong positive correlations between SHY-SV and AdAS Spectrum domain scores.

Our results are in line with previous studies, confirming the significant presence of autistic traits in adults with SAD. Previous researches, mainly conducted in children, adolescents or young adults, while exploring the relationship between ASD and SAD in clinical and non-clinical samples (83–85) reported that the symptoms of SAD and ASD significantly overlap in many fields, to the point that it can sometimes be challenging to distinguish between SAD and the social avoidance that is frequently described in ASD (58, 60). The recent literature reported how the symptomatologic overlap between the two conditions has been mainly identified, in children and adolescents, in the areas of social interaction and social skills (61), including difficulties in talking in front of others (62) and the avoidance of eye contact (63). Moreover, many studies highlighted not only that traits of both disorders can co-occur and are highly correlated, but also that the correlation is not exclusively due to the symptomatologic overlap between the disorders, nor to artefacts of measurement errors. Additionally, alongside the evidences of a high prevalence of SAD in ASD subjects (67–70) and similarly of autistic traits in SAD patients (67, 70), some studies reported how autistic traits and SAD symptoms are correlated even in subjects that do not meet the full diagnostic criteria while, in neurotypical children, higher autistic traits have been associated with a greater risk of developing SAD later in life (86).

According to our results, the AdAS Spectrum total score and AdAS Spectrum *Childhood/Adolescence, Non Verbal Communication,* the *Empathy* and the *Restricted interests and Rumination* domains were significant positive predictors of higher scores in the SHY-SV. While previous studies in children and adolescents also reported how greater autistic traits significantly predict higher SAD symptoms (60, 68), the finding of *Non Verbal communication* and *Empathy* domain scores being positive predictors of SAD is consistent with a large body of research that identified in deficits of social competence the main common background for the relationship between SAD and autistic traits (80). Indeed, subjects with elevated autistic traits are more likely to have lower social skills, which can be shown as difficulties in social interactions with their peers as well as a higher vulnerability to bullying and victimization (87). Similarly, reduced social competence may predict, also in neurotypical subjects, negative changes in peer interactions and stressful social experiences, playing a crucial role in the development of SAD (88–90). According to other authors, the combination of increased physiological arousal and decreased social competence, significantly predicted social anxiety symptoms in children with and without ASD (89, 90). Furthermore, somewhat in line with our finding of a predictive role of impaired empathy skills for SAD symptoms, studies that focused on evaluating the Theory of Mind (ToM) in SAD samples reported how higher levels of SAD were related to reduced ToM ability (91–96) and empathic accuracy, especially for positive stimuli (91). As a matter of fact, the use of strategies of social camouflaging have been reported among autistic people in order to cope with social difficulties: while the use of these strategies may actually improve social functioning, it was associated with higher anxiety and depressive symptoms (47). Subjects with high functioning ASD or autistic traits may be more aware of their social incompetence than subjects with more severe forms of ASD, thus more frequently developing SAD symptoms. At the same time, the increased tendency towards ruminative thinking may further increase the risk of brooding about social difficulties and fear of judgment (58, 97). In this context, in light of recent findings that highlighted how the presence of higher autistic traits predicts worse treatment results, it is crucial to understand the mechanisms and processes through which ASD symptoms increase the risk of co-occurring social anxiety symptoms (98, 99). Social competence is a skill that both typically developing children (100) and children with ASD (101) can learn with proper support; therefore, it is critical to investigate how emphasizing social competence development in all children, and particularly in those with neuroatypical traits, may reduce the risk for future distress and impairment, such as increased social anxiety. Social competence has been previously identified as a suitable intervention target to reduce overall social anxiety symptoms both in the clinical and non-clinical population (102, 103). Additionally, it could be a crucial target for the prevention of SAD also among subjects with elevated autistic traits, in line with most first-line psychosocial treatments for ASD (103), but also in neurotypical subjects and even those with psychiatric disorders other than ASD (74). Due to the continuous distribution of autistic and social anxiety traits in the general population, disorders like SAD and ASD could be better conceptualized as extremes along continuum phenotypes of traits, implying the absence of clear-cut borderlines between having no symptoms, increased sub-clinical traits and a formal diagnosis (74–78, 104, 105).

This study should be considered in light of important limitations. First of all, the cross-sectional design prevented us to make inferences about temporal or causal relationship between the investigated variables. In addition, Moreover, the relatively small sample size limits the extensibility of our results. Globally, more studies, possibly with a longitudinal design are needed to clarify the role of underlying autistic traits in the development and militainment of SAD symptoms.

5 Conclusion

In conclusion, our results confirm the link between SAD and autistic traits also in adult population, describing not only high levels of autistic traits in SAD adults, but also significant correlation between many core features of the two disorders and a predictive role of autistic traits on higher SAD symptoms. This data may support the hypothesis of a possible neurodevelopmental basis for different psychiatric conditions: in particular, several psychiatric illnesses may arise as a result of a neurodevelopmental alteration similar to the one associated with ASD (33, 52, 65) where the wide range of ASD manifestations can be seen as the tip of a wider iceberg featuring clinical and non-clinical phenotypes. In this framework, as hypothesized for eating disorders, SAD could also be conceptualized as a specific phenotype of the autism spectrum (93). On this basis and in light of the now recognized existence of an ASD presentation unique to females that differ from the typical male conceptualization, future researches

should also delve deeper into the possibility of considering some disorders as gender influenced autistic phenotypes.

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 humans were approved by Ethical Committee of Azienda Ospedaliera Universitaria Pisana. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

BC: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. BN: Investigation, Writing – original draft, Writing – review & editing. CB: Investigation, Writing – review & editing. EM: Formal analysis, Writing – review & editing. GA: Investigation, Writing – review & editing. IC: Conceptualization, Supervision, Writing – review & editing. SP: Conceptualization, Supervision, Writing – review & editing. LD: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

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

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Discovery of a novel cytokine signature for the diagnosis of autism spectrum disorder in young Arab children in Qatar

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Background: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by impaired social interaction and communication and the occurrence of stereotyped and repetitive behaviors. Several studies have reported altered cytokine profiles in ASD and hence may serve as potential diagnostic biomarkers of the disorder. This study aims to identify diagnostic biomarkers for ASD in a well-defined study cohort in Qatar.

Methods: We measured the protein levels of 45 cytokines in the plasma samples of age- and gender-matched children (2–4 years) with ASD (n = 100) and controls (n = 60) using a Luminex multiplex assay. We compared the differences in the levels of these cytokines between the two study groups and then fitted the significantly altered cytokines into a logistic regression model to examine their diagnostic potential for ASD.

Results: We found elevated levels of IFN-γ, FGF-2, IL-1RA, and IL-13 and reduced levels of eotaxin, HGF, IL-1 alpha, IL-22, IL-9, MCP-1, SCF, SDF-1 alpha, VEGFA, and IP-10 in the plasma of children with ASD compared to controls. Furthermore, we observed that elevated levels of IFN-γ (odds ratio (OR) = 1.823; 95% (confidence interval) CI = 1.206, 2.755; p = 0.004) and FGF-2 (OR = 2.528; 95% CI = 1.457, 4.385; p < 0.001) were significantly associated with increased odds of ASD, whereas reduced levels of eotaxin (OR = 0.350; 95% CI = 0.160, 0.765; p = 0.008) and HGF (OR = 0.220; 95% CI = 0.070, 0.696; p = 0.010) were significantly associated with lower odds of ASD relative to controls. The combination of these four cytokines revealed an area under the curve (ROC-AUC) of 0.829 (95% CI = 0.767, 0.891; p < 0.001), which demonstrates the diagnostic accuracy of the four-cytokine signature.

Conclusions: Our results identified a panel of cytokines that could discriminate between children with ASD and controls in Qatar. In addition, our findings support the predominance of a Th1 immune phenotype in ASD children and emphasize the need to validate these results in larger populations.

KEYWORDS

autism spectrum disorder, ASD, cytokines, biomarkers, luminex multiplex assay, logistic regression

Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by stereotyped, repetitive behaviors and impaired social communication skills. The worldwide prevalence of ASD is estimated to be 1 in 100 children with a global male-to-female ratio of 4.2 (1). Individuals with ASD generally show symptoms during the first three years of life, and the clinical severity of symptoms is largely variable among the affected individuals (2). Currently, there is no cure for ASD; however, studies have shown that early intervention programs are effective strategies in alleviating some of the severity symptoms (2). Nevertheless, there is often a long delay between referral and clinical evaluation and diagnosis of ASD by an expert team (3). This long delay in the clinical diagnosis of ASD impedes access to early intervention programs and hence may negatively impact the behavioral outcomes in the affected individuals. Accordingly, a major challenge remains to identify reliable biomarkers to support an early prediction of ASD, which could facilitate a timely access of individuals with ASD to the required support services (2).

Cytokines are signaling molecules that play key roles in the immune response. Current evidence supports a link between cytokines and ASD development (4, 5). Previous studies have reported abnormal levels of several cytokines in the peripheral blood of subjects with ASD (6). Remarkably, these dysregulated cytokines are associated with an increased severity of ASD symptoms (4, 5), suggesting a functional role of these cytokines in the disorder. For example, abnormal levels of several cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β, have been reported in the blood of subjects with ASD and are correlated with worse behavioral outcomes (7–11). Importantly, peripheral blood cytokines can cross the blood–brain barrier and signal to the brain, directly affecting brain function and behavior (12–15). Hence, circulating blood cytokines could present a promising source of potential biomarkers for ASD.

Several studies have investigated the utility of cytokines as biomarkers for ASD. However, the results of these studies have been inconsistent, which could be due to several factors. First, cytokines exist in a wide range and different studies have been selective in their measurement of certain types of cytokines compared to others (6). In addition, age, gender, and environmental exposures are other factors that may contribute to the discrepancies observed across studies. For example, most of the current studies analyzed cytokine levels in subjects with a wide age range of 3–12 years, and only a few studies have restricted the age range to 2–4 years to reduce the influence of age variations on the results (6). Finally, there may be other factors that could influence cytokine levels, such as medications or co-occurring conditions, which can further complicate the interpretation of the results. Adequate control of these variables is important for establishing more reliable cytokine biomarkers for ASD.

In this study, we sought to determine predictive biomarkers for early ASD diagnosis in a well-defined study cohort. Hence, we recruited a case–control study cohort of the Arab population in Qatar and used well-defined eligibility criteria to reduce the influence of confounding factors on the results. We utilized a Luminex multiplex assay to perform a simultaneous analysis of 45 cytokines in the plasma samples of the study cohort. We identified a unique panel of four cytokines that could predict ASD diagnosis in young children aged 2–4 years.

Materials and methods

Study participants

A total of 160 children were included in this study. We have employed a convenience sampling technique, in which the selection of the study participants was based on their accessibility and availability to take part in this study. Participants with ASD were recruited during the follow-up visits of the families to the Child Development Center in Rumailah Hospital of Hamad Medical Corporation (HMC) in Doha, Qatar and their matched control participants were recruited during the routine visits of families to the well-baby clinics or general clinics Al-Wajbah Health Center of Primary Health Care Corporation (PHCC) in Doha, Qatar.

All subjects were initially screened using a questionnaire to ensure that they met our study eligibility criteria. All enrolled subjects met the following criteria: age 2–4 years; Arabic ethnicity; born in Qatar; their mothers lived in Qatar during most of their pregnancy; enrolled subjects mostly lived in Qatar since birth; no immune conditions, such as autoimmune disease, asthma, allergy, and eczema; no neurological conditions, such as epilepsy; no suspected vision, hearing or walking problems; no other health problems, such as cardiovascular, lung, and kidney diseases; and not taking any medications and did not have any recent infection or vaccination at the time of study enrollment. No family history of ASD was another eligibility criterion for the control subjects. In addition, control subjects were screened using the validated Arabic version of the Social Communication Questionnaire (lifetime version) with a cutoff score < 12 for eligibility to rule out the risk of ASD in our control subjects (16). Control subjects were frequency matched to children with ASD based on age, gender, and nationality.

All participants with ASD had a confirmed clinical diagnosis of ASD by qualified professionals according to the Statistical Manual of Mental Disorders (DSM-5) and Autism Diagnostic Observation Schedule-second edition (ADOS-2) (17). Subjects with ADOS-2 scores < 7 were considered to have mild-to-moderate ASD, while subjects with ADOS-2 scores ≥ 7 were considered to have severe ASD. All families of the enrolled subjects completed a medical history questionnaire to collect their demographic data, as listed in Table 1.

Plasma isolation and processing

Peripheral blood samples were extracted from study participants during the day or evening depending on the availability of the study participants and fasting was not requested for this study. The extracted

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TABLE 1 Demographic characteristics of the study population.

	Total (n = 160)	Control (n = 60)	ASD (n = 100)	p-value
Age in years	3.38 (2.99–3.73)	3.56 (2.98–3.81)	3.37 (2.99–3.70)	0.376
Gender				
Male	127 (79.4)	48 (80)	79 (79)	0.880
Female	33 (20.6)	12 (20)	21 (21)	
Family history of ASD				
Yes	–	NA	19 (19)	–
No	–	NA	81 (81)	
Consanguinity				
Yes	48 (30)	21 (35)	27 (27)	0.285
No	112 (70)	39 (65)	73 (73)	
Method of reproduction				
Natural	153 (95.6)	59 (98.3)	94 (94)	0.257
Assisted (IVF)	7 (4.4)	1 (1.7)	6 (6)	
Maternal complications				
Yes	62 (38.4)	19 (31.7)	43 (43)	0.154
Diabetes	39 (24.5)	14 (23.3)	25 (25.3)	
Hypertension	5 (3.1)	0 (0)	5 (5.1)	
Asthma	2 (1.3)	1 (1.7)	1 (1.0)	
Allergy	3 (1.9)	0 (0)	3 (3.0)	
Multiple conditions (asthma, allergy, diabetes, and/or hypertension)	12 (7.5)	4 (6.7)	8 (8.1)	
No	98 (61.6)	41 (68.3)	57 (57)	
Pregnancy duration				
< 9 months	10 (6.3)	2 (3.3)	8 (8)	0.323
≥ 9 months	150 (93.8)	58 (96.7)	92 (92)	
Maternal age at labor				
Age in years	30.00 (26.00–34.00)	29.50 (25.00–33.00)	30.00 (26.00–34.00)	0.289
< 35 years	126 (78.8)	51 (85)	75 (75)	0.134
≥ 35 years	34 (21.3)	9 (15)	25 (25)	
Type of delivery				
Normal	101 (63.1)	42 (70)	59 (59)	0.242
C-section	52 (32.5)	17 (28.3)	35 (35)	
Induced	7 (4.4)	1 (1.7)	6 (6)	
Postnatal complications				
Yes	14 (8.8)	3 (5)	11 (11)	0.193
Hypoxia	7 (4.4)	2 (3.3)	5 (5.0)	
Jaundice	4 (2.5)	0 (0)	4 (4.0)	
Hypoxia and Jaundice	1 (0.6)	0 (0)	1 (1.0)	
Others	2 (1.3)	1 (1.7)	1 (1.0)	
No	146 (91.3)	57 (95)	89 (89)	
Birth weight				
Weight in kg	3.00 (2.77–3.50)	3.00 (2.92–3.50)	3.00 (2.62–3.50)	0.484
< 2.5 kg	23 (14.4)	6 (10)	17 (17)	0.222
≥ 2.5 kg	137 (85.6)	54 (90)	83 (83)	
Nationality				
Qatari	44 (27.5)	17 (28.3)	27 (27)	0.563
Egyptian	28 (17.5)	12 (20)	16 (16)	
Syrian	25 (15.6)	12 (20)	13 (13)	
Yemeni	23 (14.4)	6 (10)	17 (17)	
Sudanese	20 (12.5)	8 (13.3)	12 (12)	
Jordanian	5 (3.1)	2 (3.3)	3 (3)	
Others	15 (9.4)	3 (5)	12 (12)	

Data are presented as medians (lower – upper quartile) or n (%).
P-values were assessed by the Mann–Whitney U test for continuous variables and Pearson's chi-square or Fisher's exact test as appropriate for categorical variables.
NA, Not Applicable.

blood samples were collected into EDTA-containing anticoagulant tubes at HMC or PHCC sites, transported, and processed in the research facility at QBRI within two hours of sample collection. Blood samples were slowly layered over Histopaque-1077 (cat #10771, Sigma–Aldrich) at an equal ratio and centrifuged at 400 × *g* for 30 min at a standard room temperature of ~ 21°C. After centrifugation, plasma samples were collected from the upper layer into new tubes and centrifuged at ~ 1800 × *g* for 15 min to remove cell debris. Plasma aliquots of 200 µl were stored at −80°C until further analysis.

Cytokine measurements

Cytokine levels were measured in the plasma samples with a Luminex multiplex assay using a ProcartaPlex Convenience Panel 45-Plex kit (cat #EPXR450-12171-901, Thermo Fisher Scientific) according to the manufacturer's instructions. The 45 cytokines analyzed were: BDNF, FGF-2, HGF, IL-1 alpha, IL-2, IL-6, IL-9, IL-13, IL-18, IL-23, IP-10, MIP-1 alpha, PDGF-BB, EGF, GM-CSF, IFN alpha, IL-1 beta, IL-4, IL-7, IL-10, IL-15, IL-21, IL-27, LIF, MIP-1 beta, PIGF-1, eotaxin, Gro-alpha, IFN-γ, IL-1RA, IL-5, IL-8, IL-12p70, IL-17A, IL-22, IL-31, MCP-1, NGF beta, RANTES, SCF, TNF beta, SDF-1 alpha, VEGF-A, TNF alpha, and VEGF-D. All samples and standards were measured in duplicate using the Bio-Plex 3D suspension array system (Bio-Rad Laboratories). Data analyses were performed using Bio-Plex Manager software (Bio-Rad Laboratories) according to the manufacturer's instructions. Since logistic regression analysis cannot be conducted with missing values, analytes that fell below the limit of detection were assigned a value of half the minimum level of detection per each analyte, as reported in previous studies (18–23), and were included in the statistical analysis.

Statistical analysis

Data were analyzed using the chi-square test for categorical variables and the Mann–Whitney U test for continuous variables. The Shapiro–Wilk normality test showed a nonparametric distribution of all data, and hence, the data are presented as median values with interquartile ranges. Data were considered statistically significant when the p-value < 0.05. Bonferroni correction was applied for the analysis of multiple comparisons.

For the binary logistic regression, data were natural log-transformed prior to the analysis. The outcome of interest was the diagnostic group of either ASD or control, and the predictors were only the significantly altered cytokines with adjusted p-values < 0.05. In the initial model, we adjusted for covariates of age, gender, sampling time (morning, afternoon, or evening), analysis batch number, and sample age (storage period from sample collection to cytokine analysis). We defined that a 10% change in the levels of the β-coefficient of the predictor determined which covariates to keep in the final model. Adjusted odd ratios (ORs) and 95% confidence intervals (CIs) were calculated to measure the association between each cytokine and ASD diagnosis relative to controls. Receiver operating characteristic (ROC) curves were constructed for the logistic regression model to assess the diagnostic accuracy of the selected cytokines in distinguishing between ASD and control cases. An area under the curve (ROC-AUC) was computed for each cytokine as well as the combination of cytokines using a nonparametric method. Data were analyzed using SPSS, version 26.0.

Results

Study population characteristics

As illustrated in Table 1, the study population showed matching demographic characteristics in terms of age, gender, and nationality. There was no significant difference in age between the ASD and control groups (p = 0.376, Table 1). The median age was 3.37 (2.99–3.70) years for the ASD group and 3.56 (2.98–3.81) years for the control group (Table 1). In addition, the study groups were gender matched at an almost 4:1 male-to-female ratio, 79/21 in ASD cases vs. 48/12 in the control group (p = 0.880, Table 1), which reflects the actual male bias in ASD. Moreover, the nationality distribution was not significantly different between the two study groups, with almost comparable percentages of Qatari (27 vs. 28.3%), Egyptian (16 vs. 20%), Syrian (13 vs. 20%), Yemeni (17 vs. 10%), Sudanese (12 vs. 13.3%), Jordanian (3 vs. 3.3%), and other citizens (12 vs. 5%) in the ASD vs. control groups (p = 0.563, Table 1).

Meanwhile, there were no differences between children with ASD and controls in terms of consanguinity, pregnancy duration, method of reproduction (natural or assisted), type of delivery (normal, c-section, or induced), maternal complications (diabetes, hypertension, asthma, or allergy), maternal age at delivery, birth weight, or postnatal complications (hypoxia or jaundice). Among the maternal complications recorded, it is worth noting the high yet comparable percentage of diabetes in the two study groups (25.3 vs. 23.3% in ASD vs. control group, Table 1), which is consistent with the previously reported high prevalence of gestational diabetes in the Qatari population (24). Finally, the ADOS-2 assessment scores of children with ASD are presented in Table 2.

Altered plasma cytokine levels in ASD

We compared the plasma levels of 45 cytokines between the ASD and control groups, as summarized in Table 3 and Supplementary

TABLE 2 Clinical characteristics of children with ASD based on the ADOS-2 assessment.

	Mild-to-moderate ASD (n = 49)	Severe ASD (n = 51)
Social affect	9.00 (7.00–11.00)	19.00 (17.00–20.00)
Restricted and repetitive behavior	2.00 (1.00–2.50)	5.00 (3.00–6.00)
Comparison score	5.00 (4.00–6.00)	10.00 (8.00–10.00)

Data are presented as medians (lower – upper quartile).

Table 1. We found significantly elevated levels of FGF-2, IFN-γ, IL-13, and IL-1RA in addition to reduced levels of eotaxin, HGF, IL-1 alpha, IL-22, IL-9, IP-10, MCP-1, SCF, SDF-1 alpha, and VEGF-A in ASD compared to the control group ($p < 0.05$, Table 3). However, the results of only five cytokines (namely eotaxin, FGF-2, HGF, IFN-γ, and SDF-1 alpha) remained significant after Bonferroni correction for multiple comparisons (Table 3) and were thus selected for subsequent analysis. None of the plasma cytokines were notably altered between the mild-to-moderate and severe ASD subgroups, which suggest that these cytokines are not relevant markers for ASD severity classification (data not shown).

Logistic regression model revealed cytokine predictors of ASD

We performed binary logistic regression analysis to investigate the ability of the significantly altered cytokines to predict ASD diagnosis. In the initial model, we included the five significantly altered cytokines (eotaxin, FGF-2, HGF, IFN-γ, and SDF-1 alpha) and we adjusted for all the covariates in the model (namely age, gender, sampling time, analysis batch number, and sample age). Since none of these covariates were significant and removing them from the final model did not change the results, this indicates that these covariates were not confounding factors and hence were removed in the final model. We found that only four cytokines remained significant and hence were retained in the final model (Table 4). Elevated levels of IFN-γ (OR = 1.823; 95% CI = 1.206, 2.755; p = 0.004) and FGF-2 (OR = 2.528; 95% CI = 1.457, 4.385; p < 0.001) were associated with higher odds of having ASD whereas reduced levels of eotaxin (OR = 0.350; 95% CI = 0.160, 0.765; p = 0.008) and HGF (OR = 0.220; 95% CI = 0.070, 0.696; p = 0.010) were associated with lower odds of having ASD compared with the control group (Table 4).

TABLE 3 Changes in the protein levels of several cytokines in the plasma of children with ASD compared to controls.

Cytokine	ASD (n = 100)	Control (n = 60)	p-value
Eotaxin	7.46 (5.12–10.83)	12.36 (7.69–16.88)	0.00087*
FGF-2	5.86 (5.30–11.44)	5.30 (1.81–5.86)	0.000219**
HGF	46.73 (37.66–61.92)	58.79 (46.67–73.09)	0.000347*
IFN-γ	15.84 (6.05–32.69)	6.24 (5.61–11.62)	0.000003***
IL-13	37.63 (21.56-49.56)	25.56 (17.60-45.12)	0.008
IL-1a	0.27 (0.26-0.44)	0.39 (0.35-0.47)	0.021
IL-1RA	97.62 (87.45-453.7)	87.45 (80.23-453.77)	0.019
IL-22	12.38 (11.01-12.74)	12.55 (12.38-12.74)	0.003
IL-9	3.73 (3.18-7.88)	4.60 (3.73-10.11)	0.023
IP-10	12.77 (10.28-16.16)	15.60 (12.28-19.78)	0.002
MCP-1	17.30 (11.39–33.62)	31.31 (18.91–44.97)	0.002
SCF	5.62 (4.17-7.77)	7.46 (4.73-9.57)	0.007
SDF-1 alpha	180.49 (68.26–403.56)	508.81 (248.55–814.41)	0.000005***
VEGF-A	27.81 (19.70-37.51)	33.92 (26.07-44.71)	0.007

Data are presented as medians (lower – upper quartile).
Mann–Whitney U test was used to assess statistical significance at $p < 0.05$.
Variables that remained statistically significant after Bonferroni correction by 45 variables are denoted with asterisks, *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Diagnostic accuracy of the identified ASD biomarkers

We fitted ROC curves to examine the performance of the four significant cytokines that remained in the final logistic regression model (Figure 1). ROC curve analysis showed that each of the four cytokines demonstrated significant performance ($p < 0.001$, Figure 1). Specifically, IFN-γ showed an area under the curve (AUC) = 0.720 with 95% CI = (0.642, 0.798), FGF-2 (AUC = 0.673; 95% CI = 0.588, 0.758), eotaxin (AUC = 0.314; 95% CI = 0.224, 0.405), and HGF (AUC = 0.331; 95% CI = 0.245, 0.417). An AUC below 0.5 for eotaxin and HGF indicates lower levels of these cytokines in the ASD group than in the control group. Remarkably, ROC curve analysis demonstrated that the combination of the four cytokines (IFN-γ, FGF-2, eotaxin, and HGF) showed the best diagnostic accuracy for ASD with AUC = 0.829 and 95% CI = 0.767, 0.891 ($p < 0.001$, Figure 1).

Discussion

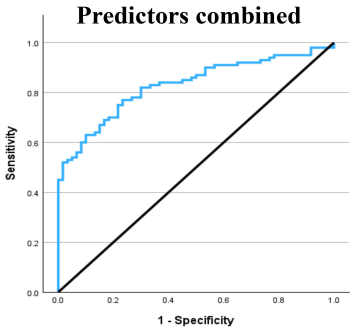
This study aimed to identify cytokine biomarkers for early ASD diagnosis. For this purpose, we recruited a well-defined cohort of ASD and control subjects in Qatar with matching age, gender, ethnicity, and clinical characteristics. We analyzed cytokine levels in

TABLE 4 Binary logistic regression[a] analysis of the altered cytokines revealed a list of cytokine predictors of ASD.

ASD vs. control			
Cytokine	Odds Ratio	95% CI	p-value
Eotaxin	0.350	(0.160, 0.765)	0.008
FGF-2	2.528	(1.457, 4.385)	< 0.001
HGF	0.220	(0.070, 0.696)	0.010
IFN-γ	1.823	(1.206, 2.755)	0.004

[a]Adjusted for age, gender, sampling time, sample age, and analysis batch number in the initial model, then removed these covariates in the final model as they were not confounding factors.

A



B

ASD vs. Control

Cytokine	AUC	95% CI	p-value
Eotaxin	0.314	(0.224, 0.405)	<0.001
FGF-2	0.673	(0.588, 0.758)	<0.001
HGF	0.331	(0.245, 0.417)	<0.001
IFN-γ	0.720	(0.642, 0.798)	<0.001
Predictors combined	0.829	(0.767, 0.891)	<0.001

FIGURE 1
Receiver operating characteristic (ROC) curves demonstrate the ability of the selected cytokines to differentiate between ASD and control cases. **(A)** ROC curve is illustrated for the combination of the four predictors. **(B)** The area under the ROC curve (AUC), 95% confidence interval (CI) and p-value are displayed in table for the individual and combined predictors. AUC values above 0.5 suggest a positive association with ASD, whereas AUC values below 0.5 suggest a negative association. The black line is the reference line.

the plasma samples of our cohort to determine their potential utility as early diagnostic biomarkers for ASD. We found that 14 cytokines were significantly altered in ASD individuals compared to controls. However, only five cytokines remained significant after correcting for multiple comparisons. We then subjected these five cytokines to a logistic regression analysis to examine their ability to differentiate between ASD and control cases. Remarkably, we found that a combination of four cytokines, namely eotaxin, FGF-2, HGF, and IFN-γ, represent the best predictors of ASD with an overall accuracy exceeding 80%. To the best of our knowledge, this is the first exploratory study to provide a cytokine-based model for predicting ASD diagnosis in young Arab children in the Qatari population. We propose the potential use of this four-cytokine panel in early ASD diagnosis, which remains to be validated in independent studies.

We observed elevated levels of IFN-γ and reduced levels of eotaxin in the plasma samples in ASD. Previous studies support our finding of increased plasma levels of IFN-γ in ASD (25–27). Furthermore, elevated IFN-γ levels were previously reported in the mid-gestational serum of mothers to children ultimately diagnosed with ASD (28) as well as in the frontal cerebral cortex of individuals with ASD (29). Remarkably, dysregulated IFN-γ signaling contributes to increased neurite outgrowth (30), abnormal neuronal connectivity and social dysfunction (31), which together reflect a typical ASD phenotype. In contrast, we found reduced levels of eotaxin in ASD, which contradicts previous studies that reported increased levels of eotaxin in ASD (8, 32). In response to innate immune activation, the proinflammatory cytokine IFN-γ maintains T helper 1 (Th1) lineage commitment and directs Th1 immune responses while inhibiting differentiation toward other Th cell subsets, including Th2 cells (33). Meanwhile, eotaxin is a chemotactic cytokine that selectively recruits eosinophils to inflammatory sites and orchestrates Th2 effector mechanisms (34). Our results of reduced levels of eotaxin and increased levels of IFN-γ suggest a dampened Th2 transcriptional program and a shift toward the Th1 phenotype in ASD. This finding supports our recently published systematic review that proposes a preferential polarization toward the Th1 phenotype in ASD (6).

On the other hand, we found elevated FGF-2 levels and reduced HGF levels in ASD. FGF-2, also known as basic fibroblast growth factor (bFGF), is a multifunctional growth factor that plays critical roles in neurodevelopment and synaptic plasticity and modulates neuroinflammatory responses (35). A previous study reported decreased serum levels of FGF-2 in individuals with ASD (36), with opposing results to our findings. However, studies on other psychiatric disorders reported increased serum levels of FGF-2 in individuals with schizophrenia (37). In addition, increased expression of FGF-2 receptor (FGFR1) was found in the hippocampus of postmortem brains of patients with schizophrenia and major depression (38). In contrast, HGF is a key factor that prevents neuronal death and promotes survival through pro-angiogenic and immunomodulatory mechanisms. Ablation of HGF or its receptor, MET, affects synaptic plasticity in the brain (39). Previous studies reported decreased serum levels of HGF in ASD (40, 41), which supports our results. Furthermore, reduced MET protein levels were found in the postmortem cerebral cortex of individuals with ASD (42). Interestingly, decreased MET gene expression and decreased HGF protein levels were associated with ASD and co-occurring gastrointestinal conditions (41, 43, 44). Taken together, dysregulated levels of FGF-2 and HGF in ASD may contribute to disrupted immune and neuronal functions associated with ASD.

Several studies attempted to identify reliable cytokine biomarkers for ASD; however, the outcomes remain largely inconsistent, which could be due to differences in cohort characteristics and sample analysis approaches across different studies. Although current studies used standard methods for cytokine detection, such as ELISA, cytokine multiplex, or flow cytometry, significant differences might still exist regarding sample handling and processing methods, the analysis platforms used, and the sensitivity and specificity of the antibodies used across different studies (6). In addition, current studies are widely variable in the clinical characteristics of study cohorts, such as age, gender, ethnicity, and co-occurring conditions, which could contribute to the variability in the results across studies. Most of the current studies included subjects in the age range between 2 and 12 years (6). However, it is important to emphasize that the immune system undergoes dynamic changes during the developmental period from early childhood to adolescence (45), and hence some variability might be introduced when comparing the results of studies that

included subjects with different age ranges. Furthermore, many of the current studies lacked details of the clinical features and co-occurring conditions of the study participants (6), which could further contribute to result variability across studies. In this study, we restricted the age range of subjects to 2–4 years to minimize the effect of age variability on the results and to identify reliable biomarkers for the early diagnosis of ASD at a timepoint during which most ASD symptoms appear. In addition, we focused on subjects without known co-occurring clinical conditions to minimize possible confounding effects of these conditions on the results. Finally, we focused on a specific ethnicity of the Arab population to reduce any influence of genetic variability on the results, and we ensured that the study population represented a 4 to 1 male-to-female ratio to reflect the typical gender distribution in ASD.

In conclusion, we report dysregulated levels of several cytokines in the plasma samples of young children with ASD. We identified a novel cytokine panel of IFN-γ, eotaxin, HGF, and FGF-2 as the best predictive markers of early ASD diagnosis with an overall diagnostic accuracy exceeding 80%. Additionally, our data imply the predominance of the Th1-like immune phenotype in ASD children. These findings require further validation in independent cohorts. We emphasize the importance of recruiting a well-defined study population in future studies on ASD to improve the accuracy and reproducibility of the results. In addition, there is a need for more longitudinal analyses in future studies to correlate the time-dependent changes in cytokine production with the clinical and behavioral phenotypes in ASD.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Institutional Review Board (IRB) Ethics Committee of HMC (approval number: MRC-02-18-116) for the recruitment of subjects with ASD and the PHCC (approval number: 2020/06/064) for the recruitment of control subjects. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

WN-E: Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Investigation, Methodology, Visualization. NM: Investigation, Methodology, Writing – review & editing. SL: Writing – review & editing, Data curation, Project administration, Resources. NA: Writing – review & editing, Supervision. MM: Supervision, Writing – review & editing. SA: Supervision, Writing – review & editing. AA-S: Supervision, Writing – review & editing, Conceptualization, Funding acquisition, Project administration, Writing – original draft, Investigation.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1333534/full#supplementary-material

SUPPLEMENTARY TABLE 1
Comparison of the plasma cytokine levels in children with ASD and the control group. Data are presented as percentages or medians (lower – upper quartile) with p-values of the Mann—Whitney U test. Bold numerals indicate statistical significance (p-value < 0.05).

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Sensory phenomena in children with Tourette syndrome or autism spectrum disorder

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Background: Tourette syndrome (TS) and autism spectrum disorder (ASD) are two neurodevelopmental disorders with an onset before the age of 18 years. TS patients frequently reported atypical sensory phenomena (SP). Sensory processing abnormalities are also particularly frequent in ASD individuals.

Objectives: Considering the higher rate of atypical sensory behaviours in both neurodevelopmental disorders, in the present study we analysed sensory experiences in patients with ASD and in patients with TS.

Methods: We enrolled patients with a primary diagnosis of TS or ASD. All participants were assessed for primary diagnosis and associated comorbidities. The presence of sensory behaviours was investigated using the University of Sao Paulo's Sensory Phenomena Scale (USP-SPS).

Results: SP were significantly more represented in the ASD-group versus TS-group, except for sound just-right perceptions and energy to released. ASD participants presented higher mean scores in all fields of USP-SPS severity scale respect on TS patients and healthy controls. The USP-SPS total score had significant positive correlations with the CYBOCS and MASC total scores in the TS cohort. In the ASD group, the USP-SPS total score was significantly negative correlated with the total IQ and marginally positive correlated with ADOS total score.

Conclusion: SP are a frequently reported characteristic both of ASD and TS. Future studies are needed to better evaluate the differences on their phenomenology in patients with TS and ASD.

KEYWORDS

Tourette syndrome, autism spectrum disorder, neurodevelopmental disorders, children, sensory phenomena

Introduction

Tourette syndrome (TS) is a neurodevelopmental disorder most diagnosed in childhood or early adolescence, characterized by multiple motor tics and/or vocal tics, which last for more than 12 months, with an onset age before 18 years (1). The reported prevalence of TS was even estimated to be 0.3-1% (2). Patients affected by TS frequently report a range of comorbid psychopathologies, such us attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), anxiety disorders and sleep disorders (3, 4). Individuals with TS experience a variety of different sensory phenomena (SP), including premonitory urges prior to tics, "just right" perceptions, or somatic hypersensitivity due to impaired sensorimotor gating (5). For this reason, sensory phenomena are recognized as core TS symptoms.

ASD is a childhood-onset neurodevelopmental disorder, characterized by significant defects of social communication and interaction across multiple contexts, associated with restricted and repetitive patterns of interests and activities (1). The reported global prevalence of ASD was approximately estimates to be 1% (6) and most recent of about 2% in the United States (US) (7). Difficulty processing, integrating, and responding to sensory stimuli has been reported as a characteristic of ASD since the first report of this neurodevelopmental condition (8). Indeed, in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), sensory reactivity symptoms were associated to the restricted and repetitive behaviour domain, as a diagnostic criterion (9). Recent estimates reported that between 45 and 96% of children with ASD manifest these sensory difficulties (10, 11).

TS and ASD frequently co-occur and both present similar clinical and behavioural features (12). The reported prevalence of comorbid ASD in subject affected by TS is variable, ranging from 2.9% to 20% (13–15). Abnormalities in corticostriatal circuits are common in both disorders, that are etiologically related (16 No more studies have explored the differences between SP in TS and ASD. The present study aimed to evaluate sensory behaviours in two large populations from a single center, TS patients and ASD patients, compared with a pediatric control group. Specifically, we used the University of Sao Paulo's Sensory Phenomena Scale (USP-SPS) to (1) examine how children with ASD or TS attend to sensory stimuli, (2) assess sensory experiences both in patients with ASD and in patients with TS, differentiating their types, (3) evaluate the reliability of the USP-SPS especially in the ASD sample.

Materials and methods

Study design

This study was performed at the Child and Adolescent Neurology and Psychiatry, Department of Clinical and Experimental Medicine, Catania University. Participants comprised 92 children with the TS diagnosis, 82 children with the ASD diagnosis and 100 typically developing (TD) controls, with a similar age and gender distribution as the patients. All participants underwent a full neuropsychiatric assessment by a team of child and adolescent neurologists with a specific expertise in the evaluation of neurodevelopmental conditions. The study was conducted in agreement with the Declaration of Helsinki and authorized by the local Ethics Committee of Catania University Hospital. The informed consent of the children's and their parents involved in the study was obtained to enter clinical and demographic data from the clinical files into this study.

Participants

Eligible participants were children aged 5-17 years that presented a primary diagnosis of TS or ASD based on DSM-V criteria (1). We excluded patients older than 18 years, who presented a moderate or severe intellectual disability, or other primary psychiatric disorders, different from TS or ASD. Comorbidity with other neuropsychiatric disorders was not established as an exclusion criterion if TS or ASD were the primary diagnosis. As a control group (n=100) we included subjects with typical development (TD) from a community sample with no neurodevelopmental disturbances and with an age and gender distribution equal to the patients with ASD or TS. TD participants' exclusion criteria included positive history for intellectual disability or other developmental, neurological, or behavioural problems. The Social Communication Questionnaire (SCQ) (17) was used to screen and exclude autism in TD children.

Clinical assessment

The clinical assessment of our sample was conducted by paediatric neuropsychiatrist with solid experience in developmental disorders. Participants underwent assessment of intelligence quotient using the Wechsler Intelligence Scale for Children (WISC-IV) (18). The clinical symptoms of TS and ASD patients were evaluated through the administration of the Yale Global Tic Severity Rating Scale (YGTSS), Children's Yale-Brown Obsessive-Compulsive Scale for Children (CY-BOCS), Autism Diagnostic Observation Schedule (ADOS), Multidimensional Anxiety Scale for Children (MASC), Child Depression Inventory (CDI), Conners' Parent Rating Scale (CPRS) and Child Behaviour Checklist (CBCL). In addition, the USP-SPS was performed to assess the presence and severity of sensory behaviours.

Measures

The YGTSS is a clinician-rated instrument administered to evaluate the motor and phonic tic severity. This scale presents two separate motor and vocal tic checklists scored from 0 to 5 on two subscales for motor and vocal tics, also combined to obtain a total tic severity score. Another score ranging from 0 to 50 was calculated for global impairment due to tic symptoms (19). To evaluate OCD, the CY-BOCS, a semi-structured clinician-administered interview evaluating the severity of obsessions and compulsions was also

conducted (20). The ADOS was used for ASD diagnosis. The ADOS is a direct observation that consists of four modules of exploration (A), social interaction (B), imagination (C), and repetitive and stereotyped behaviours (D) (21). The CPRS is a practical instrument for acquiring parental reports of childhood behaviour problems that contains summary scales supporting ADHD diagnosis and quantifying ADHD severity (22). The CBCL is a very useful questionnaire administered to assess a variety of behavioural and emotional problems (anxiety, depression, introversion) in the children (23). The CDI is a self-report tool that evaluate depressive symptoms in children and adolescents (24). All participants also completed the MASC, a standardized measure of anxious symptoms (25). In addition, the presence and severity of sensory phenomena was evaluated through the administration of the USP-SPS, a semi structured scale that contain a checklist and a severity scale (26). The USP-SPS checklist evaluate the occurrence of possible different subtypes of SP including physical sensations, "just-right" perceptions, feelings of incompleteness, energy that builds up and needs to be released, and just an urge to do repetitive behaviours. The USP-SPS severity scale measures the severity of the SP considering the frequency of symptoms, the amount of distress that they determined, and the degree to which they interfere with patient's quality of life (26).

Statistical analysis

Data were analyzed using SPSS software (SPSS, Inc., Chicago, IL, USA, IBM, Somers, NY, USA). Continuous variables were reported as mean (standard deviation), while categorical variables were reported as absolute values (n) and relative values (%). The distribution of quantitative data was normality assessed by the Shapiro-Wilk test. Student's t tests were conducted to compare clinical variables and rating scales between ASD and TS groups. Pearson's chi-square tests were performed to compare categorical variables between ASD and TS, and between TD subjects for the evaluation of SP. In addition, Pearson's correlation coefficients were determinate to investigate the correlation between the total USP-SPS score and other scale scores. A p-value < 0.05 was considered to reveal statistical significance.

Results

Sample characteristics

In this study, we enrolled a clinical cohort of 274 individuals aged 5-17 years (mean age = 10.4 ± 2.6; male (M)/female (F) = 183:91; male = 66.8%). Of the entire cohort, 92 subjects were affected by TS, 82 patients presented a diagnosis of ASD. Participants comprised also 100 TD subjects, with a similar age and gender distribution as the patients (75 males, 25 females; mean age 9.5 ± 0.6). TS patients were 70 males and 22 females, with a mean age of 10.65 ± 2.8 years. The mean age of tic onset was 6.6 (± 2.1) years, while the mean age of the diagnosis was 8.8 (± 2.5) years. Of the 92 patients affected by TS, 35 subjects (38.04%) had a family history of TS, 33 subjects (35.09%) had a family history of OCD, 6 subjects (6.5%) had a family history of ADHD, and another 20 (21.7%) had a family history of depression. Among the individuals affected by TS, the most common neuropsychiatric comorbidities were OCD (64.1%) and conduct disorder – CD (26.1%); 9.8% of the TS-affected participants also met the diagnostic criteria for ADHD. Only 24 patients (26.1%) presented "pure-TS" phenotype; conversely, 68 patients (73.9%) presented also associated comorbidities, in particular one (n=46), two (n=18) or more (n=4) comorbid disorders. Patients with ASD (n= 82) included 71 males and 11 females, with a mean age of 11.2 ± 3.4. The mean age of symptoms 'onset was 2.76 (± 0.8) years, while the mean age of the diagnosis was 5.2 (± 2.3) years. Of the 82 patients affected by ASD, 8 subjects (9.8%) had a family history of OCD, 9 subjects (10.98%) had a family history of ADHD, and another 9 (10.98%) had a family history of depression. None of the ASD cohort reported a family history of TS. Considering ASD sample, 57 patients (69.5%) presented associated comorbidities, in particular one (n=23), two (n=18) or more (n=16) comorbid disorders. 41.5% of the ASD-affected participants had a comorbid OCD, 37.8% had a comorbid CD, and another 28.05% a comorbid ADHD. Demographic data and clinical features of all participants are displayed in Table 1. Compared with TS, patients with ASD were younger at symptom onset (mean age 2.76 vs 6.6, t = 15.269, p < 0.00001) and at the time of diagnosis (mean age 5.2 vs 8.8, t = 10.08, p < 0.00001) (Table 1). Participants with ASD were more likely to have echolalia (74.4% vs 10.9%, χ^2(df) = 72.425, p < 0.00001), self-injurious behaviours (13.4% vs 2.2%, χ^2(df) = 7.924, p = 0.0049), and a comorbid diagnosis of ADHD (28.05% vs 9.8%, χ^2(df) = 9.638, p = 0.0019) or sleep disorders (24.4% vs 3.3%, χ^2(df) = 16.874, p = 0.00004) (Table 1). Conversely, TS patients were more likely to have a positive family history for tics (38.04% vs 1.2%, χ^2(df) = 35,829, p < 0.00001) or OCD (35.9% vs 9.8%, χ^2(df) = 16,415, p = 0.00005), and a comorbid diagnosis of OCD (64.1% vs 41.5%, χ^2(df) = 8.953, p = 0.0028) (Table 1). Compared to ASD participants, TS patients were more likely to have a single comorbid diagnosis (50.0% vs. 28.05%, χ^2(df) = 8,73, p = 0.0031). Conversely, participants with ASD were more likely to have ≥ 3 associated comorbidities (19.5% vs. 4.3%, χ^2(df) = 9,801, p = 0.0017). Instead, there was no significant difference between the TS group and the ASD group considering the other clinical and demographic variables (Table 1).

Neuropsychiatric evaluation

The results of the neuropsychiatric evaluation are summarized in Table 2. TS patients compared to ASD patients presented significantly higher mean total IQ (total IQ: mean 93.6, SD ± 18.2 vs. mean 86.1, SD 21.4, t = 2.4853, p = 0.00695) (Table 2). Participants with TS presented a mean total YGTSS score of 17.4 (± SD 9.4). Instead, evaluation through ADOS-2 in ASD patients showed total ASD score (Social Affect +Restricted and repetitive behaviours) of 10,7 (± SD 4.0). The mean scores for CY-BOCS were statistically significant higher in TS patients (total CY-BOCS: mean 13.9, SD ± 8.4 vs. mean 9.1, SD ± 5.8, t = 4.3427, p < 0.00001) (Table 2). No statistically significant differences were also observed between the two groups based on total CDI (p = 0.246) and MASC

TABLE 1 Demographic and clinical features of the participants.

Partecipant characteristics	Total sample (n=174)	ASD (n=82)	TS (n=92)	p-value
Male (%)	141 (81.0%)	71 (86.6%)	70 (76.1%)	0.078
Mean age (years) ± SD	10.4 (± 2.6)	11.2 (± 3.4)	10.65 (± 2.8)	0.2287
Age of onset (mean ± SD)	4.8 (± 2.5)	2.76 (± 0.8)	6.6 (± 2.1)	< 0.00001
Age of diagnosis (mean ± SD)	7.1 (± 2.99)	5.2 (± 2.3)	8.8 (± 2.5)	< 0.00001
Echolalia	71 (40.8%)	61 (74.4%)	10 (10.9%)	< 0.00001
Coprolalia	5 (2.9%)	1 (1.2%)	4 (4.3%)	0.2176
Palilalia	7 (4.0%)	3 (3.66%)	4 (4.3%)	0.817
Self-injurious behaviors	13 (7.5%)	11 (13.4%)	2 (2.2%)	0.0049
Family history (n, %)				
TS	36 (20.7%)	1 (1.2%)	35 (38.04%)	< 0.00001
OCD	41 (23.6%)	8 (9.8%)	33 (35.9%)	0.00005
ADHD	15 (8.6%)	9 (10.98%)	6 (6.5%)	0.296
Depression	29 (16.7%)	9 (10.98%)	20 (21.7%)	0.057
Comorbid diagnosis (n, %)	125 (71.8%)	57 (69.5%)	68 (73.9%)	0.519
+ 1 comorbid diagnosis	69 (39.66%)	23 (28.05%)	46 (50.0%)	0.0031
+ 2 comorbid diagnosis	36 (20.7%)	18 (21.95%)	18 (19.6%)	0.698
≥ 3 comorbid diagnosis	20 (11.5%)	16 (19.5%)	4 (4.3%)	0.0017
Comorbid diagnosis (n, %)				
OCD	93 (53.4%)	34 (41.5%)	59 (64.1%)	0.0028
ADHD	32 (18.4%)	23 (28.05%)	9 (9.8%)	0.0019
CD	55 (31.6%)	31 (37.8%)	24 (26.1%)	0.097
Sleep disorders	23 (13.2%)	20 (24.4%)	3 (3.3%)	0.00004

SD, standard deviation. ASD, Autism Spectrum Disorder; TS, Tourette Syndrome; OCD, Obsessive-Compulsive Disorder; ADHD, Attention-deficit hyperactivity disorder; CD, conduct disorder. p-values refer to Pearson's chi-square tests in case of categorical variables (summarized by absolute and percent frequencies), and to Student's t tests in case of quantitative variables (summarized by means and SD).

scores (p = 0.141) (Table 2). The comparison between the mean CBCL scores in the two clinical groups showed statistically significant differences for total scores (total CBCL score: mean 46.8, SD ± 20.5 vs. mean 38.9, SD ± 24.5, t= - 2.3033, p = 0.0112) and "internalizing problems" (mean 13.7, SD ± 6.6 vs. mean 11.3, SD ± 9.6, t= - 1.8544, p = 0.0327); in contrast, the mean scores for "externalizing problems" were not statistically significant different (p = 0.4537) (Table 2). Furthermore, the two cohorts presented non-statistically significant different scores in all fields of CPRS, except for "ADHD index" (total "ADHD index": mean 9.75, SD ± 8.7 vs. mean 4.1, SD 2.9, t = - 2.9571, p = 0.0018) (Table 2).

Evaluation of sensory phenomena

All participants of the entire cohort (n = 274), also including a control group, completed the USP-SPS to evaluate the presence and severity of different types of SP. All 82 participants affected by ASD experienced some SP. SP were present also in 76 TS patients (82.6%) and 31 TD subjects (31%) (Table 3). As for types of SP in ASD cohort, 81 participants (98.8%) presented hypersensitivity, followed by tactile physical sensations (n = 68, 82.9%) and look "just-right" perceptions (n = 62, 75.6%) (Table 3). In the TS cohort, 54 patients (58.7%) referred tactile physical sensations, followed by look "just-right" perceptions (n = 47, 51.1%) (Table 3). Furthermore, 31 TD subjects (31%) experienced some SP, frequently look "just-right" perceptions (n = 22, 22%) and tactile physical sensations (n = 17, 17%) (Table 3). Statistically significant differences were detected based on all subtypes of SP in the TS-group versus the ASD-group, with some exceptions. Furthermore, all subtypes of SP were significantly more represented in the ASD-group versus TS-group, except for sound just-right perceptions (32.9% vs 29.35%, χ^2(df) = 0.259, p = 0.6105) and energy to released (34.1% vs 25%, χ^2(df) = 1.751, p = 0.186). All subtypes of SP were also significantly more represented in the ASD group versus TD group, and in TS group versus TD group (Table 3). The mean USP-SPS total severity scores for all groups are displayed in Figure 1. In the current study, the ASD clinical cohort had a significantly higher mean USP-SPS total score than that of the TS patients (mean USP-SPS total score: 8.7 vs 4.5, t = -8.40554, p < 0.00001). ASD participants presented

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TABLE 2 Neuropsychiatric evaluations of TS and ASD participants.

Measures	ASD (n=82)	TS (n=92)	p-value
IQ			
TIQ	86.1 (± 21.4)	93.6 (± 18.2)	0.00695
VIQ	87 (± 23.1)	95 (± 19.1)	0.0063
PIQ	88.1 (± 21.4)	94.1 (± 17.2)	0.0207
YGTSS			
Total	3.7 (± 4.9)	17.4 (± 9.4)	<0.00001
Motor	2.9 (± 3.7)	10.8 (± 5.4)	<0.00001
Phonic	0.8 (± 2.2)	6.4 (± 5.4)	<0.00001
CY-BOCS			
Total	9.1 (± 5.8)	13.9 (± 8.4)	<0.00001
Obsessions	4.9 (± 3.3)	7.2 (± 4.4)	0.0001
Compulsions	4.1 (± 2.9)	6.7 (± 4.8)	0.000015
CPRS			
Total	30.7 (± 16.4)	27.1 (± 20.4)	0.1054
Oppositional problems	6.1 (± 3.6)	6.6 (± 5.2)	0.2441
Cognitive Problems/Inattentive	6.2 (± 4.4)	5.7 (± 4.96)	0.2461
Hyperactivity-Impulsivity	4.6 (± 3.8)	5.8 (± 8.5)	0.1186
ADHD index	4.1 (± 2.9)	9.75 (± 8.7)	0.0018
CDI	10.1 (± 6.4)	9.4 (± 7.1)	0.246
MASC			
Total	44.4 (± 13.4)	42.2 (± 14.0)	0.141
Physical symptoms	11.7 (± 4.97)	11.6 (± 5.3)	0.4795
Harm avoidance	14.66 (± 4.5)	13.9 (± 5.96)	0.186
Separation anxiety/phobias	10.0 (± 4.95)	10.2 (± 5.6)	0.3775
CBCL			
Total	46.8 (± 20.5)	38.9 (± 24.5)	0.0112
Internalizing problems	13.7 (± 6.6)	11.3 (± 9.6)	0.0327
Externalizing problems	16.26 (± 9.9)	16.05 (± 12.6)	0.4537
ADOS			
Social affect (SA)	7.7 (± 2.3)	0.02 (± 0.1)	<0.00001
Restricted and Repetitive Behaviors (RRB)	3.0 (± 1.7)	1.5 (± 1.2)	<0.00001
SA + RRB	10.7 (± 4.0)	1.52 (± 1.3)	<0.00001

ASD, Autism Spectrum Disorder; TS, Tourette Syndrome; IQ, Intelligence quotient; TIQ, Total Intelligence quotient; VIQ, Verbal Intelligence quotient; PIQ, Performance Intelligence Quotient; YGTSS, Yale Global Tic Severity Rating Scale; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale for Children; CPRS, Conners' Parent Rating Scale; ADHD, Attention-deficit hyperactivity disorder; CDI, Child Depression Inventory; MASC, Multidimensional Anxiety Scale for Children; CBCL, Child Behaviour Checklist; ADOS, Autism Diagnostic Observation Schedule; SA, Social affect; RRB, Restricted and Repetitive Behaviors. p-values refer to Student's t tests conducted to compare rating scale between ASD and TS groups (summarized by means and SD).

also higher mean scores in all fields of USP-SPS severity scale respect on TS patients and TD subjects (p< 0.00001) (Table 4).

Correlations between sensory phenomena and other symptoms

Considering the TS cohort, The USP-SPS total score had significant positive correlations with the CYBOCS total score (r = 0.3015, p = 0.0035) and the MASC total score (r = 0.2365, p = 0.0232). The other relationship between the USP-SPS total scores and the other rating scales did not reach significance (Table 5). Conversely, in the ASD group the USP-SPS total score was significantly negative correlated with the total IQ (r = -0.2816, p = 0.0106) and marginally positive correlated with ADOS total score (r = 0.217, p = 0.0502). Instead, the other relationship between the USP-SPS total scores and the other rating scales did not reach statistical significance in the ASD cohort (Table 5).

Discussion

This study investigates differences between sensory behaviours in TS patients versus ASD patients, compared with a paediatric control sample, through the administration of USP-SPS. So far, a few studies have evaluated sensory phenomena using USP-SPS. Most literature studies were conducted on OCD and/or TS subjects (26–37). Preliminary results of a study conducted on an adult cohort of OCD patients suggested the reliability of USP-SPS for the assessment of sensory behaviours (26). SP were present in 51 OCD patients (67.1%), with a mean USP-SPS total score of 5.5 (SD ± 4.6); among the entire cohort, 16 subjects also presented tics (21.1%), and 13/16 (81.3%) of them presented sensory behaviours (26). Furthermore, tics were twice as common in the patients with SP, but this difference did not reach statistical significance (26). Lee

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TABLE 3 Assessment of sensory phenomena (SP) through USP-SPS checklist.

USP-SPS	Current	ASD (n=82) Previous/ Absence	Current	TS (n = 92) Previous/ Absence	Current	TD (n=100) Previous/ Absence	ASD vs TS p-value	ASD vs TD p-value	TS vs TD p-value
Presence of any SP	82 (100%)	0 (0%)	76 (82.6%)	16 (17.4%)	31 (31%)	69 (69%)	<0.0001	<0.0001	< 0.0001
Subtypes of SP									
Tactile Physical Sensation	68 (82.9%)	14 (17.1%)	54 (58.7%)	38 (41.3%)	17 (17%)	83 (83%)	0.0005	<0.0001	<0.0001
Muscle-joint or bone Physical Sensations	39 (47.6%)	43 (52.4%)	28 (30.4%)	64 (69.6%)	1 (1%)	99 (99%)	0.0205	<0.0001	<0.0001
Look just-right perception	62 (75.6%)	20 (24.4%)	47 (51.1%)	45 (48.9%)	22 (22%)	78 (78%)	0.0008	<0.0001	0.00003
Sound just-right perception	27 (32.9%)	55 (67.1%)	27 (29.35%)	65 (70.65%)	3 (3%)	97 (97%)	0.6105	<0.0001	<0.0001
Feel just-right perception	43 (52.44%)	39 (47.6%)	21 (22.8%)	71 (77.2%)	2 (2%)	98 (98%)	0.00005	<0.0001	<0.0001
Feeling of incompleteness	30 (36.58%)	52 (63.4%)	15 (16.3%)	77 (83.7%)	1 (1%)	99 (99%)	0.0002	<0.0001	0.00013
Energy to released	28 (34.1%)	54 (65.9%)	23 (25%)	69 (75%)	0 (0%)	100 (100%)	0.186	<0.0001	<0.0001
Urge to do repetitive behaviours	37 (45.1%)	45 (54.9%)	20 (21.74%)	72 (78.3%)	0 (0%)	100 (100%)	0.0010	<0.0001	<0.0001
Hypersensitivity	81 (98.8%)	1 (1.2%)	14 (15.2%)	78 (84.8%)	0 (0%)	100 (100%)	<0.0001	<0.0001	<0.0001

ASD, Autism Spectrum Disorder; TS, Tourette Syndrome; TD, typically developing; USP-SPS, University of Sao Paulo's Sensory Phenomena Scale; SP, sensory phenomena; p-values refer to Pearson's chi-square tests to compare categorical variables between ASD, TS and TD groups (summarized by absolute and percent frequencies).

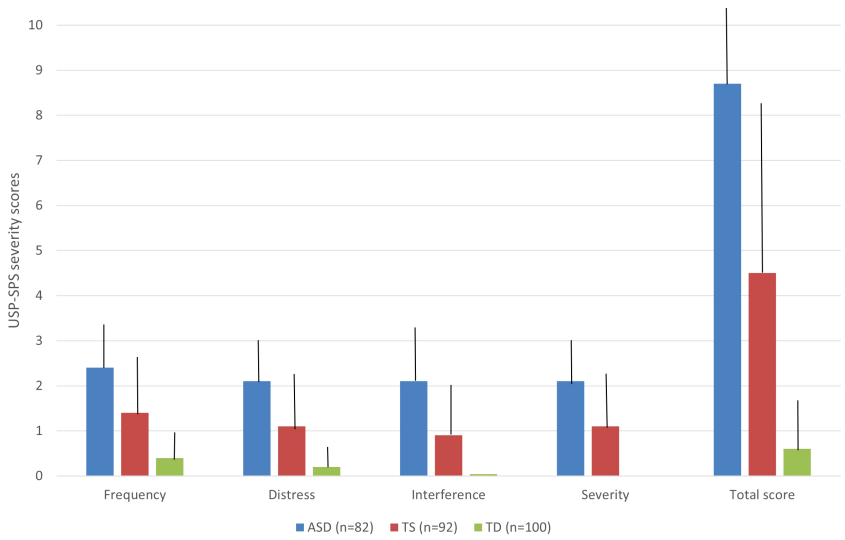

FIGURE 1
Severity scores of sensory phenomena (SP). The figure reports the results of USP-SPS total severity scores across the three groups (ASD in blue, TS in red, and TD in green). Bars indicate the standard deviations; all fields of USP-SPS severity scale were significantly higher in ASD-group respect on TS-group and TD-group.

TABLE 4 Assessment of sensory phenomena (SP) through USP-SPS severity scale.

USP-SPS severity scale	ASD (n=82)	TS (n=92)	TD (n= 100)	p (ASD vs TS)	p (ASD vs TD)	p (TS vs TD)
Frequency	2.4 (± 0.9)	1.4 (± 1.3)	0.4 (± 0.6)	< 0.00001	< 0.00001	< 0.00001
Distress	2.1 (± 0.9)	1.1 (± 1.1)	0.2 (± 0.4)	< 0.00001	< 0.00001	< 0.00001
Interference	2.1 (± 1.1)	0.9 (± 1.01)	0.04 (± 0.2)	< 0.00001	< 0.00001	< 0.00001
Severity	2.1 (± 0.9)	1.1 (± 1.2)	0 (± 0)	< 0.00001	< 0.00001	< 0.00001
Total score	8.7 (± 2.8)	4.5 (± 3.7)	0.6 (± 1.1)	< 0.00001	< 0.00001	< 0.00001

ASD, Autism Spectrum Disorder; TS, Tourette Syndrome; TD, typically developing; USP-SPS, University of Sao Paulo's Sensory Phenomena Scale; p-values refer to to Student's t tests conducted to compare USP-SPS rating scores between ASD, TS and TD groups (summarized by means and SD).

et al. (27) explored the interaction between SP and OCD and showed that all subtypes of SP were significantly more common and severe in OCD than in controls subjects (27). Another study conducted by Sutherland Owens et al. (37) in 18 TS subjects and 22 healthy controls showed a statistically significant positive correlation between USP-SPS and Premonitory Urge for Tics Scale (PUTS) scores in TS subjects (37). In this cohort, USP-SPS total scores tended to grow with age, in line with the clinical experience regarding the age-dependent reporting of premonitory events (38). In a big cross-sectional study that reported data on a large OCD sample, SP were reported in the 72% of the total sample (29). Moreover, compared to OCD patients without comorbid tics, OCD patients affected also by tic disorders showed a higher rate of SP (80.1% vs. 68.6%), but the difference in USP-SPS score was not significant (29). In another study, 1001 OCD patients were assessed to evaluate OCD, tics, comorbidities, level of insight and SP (28). In this sample, 651 (65.0%) presented at least one subtype of SP associated to repetitive behaviours (28). The comparison of OCD patients with and without SP showed also a significantly more common comorbid diagnosis of TS and Chronic tic disorders (CTD), and a positive family history of tic disorders in the OCD group with SP, that in the other group (28). In addition, the same author's group compared the subtypes of SP in OCD participants with and without tics and showed that patients affected by OCD associated with tic disorders endorsed SP significantly more frequently than OCD patients without tics (31). In 2014, Sampaio et al. conducted a study to validate and investigate the psychometric properties of the English version of the USP-SPS (30). In this study, SP were detected in 89.1% of OCD sample, and 100% of patients with tic disorders, supporting the high presence of SP in OCD and TS sample (30). In another study, a structural correlate of SP involving grey matter volume increases within the sensorimotor cortex was identified in patients with OCD (33), in line with the results reported in another study conducted in patients with tic disorders, showing abnormal activity and volume increases within this region are associated with the urges preceding tic onset (39). Furthermore, another study investigated such phenomena associated to tics, obsessive-compulsive symptoms (OCS), and global functioning in a small sample of TS patients (32). The authors reported a significant correlation between the PUTS and the USP-SPS total score; in addition, USP-SPS and PUTS total scores were significantly correlated with YGTSS total scores and Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) total scores (32). Moreover, de Avila et al. (34) investigated factors associated with poor insight in subjects with OCD and demonstrated that patients with poor insight differed from those with good insight regarding more prevalent SP (34). In addition, another recent report on a small TS sample by the same author's group described changes in SP, tics, OCD after 4 years (35). A significantly correlation between previous USP-SPS and PUTS total scores and previous YGTSS and Y-BOCS total scores was revealed, while current USP-SPS total scores were significantly correlated with current YGTSS global severity scores (35). Additionally, current USP-SPS and PUTS total scores were significantly correlated with current YBOCS total scores, while previous USP-SPS total scores were significantly correlated with current Y-BOCS total scores and marginally correlated with current YGTSS global severity scores (35). Recently, Vellozo et al. (36) compared OCD patients with and without symptoms of the symmetry dimension to evaluate their clinical profiles and reported that the OCD group with symmetry symptoms presented higher frequency and severity of SP (36) Previous studies regarding the assessment of SP using USP-SPS in TS and/or OCD patients are summarized in Table 6.

TABLE 5 Pearson's correlation between sensory phenomena and other symptoms.

TS cohort (n= 92)	USP-SPS total scale		ASD cohort (n= 82)	USP-SPS total scale	
	r	p		r	p
Total IQ	-0.0436	0.7050	**Total IQ**	-0.2816	0.0106
Total YGTSS	0.0999	0.3478	**Total YGTSS**	0.0343	0.7597
Total CYBOCS	0.3015	0.0035	**Total CYBOCS**	0.1736	0.1188
Total CPRS	0.1001	0.3424	**Total CPRS**	0.1483	0.1836
Total CBCL	0.0294	0.7809	**Total CBCL**	0.127	0.2555
Total MASC	0.2365	0.0232	**Total MASC**	0.0493	0.6605
Total CDI	0.0294	0.7809	**Total CDI**	-0.1032	0.3571
Total ADOS	0.1857	0.07635	**Total ADOS**	0.217	0.0502

ASD, Autism Spectrum Disorder; TS, Tourette Syndrome; USP-SPS, University of Sao Paulo's Sensory Phenomena Scale.

The results of our study show that SP were present in 76 TS patients (82.6%), 82 ASD patients (100%) and 31 TD subjects (31%). In the TS cohort, the mean USP-SPS total score was

slightly lower (mean 4.5, SD ± 3.7) respect to other reported samples (32, 35, 37). Furthermore, the most frequently reported types of SP in the TS cohort are tactile physical sensations (58.7%) and look "just-right" perceptions (51.1%). Other studies conducted on TS samples by the same author's group (32, 35) reported a higher frequency of muscle-joint physical sensations, tactile "just-right" perception, and urge only. The differences detected between our results and other literature studies are probably due to the different range of age of other reported cohorts, that included more adult TS patients, respect to our paediatric sample. In addition, a broader spectrum of comorbidities was described in our sample, compared to other literature studies, that reported cohorts of TS patients with a concomitant diagnosis of ADHD and/or OCD (32, 35, 37).

In this study, we detected a significant positive correlation between the USP-SPS total score and the CYBOCS total score ($r = 0.0909$, $p = 0.0035$), in line with previous results (32, 35). There results suggested that both tics and OCD symptoms have strong relationships with SP, in line with other reports. Instead, there are few data available regarding the assessment of SP in TS cohort through the USP-SPS. Further studies are needed to better characterize these kinds of phenomena in patients with tic disorders. To the best of our knowledge, this is the first study in which SP were assessed administering the USP-SPS scale in ASD cohort. Considering the psychometric properties of USP-SPS for the assessment of presence and severity of SP, further research is required to understand the complexity of these kind of phenomena in larger ASD cohorts. Conversely, several studies have focused on the

TABLE 6 Summary of studies regarding SP using USP-SPS in TS and/or OCD patients.

Reference	Patients (n)	Mean age	Comorbidities	USP-SPS Total Score	Results
Rosario et al. (26)	76 OCD	35.4	-Tics (21.1%)	5.5 (SD = 4.6)	SP were present in 67.1% of patients. There were no significant differences in the presence of SP according to comorbidity with tics.
Lee et al. (27)	37 OCD	37	-Tic disorders (20%) -OCPD (35%)	n.a.	The frequency of any kind of SP was significantly higher in OCD patients (67.6%) when compared to controls (35.1%).
Sutherland Owens et al. (37)	18 TS	9 adults (25.5) 9 children (13.2)	-OCD (50%) -ADHD (11.1%)	8.5 (SD = 3.7)	Statistically significant positive correlation between USP-SPS and PUTS total scores.
Gomes de Alvarenga et al. (29)	813 OCD	34.9	-Tic disorders (29.0%) -Mood disorders (70.7%) -Anxiety disorders (33.8%) -ADHD (16.1%) -Impulsive control disorders (37.3%) -Body dysmorphic disorders (11.9%) -Others	37.08	SP were reported by 72% of the entire sample. Compared to OCD patients without comorbid tics, OCD patients with comorbid tic disorders were more likely to present SP.
Ferrão et al. (28)	1001 OCD	34.85	-TS (8.8%) -CTD (13.7%) -Trichotillomania (4.5%) -Skin picking (15.4%)	7.7 (SD = 3.49)	651 (65.0%) subjects reported at least one type of SP preceding the repetitive behaviours. The presence of SP was associated with comorbid TS, and a family history of tic disorders.
Shavitt et al. (31)	1001 OCD	34.85	-TS (9%) -CTD (15.4%) -Mood disorders (42.6%) -Anxiety disorders (65%) -Impulse control disorders (30.8%) -ADHD (12.7%) -Others	4.88 (SD = 4.63)	Most OCD patients endorsed SP (60.4%). OCD + TS and OCD + CTD endorsed SP significantly more frequently than OCD patients without tics.
Sampaio et al. (30)	60 OCD and/or TS	18.98	-OCD (91.7%) -TS (26.7%) -CTD (5%)	n.a.	The prevalence of SP in total sample was 88.5%. SP were presented in 89.1% of OCD sample, and 100% of TS and CTD sample.
Subirà et al. (33)	106 OCD	33.11	n.a.	8.4 (SD = 3.5)	Patients with SP (67%) showed grey matter volume increases in the left sensorimotor cortex in comparison to Patients without SP and bilateral sensorimotor cortex grey matter volume increases in comparison to controls.
Kano et al. (32)	41 TS	23.1	-OCD (20%)	6.4 (SD = 3.1)	The PUTS total score had significant correlations with the USP-SPS total score. USP-SPS and PUTS total scores were significantly correlated with YGTSS total scores and DY-BOCS total scores.

(Continued)

TABLE 6 Continued

Reference	Patients (n)	Mean age	Comorbidities	USP-SPS Total Score	Results
de Avila et al. (34)	272 OCD	Poor insight (n= 124, median 35.5), Good insight (n=148, median 32)	-Tics (median 34 in poor insight, 41 in good insight); -TS (median 10 in poor insight, 9 in good insight); -ADHD (median 22 in poor insight, 14 in good insight); -Others	9 (median)	Individuals affected by OCD in the poor insight group presented more prevalent SP compared to those with good insight.
Kano et al. (35)	20 TS	30.2	-OCD (30%) -ADHD (20%)	5.0 (SD = 3.2)	Current USP-SPS total scores were significantly correlated with current YGTSS global severity scores. Both current USP-SPS total scores and PUTS total scores were significantly correlated with current CY-BOCS total scores.
Vellozo et al. (36)	1001 OCD	34.8	-TS (8.8%) -Tic disorders (28.4%) -ADHD (13.7%) -Mood disorders (60.8%) -Anxiety disorders (69.8%) -Others	4.9 (SD = 4.6)	The OCD group with symmetry symptoms presented higher frequency and severity of SP.

SP, sensory phenomena; USP-SPS, University of Sao Paulo's Sensory Phenomena Scale; TS, Tourette Syndrome; OCD, obsessive-compulsive disorder; SD, standard deviation; OCPD, Obsessive compulsive personality disorder; ADHD, Attention-deficit hyperactivity disorder; PUTS, Premonitory Urge for Tics Scale; CTD, Chronic tic disorders; n.a., not available; DY-BOCS, Dimensional Yale-Brown Obsessive-Compulsive Scale; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale for Children.

characterization of SP in children with ASD, using other instruments (40, 41). In our ASD cohort, hypersensitivity was the type of SP most represented (98.8%), in line with literature studies that reported a higher prevalence of sensory over-responsivity (SOR) involving different sensory modalities (42). Furthermore, tactile physical sensations (82.9%) and look "just-right" perceptions (75.6%) are more frequent in our ASD-group. Of note, atypicality in visual and tactile processing were frequently reported as a typical sensory difficulty in children with ASD (43). Certainly, it would be desirable to make a thorough assessment of SP in ASD, comparing USP-SPS with other tools evaluating abnormalities in sensory processing. Our results show that SP are more frequently reported in ASD cohort than TS population. Furthermore, unusual sensory behaviours have been described for other neurodevelopmental disorders, but they are particularly frequent in individuals with ASD, with about 90% of autistic individuals presenting an atypical sensory profile and with an elevated variability among individual sensory modalities (44). Given the higher rate of sensory processing abnormalities in ASD, sensory abnormalities were added as core diagnostic features of ASD in DSM-5 (1).

Several limitations in our study must be discussed. First, larger cohorts would be needed to improve our knowledge on the differences in sensory behaviours between ASD and TS. Second, complementing the assessment of SP with other questionnaires could be useful to more characterize the phenomenology of SP. Third, considering that the recruitment was done in a tertiary centre, it may be argued that only moderate to severe patients were included in the study. In addition, it is important to underline that most patients recruited were not affected only by TS or ASD, but presented associated comorbid psychopathologies. Furthermore, it would be helpful to explore the possible influence of associated comorbidities on the prevalence of SP in children with TS and/or ASD, with particular reference to OCD, taking into account the results reported in the literature studies conducted on OCD samples. Due to these limitations, further investigations that evaluating SP using USP-SPS in TS and ASD groups would be meaningful, considering the paucity of literature reports on paediatric cohorts.

Conclusions

This study highlights that SP are a common characteristic both of ASD and TS. Considering the heterogeneity of these conditions, a more detailed exploration of the SP and their subtypes could help to better understanding the differences on their phenomenology in patients with TS and ASD. Future studies should include the application of tools such as USP-SPS that evaluate these phenomena in larger paediatric cohorts of patients with ASD and TS, also exploring the possible impact of comorbid conditions.

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 humans were approved by Local Ethics Committee (Catania 1) of Catania University Hospital. The studies

were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

AP: Data curation, Formal analysis, Writing – original draft. FS: Data curation, Formal analysis, Writing – original draft. MF: Data curation, Writing – original draft. VF: Data curation, Writing – original draft. RB: Methodology, Writing – review & editing. RR: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

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

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A qualitative evaluation of the pathway for eating disorders and autism developed from clinical experience (PEACE): clinicians' perspective

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Introduction: The Pathway for Eating disorders and Autism developed from Clinical Experience (PEACE pathway) is a clinical pathway of adapted treatment for individuals with eating disorders and autism in the UK. This study aims to investigate multidisciplinary clinicians' views of the strengths and challenges of PEACE pathway adaptations, while identifying areas where further improvement is needed.

Method: Semi-structured interviews were conducted with 16 clinicians who worked on the PEACE pathway. Themes relevant to the benefits, challenges and areas of improvement were identified, and a thematic map was produced.

Results: PEACE Pathway brought clinical benefits such as improved understanding of patients' perspective, improved flexibility and individualisation in clinicians' approach, increased patient engagement, and provision of resources that are helpful to all patients with or without autism. Benefits to the service included increase in autism awareness, clinicians' confidence, and team collaboration. Challenges were also identified, including difficulties in incorporating autism adaptations into existing treatment protocol, implementing PEACE at different levels of care, staff schedule conflicts, and increased pressure to meet patients' needs. Overall, there is a need for systemic improvement in aftercare and community support for autism, more suitable autism screening tool, and more structured guidelines for making adaptations.

Conclusions and implications: PEACE Pathway has brought clinical and service benefits, while also bringing practical challenges rooted in the difficulty in distinguishing between autism and eating disorder in comorbid population. Future areas of improvement are highlighted for PEACE resources as well as in the national support system for autistic individuals.

KEYWORDS

eating disorder, comorbidity, autism, adaptation, clinician interview

1 Introduction

In recent years, there has been a growing interest in the marked overlap between autism and eating disorders (ED) in adults (1, 2), with studies estimating the mean prevalence rate of autism in ED populations to be 23% (3, 4). It has been proposed that co-occurring autism and ED can lead to increased social impairment (5), depression and anxiety symptoms (6), longer admissions in ED treatment services (5, 7) and poorer treatment outcomes (8, 9). Therefore, there is an urgent need for ED services to effectively identify this patient group and ensure that their needs are supported. Individuals with both conditions themselves also highlight the importance of adapting ED treatment to take characteristics of autism into account (10–12).

The Pathway for Eating disorders and Autism developed from Clinical Experience (PEACE pathway) (13) is, to our knowledge, the first clinical pathway of adapted treatment for adults with ED and autism in the UK (14). The pathway was developed following needs assessment with all stakeholders including clinicians (15), carers (16), and patients themselves (10). These early studies highlighted needs for environmental adjustments, clinician education and training in autism, refeeding programme adaptations to accommodate sensory sensitivities, tools to address communication difficulties and improve patient engagement, and improved recognition and understanding of autism within ED services.

In an attempt to respond to these concerns, the South London and Maudsley (SLaM) NHS Foundation Trust National Eating Disorders Service piloted the implementation of the PEACE pathway (13), introducing adaptations such as autism screening, environmental changes including refurnishing and decoration of the service to ensure a more sensory-friendly environment, sensory tools and psychoeducation about sensory sensitivity, clinician training on autism assessment and adapting therapeutic modules and language for autistic people, development of an alternative menu, and communication support to aid communication between patients and the treatment team.

The SLaM ED service primarily serves adult women, a demographic in which autism is frequently underdiagnosed. Recent research using primary care data has indicated significant levels of underdiagnosis in adults, particularly among older age groups in the UK (17). Furthermore, previous studies have identified a gender gap in autism diagnosis, highlighting that women and girls who meet criteria for autism are at a high risk of not receiving a diagnosis (18). This disparity may be attributed to differences in behavioural characteristics compared to males (19) and a greater likelihood of camouflaging in women and girls (20). PEACE adopted a trait-focused approach in this patient group to prevent the exclusion of underdiagnosed patients whose needs would otherwise go unrecognised. This was also due to practical concerns given the long NHS waiting time for formal diagnostic assessments. As part of the PEACE Pathway, all admissions at SLaM ED service are screened using the Autism Spectrum Quotient short version (AQ-10; 21, 22) questionnaire for autistic features. In some cases where there are uncertainties about a possible autism presentation, follow up measures are used; the team would enquire more about family history of autism, developmental milestones, further observe the patient's presentation at the service, and/or follow up with the Social Responsiveness Scale 2nd Edition (SRS-2; 23) to investigate their difficulties in more depth. Adaptations are made for those who have high autistic features, identified through screening, as well as those with confirmed past diagnoses. In line with the views and preferences of the autism community (24), identity-first language (i.e., 'autistic person' rather than 'person with autism spectrum disorder') is used in this study.

To ensure consistent implementation of the adaptations, PEACE also introduced regular 'huddle' meetings to facilitate communication and case discussions between the multidisciplinary health professional teams at the ED service (25). Preliminary evaluation of survey feedback has shown that 92% of trained clinicians agreed that their knowledge and skills improved and 97% agreed that the training sessions should be recommended to other ED clinicians (13). It is important that the practicalities and challenges in PEACE implementation are fully explored before trialling similar adaptation pathways at more ED services. This study, therefore, aims to investigate the feasibility of PEACE through interviewing the clinical team about their experience of implementation.

When introducing adaptations to evidence-based interventions, transparent reporting of what does or does not work is essential, to ensure that the adapted intervention is acceptable, feasible and maximises benefits for patients. Seeking feedback from clinicians is critical in this process to gauge acceptability, the degree of adaptation required and sustainability of the adaptation (26). In the development of PEACE pathway, qualitative feedback from stakeholders is regularly consulted to ensure that the adaptations made are acceptable and appropriate (10, 15, 16). However, adapting an intervention is often a dynamic process, as the context in which adaptations are made constantly changes (27). In this study, five years into the implementation of PEACE, we investigated multidisciplinary clinicians' views of the PEACE pathway adaptations to gauge their feasibility and sustainability. Specifically, we investigated their thoughts about the following:

- Objective 1: Benefits of the PEACE pathway;
- Objective 2: Challenges in implementing the PEACE pathway;
- Objective 3: Areas where further improvement is needed.

2 Methods

2.1 Participant selection

Semi-structured interviews were conducted with multidisciplinary clinicians who worked at the SLaM adult ED service between 2017 and 2022, when the PEACE Pathway was developed and implemented at the service. A meeting was conducted first with the principal investigator of the PEACE Pathway (KT) to identify clinicians working at the service during this time period with good knowledge and involvement with the PEACE Pathway (i.e., participated in PEACE Pathway training and regular meetings). A list of potential interviewees with varied roles representative of the multidisciplinary team was identified (for example, counselling psychologists, consultant psychiatrists, psychology assistants, dietitians, family therapists, and occupational therapists). All potential interviewees identified were invited by the lead author (ZL) by email to participate in the study. The invitation email explained the purpose of the study and that clinicians were invited based on their involvement with the PEACE Pathway. Clinicians who expressed interest then received an information sheet and a consent form to be signed if they agreed to be interviewed. Written consent was acquired prior to interviews, including consent for the interview to be recorded. Ethical clearance for this project was granted by King's College Research Ethics Committee (MRSP-21/22-28800).

2.2 Interview

Participants were interviewed by ZL face to face or online, depending on clinicians' preference. During the interview, a topic guide was used to ask participants the following questions:

1. Could you tell me about your involvement with the PEACE Pathway? (Gatekeeping question to gauge participant's involvement and identify focus points for follow-up questions)
    - Follow up: did you find the [PEACE component that the participant mentioned in their reply to Question 1] helpful or unhelpful? How?
2. Was there anything from the training that really stuck with you? (To gauge participant's exposure to PEACE Pathway training)
3. Have you used any other PEACE resources during clinical practice? How helpful or unhelpful did you find them?
4. Do you have any suggestions for how the PEACE Pathway can be improved?

The interviewer also used follow-up questions asking for further details and examples after asking the main interview questions. All interviews lasted between 30 minutes and one hour. Recordings of the interviews were then transcribed verbatim by ZL with all identifying information removed at the point of transcription. The interviews continued until no new information emerged, indicating data saturation.

2.3 Analysis

Interview data were analysed in NVivo 12 using thematic analysis (28, 29). Firstly, transcripts were read and reread by ZL and CHH for content familiarisation. A coding framework was developed deductively based on the research objectives and topic guide questions. Transcripts were read and reread by ZL and CHH, and the coding framework was further refined based on data content, agreed by all authors, and applied to the data by ZL. Preliminary themes emerged from analysis of the coded data, which were then reviewed and modified by scrutinising the data associated with each theme in the context of the entire data set. Finalised themes were re-worded for clarification where appropriate. The relationships between themes and subthemes were checked for overlap. All results are reported according to the Consolidated Criteria for REporting Qualitative studies (COREQ) checklist (30).

3 Results

In total, 16 clinicians were approached, consented and interviewed before data reached saturation. All clinicians worked at the SLaM ED service where PEACE Pathway was implemented. The sample represented the multidisciplinary team structure including a range of professions: assistant psychologists, clinical psychologists, consultant psychiatrists, dietitians, family therapists, and occupational therapists. Clinicians all had experience treating patients with co-occurring ED and autism. Among the participants, 12 (75%) were female and 4 (25%) were male.

Three main themes emerged from the analysis: benefits of the PEACE Pathway (including clinical benefits and benefits to the service), practical challenges, and future needs and suggestions for improvement. All themes and sub-themes are presented in a

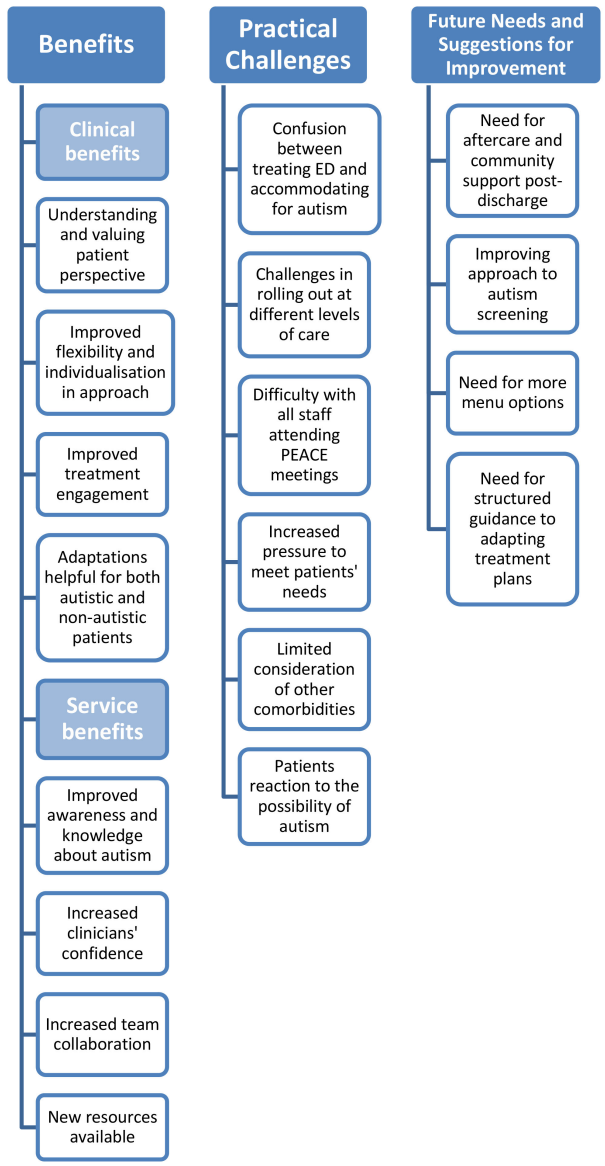

FIGURE 1
Thematic map of clinicians' views.

thematic map (Figure 1). Key findings are reported below, supported by participant quotes. All quotes are anonymised with participant numbers.

3.1 Clinical benefits

Clinicians described several clinical benefits of the PEACE Pathway on their treatment approaches. Firstly, they highlighted the collaborative nature of the pathway development and how this helped them understand and value patients' perspectives. Patient involvement in the decision-making process was highlighted as particularly beneficial in the earlier stages of pathway development. Clinicians described seeking patient feedback on their preferred sensory adaptations (e.g., introducing silent key caps to reduce the sound of the ward keys and decluttering ward environment), communication needs (e.g., designing and giving out the communication passport for patients to fill in and having conversation cards available in the public area on the ward), and preferred colour scheme for environmental adaptations.

> "This wasn't, sort of, 'okay, this is a clinician project', or 'this is a carers' [project]', this was our project in terms of the patients, the carers and the clinicians all working together in deciding and making sure they had a voice about how would they want the sort of dining room, or the sort of corridors to kind of be. I remember even doing the psychology board with them, and we've kind of done that all together, as well, sort of during Christmas break that time, designing it together. So, making sure that they were very involved." – Participant 3

> "We talked to them about kind of their communication style, what kind of-, how do they seek support, what they find helpful, not helpful and tried to adapt it in such way." – Participant 4

Participants also described improved flexibility and individualisation in their approach to meeting unmet needs of patients. Firstly, this was reflected in clinicians creating autism-friendly version of documents that were given out, such as colour-coding menus or adding bullet points and using concise language on information pamphlets and post-session summaries. Secondly, adaptations were made on an individual basis during sessions, such as adjusting environmental settings (e.g., lighting or seating positions), using clearer language and reducing metaphors, giving advanced notice about changes taking place, covering fewer topics in one session, as well as adjusting the structure and pace of the sessions (e.g., having shorter sessions that are more frequent). Participants also highlighted the importance of clarifying patients' sensory needs and communication needs at the start of treatment using PEACE resources such as the communication passport (31) to ensure that appropriate adaptations are made. Thirdly, participants described being able to tailor treatment goals and make informed clinical decisions based on patients' autistic features. This involved establishing realistic expectations of what patients can achieve in treatment, and how the care plan can be adjusted to accommodate patients' needs while ensuring safe recovery from ED. For patients whose autistic needs posed challenges to treatment, some clinicians would share information from the PEACE book and work collaboratively with patients to establish treatment priorities, such as asking questions like "What is your priority for change?" and "What do you actually want to work on?" while also considering what is realistic for the individual.

> "And it's so easy to do, it takes like, three, four minutes just to, you know, turn the lights off, open the blinds, or close the blinds, or windows, you know, either sit side by side, lots of people like that, rather than like giving all that eye contact. And yeah, just like the length of the session, you know, some people wanted shorter sessions, some people wanted more regular

> sessions, some people wanted less regular [sessions]. So, you could be a little bit more bespoke." – Participant 10

> "For example, in one case, we talked about, you know, sensory and taste difficulties and also other hypersensitivities the patient had, for example with the sunlight, and that we made some adaptations like closing the curtains. We also discussed whether she should be allowed to go on walks in the evening when it was already quite dark. Yeah, so that was balancing the autistic needs and the safety of the patients and also health aspects as this patient needed vitamin D supplementation because she didn't have enough sunlight." – Participant 5

Improvement in treatment engagement was also noted, with some participants suggesting that this occurred after patients' needs were met. Clinicians gave examples of patients who were disengaged in the past but came into treatment more once their needs were met by individualised support, and of patients who were able to go on to more complex psychological work with appropriately adapted communication methods. Novel adaptations that led to better engagement were often shared in case discussions at PEACE meetings to ensure other staff were also aware of the approach, and could use it in their practice.

> "[The patient] never engaged in psychological therapy, […] because: one, her, she said her needs weren't being met; and also it was rather, sort of sensory sensitivities, she was experiencing. […] So we were making sure that we were thinking about things much more holistically. […] It was a lot of adaptations, she engaged in all our sessions together. And even after that, we were able to kind of go on to more complex psychological work with her such as, like, cognitive behavioural therapy, because she felt like we were listening and her needs were being met." – Participant 3

> "[The patient] hated being in the room and found it really daunting. So I sort of tried to think outside the box and I said, let's do an experiment. And we'll do like a telephone conference. So we can all dial in. And then that will take away some of like the social, overwhelming social nature of it. I mean, it was very interesting because he loved it. And he really got a lot out of it and kept coming back as he disengaged in the past." – Participant 11

Clinical benefits of PEACE Pathway adaptations were not limited to autistic patients only. Some of the resources such as the communication passport and sensory tools are available to all patients admitted to the service, and this was helpful as even patients without autistic features can have communication preferences and/or sensory needs. It was also highlighted that sensory adaptations were particularly useful for trauma informed approaches, as sensory sensitivity is commonly seen in patients who had experienced trauma.

> "Everyone is different and everyone has different sensory needs, whether you're on the autistic spectrum or not." – Participant 4

> "We wanted it to be a peaceful calming environment for, for everybody. And I think that's the important thing – it is for everybody because we know that … would suit an awful lot for the folks we work with eating disorders, not just those with a diagnosis of ASD." – Participant 7

3.2 Benefits to the service

Participants also reflected on PEACE Pathway's impact on the service overall, and highlighted improvement in the clinical team's knowledge, skill, and awareness of autism in their daily practice. Many participants mentioned the benefits of attending PEACE training sessions, which covered a wide range of topics, including autism assessment and formulation, which helped clinicians identify autistic features such as camouflaging that could interfere with treatment, and therapeutic and environmental adaptations for autism, which supported the development of strategies for individualising treatment approaches. Moreover, participants mentioned that PEACE raised the level of autism awareness across the team, and it was easier to have autism-related discussions when the team overall became better informed about autism.

> "We would have a lot of experts in the field, come in and teach us and train us, whether that was to do with formulations, adapting CBT, it was all so helpful." – Participant 3

> "The fact that the team as a whole was becoming better informed about autism, it was really helpful because then there were various sort of places that you could go, people that you could discuss things with." – Participant 6

With enhanced knowledge and skills, clinicians felt a greater sense of confidence and credibility when working with autistic individuals. Consequently, they felt more at ease engaging in open, transparent discussions about autism when necessary. This increased willingness to address autism-related topics contributed to the improvement of therapeutic relationships and fostered greater trust.

> "I feel more confident working with people with autism because I have that background. And I also think I'm more credible to working with them." – Participant 7

Participants highlighted PEACE Pathway's positive impact on team collaboration. This was mainly achieved through PEACE

huddles, which are brief, regular meetings for case discussions and updates joined by clinical teams across the ED service. It was described as a valuable forum for hearing different perspectives from multidisciplinary team members, collective problem solving, and sharing formulations and dilemmas about patient cases.

> "It really brought the team together across the services. You've got people from day care, from outpatient, inpatient, step up." – Participant 11

> "It was also a good space to know about what was happening where, because like I said, I'm a little bit out of touch with what's happening on the ward. But that was a place where I could find out what they were doing, and vice versa." – Participant 13

Lastly, many participants highlighted that the PEACE Pathway has made available a wide variety of resources to use flexibly in practice. Participants appreciated the low stimulus room, the autism-friendly introduction packages for patients, the sensory psychoeducation materials, and the communication passport. The PEACE website (peacepathway.org) and PEACE book (32) were also highlighted by most participants as good sources of information for themselves as well as for signposting patients and families to.

> "I think there's some useful information and signposting on there. And I know […] from having discussed with patients that they found it helpful. They've used it and have spoken about it in therapy. One patient in particular said that they wish this had been, this had been known sooner." – Participant 10

3.3 Practical challenges

Many participants described their dilemma between treating ED and accommodating for autism. For example, it can be difficult to disentangle which symptoms arise from the core symptoms maintaining ED or difficulties associated with autism. This complexity is particularly evident when patients' restrictive behaviours are influenced by factors from both conditions, such as body image concerns coupled with a preference for routine and predictability. Clinicians often worried that making accommodations for autism would inadvertently exacerbate the ED. This issue was highlighted particularly with the use of the PEACE menu, which is an alternative autism-friendly menu mainly consisting of bland tasting food with homogeneous texture that is calorie-matched with the regular menu used at the service. Food items on the PEACE menu are also photographed and pre-packaged where possible to maximise predictability and reduce patient anxiety. However, clinicians expressed concerns that some patients would choose the alternative menu not necessarily because of autism, but out of the desire to restrict because although the alternative menu is calorie-matched, some of the items may be perceived as lower calorie due to their blandness. There were also concerns that patients who chose the alternative menu all the time in order to avoid the standard menu would risk being on a restrictive and rigid diet with limited variety. Some clinicians noted that reasonable adaptations should be made in the beginning of treatment, but suggested that therapeutic challenges need to be introduced in the process to encourage improvement, for example to increase variety in food intake or to challenge rigid behaviours. Such challenges can be crucial to ensuring good transitioning into everyday life, but it is difficult to conclude from PEACE Pathway guidance when to reduce adaptations and introduce these challenges.

> "In the beginning, we make a lot of adaptations to not challenge [the patients] too much with the texture of food, with the sunlight or with a, with the noise, etc. But there also needs to be some improvement and some therapeutic challenges. And it's not always clear for me from the information I get from the PEACE huddles etc. how quick we should make improvements and challenge these things." - Participant 5

> "The [PEACE] menu doesn't represent what's available in cafes, and [supermarkets] and stuff like this. And I think it is difficult with the eating disorder patients who tried to elicit … using all of the adaptations, because then effectively, they're just facilitating a very restricted diet." - Participant 12

Clinicians' uncertainty between ED treatment and autism adaptations was intensified when PEACE was rolled out to different levels of care, where treatment goals and service structures can vary. For example, participants noted that implementation of the PEACE Pathway was stronger on the inpatient unit than it is in the outpatient unit. Differences in treatment goals were also highlighted by participants, with inpatient services noted as prioritising weight restoration, whereas day service and outpatient teams aim to support weight stabilisation and transition into the community. As a result, clinicians in outpatient and day services tend to prioritise therapeutic challenges and may be more focused on manualised sessions rather than making adaptations. Lastly, participants pointed out differences in treatment format, where day services are essentially a group programme, which presents greater difficulties for clinical staff to support patients individually. Clinicians described that as much as they would like to tailor to individual needs, this also has an impact on the group elements of the treatment. For example, a clinician described that when one group member gets adapted treatment and is allowed to wear headphones during mealtimes, other members would be aware and would question the fairness of this. The impact of adaptations on patient dynamics in a group can be particularly challenging.

> "I do think it's such an important thing to hold in mind the comorbidity and the crossover of traits, but I guess there is also sometimes the adjustment of what can be adapted on the inpatient ward to then when they come to day services, or

> outpatients, [where] we are not able to meet that level of adaptation. Or we are a bit more hesitant to." – Participant 12

> "In day service, the nature of the intervention is that you are going to be raising people's anxiety. They are confronting anxiety provoking situations around food and around emotions. And that's the nature of the intervention. And I suppose sometimes people might say in their [communication] passport, you know, don't, don't say this or that to me. But that might be something that we need to speak to them about, in order to sort of challenge the eating disorder, or challenge unhelpful ways of communicating." – Participant 13

Participants also discussed difficulties with not all staff members being able to attend PEACE huddle meetings. Despite the importance of multidisciplinary team cohesion for disseminating clinical innovations to team members, participants highlighted the struggle for all disciplines to attend the meetings regularly given their already demanding workload.

> "It can be hard in terms of sort of staff time. It can be a struggle for, say, for instance, some disciplines to find the time to attend these, due to various other demands on the ward as well." – Participant 3

In addition, clinicians mentioned that some PEACE adaptations have increased the pressure they are under to meet patients' needs, which sometimes can be unrealistic and unhelpful in terms of recovery:

> "I think, another thing about the communication passport, I would say that it needs to be used with caution, and also to think together with the patients. I don't think it's humanly possible for us to remember, in such fine details, some communication passports are so detailed in terms of how they like and not like to be spoken to, and so on. And to hold all these patients in mind is going to be very difficult. So I think it's helpful to have an idea, but we also need to invite the patients to think about how can we be more flexible with it? And some patients will say in the communication passport, I don't, I don't ask for support. And we can't just accept that, because that's not going to be helpful for them." – Participant 4

Some participants raised concerns that there can be a lot of crossover between potential diagnoses in complex cases, for example personality disorder and autism, or complex post-traumatic stress disorder and autism. Focusing prematurely on autism can lead to overshadowing of other possible diagnoses, stopping patients from getting appropriate treatments. This is exacerbated by the fact that waiting lists for a formal autism assessment in the UK are long, often exceeding two years, thus there is a danger of premature suggestions of autism.

> "The PEACE Pathway – although I think it's really good, and it has lots of resource and it has helped loads of people – I think runs the risk of having an autism bias to the extent where it gets over thought about at the cost of being able to distinguish other stuff." – Participant 12

In addition, suggestions of possible autism are sometimes met with negative reactions from patients and families. Some may reject the idea, and some may not be prepared to receive a suggestion of autism from an ED service. Disclosing this possibility to patients and families may therefore be a stressful experience for clinicians.

> "But her parents, well, her mum is very rejecting of the diagnosis and is embarrassed about it. So I think you might have, yeah, just be prepared that some people might not be as understanding. … You know, it's been really upsetting for her. Whilst it's like an epiphany, it's also really upsetting because she's like, ah, so like, I've got this thing, and it's about me, and it's with me." – Participant 11

3.4 Suggestions for improvement

In the context of the challenges of and barriers to PEACE implementation, participants also reflected on potential areas of improvement in the future. The need for aftercare and community support was highlighted by many, not only as a suggestion for PEACE but more as a national urgent need for support for autistic individuals. Clinicians mentioned that the discontinuation of adaptations once patients leave the ED service is worrying. The PEACE Pathway therefore needs to be developed further, taking into account aftercare needs.

> "So I think management of the aftercare needs to be improved, because you create a lot of expectations in the patients if you offer ASD and anorexia nervosa service on the ward, and the patients think this really continues afterwards. And it doesn't. Where the patient then has identified all the problems with the therapists, but will become a bit hopeless, if those identified needs are not met, after the treatment on the ward." – Participant 5

Participants also pointed out that the autism screening approach needs to be improved. PEACE uses screening However, participants raised several concerns about this process. Firstly, the participants cautioned against exploring autism with patients immediately after they score over the threshold on the AQ-10 without seeking further evidence. Participants pointed out that there is need for structured guidance and clear decision points for the follow up procedure after the initial AQ-10 screening, for example what additional features to look for in patients' presentation, and when to mention the possibility of autism with patients. Secondly, participants were concerned that the

AQ-10 is not accurate enough with possible overlap with other diagnoses and starvation effect. The result therefore requires careful interpretation.

"I think with women as well, [AQ-10] is not quite, I think, if you look at its psychometric properties, it's never, the internal consistency is never that high." – Participant 11

> "So [score on the AQ-10] was just flagged up as being positive. And then it's not as clear what do we then do with it? Often, we then decide to do something with it if we're really struggling with management, and we thought, actually, we need to think more about autism, then it becomes kind of more, more kind of on the forefront of our mind." – Participant 4

Clinicians also mentioned that the PEACE menu could be improved to include more options, for example a version with more vegan options. It was also noted that a version for people with sensory hyposensitivity could be developed, in addition to the current version which is for people with hypersensitivity and dislike strong smells or tastes. The hyposensitivity version, for example, could include food items that have stronger smells and tastes and would satisfy sensory seeking needs.

> "I think quite a lot of that group are vegan. So if they were to be another vegan option on the PEACE menu that might actually support them having more than just one food every single day, maybe there'd be two." – Participant 9

Some participants preferred more structured, step-by-step treatment plans from PEACE, instead of general guidance on how to adapt sessions. Two benefits were proposed for this structured approach: easier and more specific treatment planning for clinicians, and clearer structure for patients with high rigidity.

> "For example, in CBT for depression, you have these manuals where you will see in, in week one, you make this formulation. Week two, you talk about positive activities. Week three you implement the first change, etc.[…] And we don't have such a clear plan developed for people with ASD and anorexia. […] We have identified the challenge, we have been given some guidance, but let's say for someone who starts on the ward, very specific guidance would be good.[…] So, coming from general guidance to a more specific treatment plan - I think that would be helpful." – Participant 5

4 Discussion

4.1 Overview

The findings of this qualitative evaluation highlighted a broad range of benefits of and challenges in the PEACE Pathway from the perspective of multi-disciplinary clinicians working in the SLaM ED service where the PEACE Pathway had been implemented. Before discussing benefits, challenges and areas of improvement subsequent to the implementation of the PEACE Pathway, it is useful to reflect on the areas identified in previous needs assessments conducted with stakeholders prior to and during PEACE Pathway development, which are summarised in Table 1. In 2017, Kinnaird and colleagues interviewed clinicians in the same SLaM ED service about their views on working with patients with ED and autism, which highlighted a lack of clinician confidence, a lack of clear pathways for autism assessment referrals, problems with patient/therapist communication, difficulties identifying and articulating emotions, and lack of systematic guidelines and staff training on adapting treatment (15). A subsequent study involved interviews with patients and found that people with co-existing eating disorders and autism struggled with the short time frames for treatment and could not engage well in refeeding due to sensory difficulties (10). The same study also highlighted the importance of involving patients in deciding how to adapt services to support patients with autism. A third study with carers raised issues such as difficulty getting an autism assessment, sensory difficulties, a need for a tailored approach to treatment and difficulty getting services to adapt treatment (16).

Table 1 summarises stakeholders' needs assessed by previous studies in parallel with relevant themes arising from the current evaluation. Some of the themes are corroborated with evidence from other studies (for example, 25). Themes from the interviews suggest that many of the previously identified challenges and needs were addressed by PEACE: clinicians reported an increase in their confidence; new resources, such as communication passports, alternative menus and sensory aids, have been developed and disseminated to help with communication and sensory difficulties; patients are now receiving a more tailored and individualised approach to treatment, with adjustable time frames and pace for treatment that better suits their needs; and clinician skills and knowledge about autism improved as a result of training. The PEACE Pathway also incorporated autism screening in order to meet the need for clear guidance on autism assessment; this was however both appreciated by clinicians and also highlighted as an area where improvement is still needed, discussed in more detail in section 4.3. Furthermore, some of the benefits highlighted in the current evaluation exceeded previously identified needs, for example PEACE Pathway adaptations and resources were beneficial not only to autistic patients, but to all patients with communication or sensory needs.

4.2 Benefits and challenges

Clinicians reported many benefits of the PEACE Pathway, such as improved understanding of patients' perspectives, improved flexibility and individualisation in approach, increased treatment engagement, and provision of resources that are helpful to all patients, with or without autism. PEACE also brought benefits to the clinical service overall, increasing general awareness and knowledge about autism, boosting clinicians' confidence in treating the comorbidity, providing platforms for team-wide

TABLE 1 Stakeholders' needs based on earlier studies and themes arising from the interviews reflecting areas addressed by PEACE.

Stakeholder	Needs based on earlier studies	Areas addressed by PEACE
Clinician	Need to improve confidence supporting the co-morbidity (15)	Increased clinician confidence (also reported in: 25)
Clinician	Need to improve expertise and experience, and sharing of expertise (15)	Increased team collaboration through huddle meetings and case studies (also reported in: 25)
Clinician	Need to improve understanding of autism and willingness to adapt (15 & 10, 16)	Improved overall awareness, skill and knowledge about autism
Clinician	Need to address communication challenges (15)	Flexible and collaborative approach leading to improved treatment engagement; new resources developed (communication passport, conversation cards)
Patient	Need to develop better relationships with clinicians and to feel better understood (10)	Flexible and collaborative approach leading to improved treatment engagement
Patient	Need to feel listened to and able to influence adaptation of their treatment (10)	Collaborative approach focused on understanding and valuing the patient perspective
Patient	Need for a flexible, tailored and individualised approach (10, 16)	Improved individualisation and flexibility in treatment format, structure, tools and goals
Patient	Need to improve response to sensory and communication difficulties (10, 16)	Environmental and sensory adaptations (also see 33) and new resources available (e.g., communication passports and alternative menus)
Carer	Need for improved access to autism assessment (16)	Autism screening tools introduced as standard screening procedure for all admissions; clinicians received training in assessing and recognising autism
Carer	Need to improve support for sensory difficulties (16)	Environmental and sensory adaptations and new resources available (e.g., service environment re-designed, sensory workshop introduced and sensory toys available, also see 34
Carer	Need for a tailored approach to treatment and for service-wide adaptations to treatment (16)	Improved individualisation and flexibility in treatment format, structure, tools and goals; improved team collaboration and awareness

collaboration, and making the treatment programme overall more resourceful. These findings may be linked to autistic patients' reduced use of intensive treatment after PEACE implementation in the preliminary cost-savings analysis of PEACE (7), suggesting that PEACE clinicians are making appropriate changes to meet the needs of autistic people. Indeed, PEACE adaptations align with the recommended adaptations for working with autistic people by the NICE guidelines (35), including having breaks in therapy, increased use of written and visual information, involving carers, and avoiding metaphoric language when needed. In addition, PEACE also introduced aspects that are similar to CBT adaptations that have been tested by other studies to be clinically effective for common mental health problems in autistic people, for example adjusting the structure and pace of therapy, and including materials and skills training to enhance patients' understanding of emotions (36, 37). A systematic review by Walters, Loades and Russell (38) found that interventions that were effective for autistic young people tended to use more modifications than those recommended by NICE. It was also found that such interventions tended to use more disorder-specific modifications i.e., tailoring to the specific psychological disorder being treated. Overall, the benefits and strengths of PEACE highlighted by clinicians in this study are encouraging.

Clinicians also identified challenges in the process of implementation, due to the difficulty in incorporating autism adaptations into existing ED treatment protocol and goals. For example, accommodating for patient's sensory needs by providing noise-blocking earbuds during mealtimes conflicted with social eating which is encouraged by clinical teams in inpatient and day patient treatment settings. Similarly, supporting patients with nutritional rehabilitation using their preferred option of an alternative bland menu conflicted with the typical goal of increasing the variety of food choices in ED treatment. At the core of these individual-level challenges lies the difficulty of distinguishing between ED and autism, and clinicians' hesitance to deviate from standard treatment protocols. Indeed, disentangling ED and autism can be complicated in a clinical setting, especially when certain presentations in people with the comorbidity can be influenced by factors from both conditions. For example, restrictive eating could be due to body image concerns (rooted in ED) combined with an autistic need for routine and predictability. In this case, it is difficult for clinicians to decide whether they should make adaptations. It is therefore important that adaptations are constantly discussed and formulated in supervision and clinical meetings on a case-by-case basis to ensure peer support for clinicians during decision making. Recent studies have also started to shed some light on distinguishing between common features in anorexia nervosa and autism (1, 2). Brede and colleagues (11) proposed a model of autism-related mechanism underlying restrictive eating behaviour, including how autistic traits could lead to restriction directly due to sensory sensitivities and/or autistic cognitive profile, or indirectly through increasing negative emotions which leads to restricted eating as a coping mechanism. This model is yet to be empirically tested, but it is a helpful theory for clinicians to consider. Meanwhile, a framework was recently

proposed to outline clinical features associated with both autism and anorexia nervosa, also highlighting the potential differences in presentation, which can provide useful guidance in clinical practice (2). However, more detailed guidelines are needed to distinguish between autism and other types of EDs such as bulimia nervosa or binge-eating disorder, and to clarify priorities for treatment in different clinical scenarios where treatment protocols may be in conflict.

Further dilemmas were highlighted in relation to the rolling out of adaptations in day service or outpatient setting, where team structures and approaches differ from those in inpatient settings, with greater emphasis placed on patients' flexibility and independence in preparation for full recovery. Indeed, it was highlighted that implementation of the PEACE Pathway was stronger and happened faster in inpatient settings compared to day service and outpatient settings. This may be due to the size of the team (the inpatient team is smaller than the day/outpatient teams and therefore barriers to communication may be lower), the nature of the psychological intervention (where the inpatient service provide more one-to-one interventions compared with the group based programme in the day service, which presents more difficulties for clinical team to adapt care for individual patients), limits on the number and time of outpatient sessions provided to each patient (and so it may become difficult to meet the needs of an autistic person in a fixed number of sessions), and frequency of team communications (team meetings are run almost daily in the inpatient service and weekly in day/outpatient services). As a result, adaptations that worked in an inpatient setting may be less meaningful in other levels of care.

One potential way to address this problem is to refine the implementation of PEACE in outpatient and day services to better align with treatment goals and structure. For example, given the emphasis on Cognitive Behavioural Therapy (CBT) in outpatient clinics, it may be beneficial to focus on adapting the structure of CBT sessions and language to ensure clarity and consistency (36). In the day service, which typically involve more group-based activities, it could be helpful to prioritise support aimed at making communication in groups more comfortable for autistic individuals, who may find group work difficult (14). When rolling out adaptations at different levels of care, constant tailoring, reviewing and supervision is required to align with core goals and the structure of alternative treatment settings. Appropriate evaluation is highlighted by previous research as a crucial step in this process (39), and future evaluation studies are warranted to gauge the impact of refining implementation of the PEACE Pathway in day or outpatient settings.

The development of the PEACE Pathway adopted an iterative Plan, Do, Study, Act (PDSA) methodology (13) to ensure best practice for service improvement (40), and involved collaboration with patients, clinicians and carers to ensure that all stakeholder values and needs were considered. This approach closely reflects the recommended models for making adaptations to evidence-based practice in implementation science (39, 41). Nevertheless, clinicians in the ED service are supporting patients rather than testing theoretical models, and individual patient differences create a variety of dilemmas which are unlikely to be fully resolved through research. Instead, it is likely that sustained use, testing, modification, and evaluation of the PEACE Pathway is essential to support clinicians navigating these dilemmas. This highlights the importance of providing continuous support for clinicians. More resources should therefore be allocated but not limited to: regular clinician training to improve their confidence and skills, lowering barriers to multidisciplinary team decision-making regarding how to manage the dilemmas, and establishing emphasis on value in addition to effects across clinical services.

4.3 Future directions

Clinicians in this study also expressed a need for more structured, preferably manualised guidance. At the ED service, clinicians are trained to use a range of structured, evidence-based ED treatment protocols in their daily practice (42–44). For treatment of coexisting disorders like ED in autistic people, however, current guidelines recommend offering interventions for the specific disorder, not for autism (35), while only listing possible adaptations for autism without specifying the order of priority or structure in which the adaptations should be made. Whilst a PEACE Pathway guide to adapting treatment for autistic people with ED has been published, which includes practical examples and guidance written in multidisciplinary perspectives (32) and was highlighted as helpful by many participants, some called for more structured, step-by-step guidance. However, it is not currently clear whether a more structured guideline would be feasible to manualise the PEACE approach, as a result of the complex interactions between the co-morbid conditions. Evident in this study was participants' perception of contradictory benefits and difficulties. For example, the PEACE menu may reduce anxiety in patients and therefore be welcomed by clinicians providing mealtime support, but this may contradict dietitian guidance to increase food variety. Similarly, noise-reducing tools such as earbuds that aim to ease a patient's sensory sensitivity might also create barriers for 'social eating', which is one of the goals of ED treatment. One strategy suggested by previous work for challenges like this is to develop complex interventions that are flexible and allow for variations (45). The structure of PEACE resembles such an intervention: it includes a wide range of resources and adaptation guidelines that can be flexibly used to tailor to the individual cases. However, this also creates barriers for clinicians who prefer structured guidance. Sustained use and testing of the PEACE Pathway, alongside development of more structured guidance, is warranted.

Clinicians in this study also expressed uncertainties about the screening procedure for autism. Prior to PEACE implementation, interviews with clinicians at the same service suggested that there was no clear pathway for ED clinicians to refer their patients for an autism assessment (15). The PEACE Pathway therefore introduced autism screening into standard practice using the AQ-10, as it is the only measure recommended by NICE for initial assessment of autism in adults (35). However, previous work has shown that the AQ-10 is not a good predictor of diagnosis in clinical samples (46). The screening tool's poor specificity was highlighted, reflecting high rates of false positives. In addition, screening for autism in people

with ED is particularly difficult, due to overlapping features between the two conditions such as cognitive rigidity and social difficulties (2). These overlaps make it more difficult for autism screening tools to distinguish between autistic features and ED symptoms. Therefore, a more suitable autism screening tool for an ED service is needed. Previous work has suggested adding subscales on auditory sensitivity, social compensation and externally orientated thinking to the AQ-10 to improve its ability to distinguish between ED and autism (47). However, this model is yet to be tested further. Another challenging aspect of the screening process is deciding how to proceed with a positive result on the AQ-10. Currently, this decision relies on the clinical expertise and experience of senior clinicians, who factor in follow-up assessments and clinical observations, including evidence of sensory sensitivities, management of social interactions, body language and eye contact, special interests, and other aspects. However, this process is not yet fully operationalised. A structured guide for decision making when a person scores on initial screening could be developed to aid this process, although it should leave enough room to consider individual differences between patient cases.

A need for improvement in aftercare for autistic people was also highlighted. This is highly relevant but exceeds PEACE Pathway's span of influence, and rather reflects a national need for destigmatising autism and improving diagnostic pathways and community support. Over the past 20 years, there has been a 7-8 times increase in recorded incidence of autism diagnoses with the greatest rises among adults (48), yet current service provision for autistic adults is in its infancy compared to health and education services for autistic children (49, 50). The COVID-19 outbreak further increased NHS backlog of autism assessment referrals by 169% from pre-pandemic level (51, 52). This systemic gap in support for autistic people affects clinicians' decision making in a range of areas. Some clinicians hesitate to discuss the possibility of autism with patients, knowing that resources and support become very limited once patients are discharged, and patients could spend years on the waitlist for a formal assessment of autism. Some are faced with negative reactions and denials from patients and families due to stigma on autism. Some worry that the adapted environment at the ED service inadvertently creates a gap with the 'real world', and once a patient is discharged, the discontinuance in autism-friendly adaptations could lead to deterioration. This affects both discharge planning and clinicians' readiness to make adaptations. Therefore, improvement in the implementation of PEACE Pathway requires a system integrated with efficient autism diagnostic and aftercare services. Research on strategies to improve adult autism services in the UK, including assessment and diagnostic services and support networks, is currently underway (53–55).

4.4 Limitations

Nursing staff were not interviewed in this study due to their lower level of engagement with the development and/or implementation of PEACE Pathway. However, their feedback could be invaluable as they have direct daily contact with patients, and should be investigated by future studies focusing on gaps and areas of improvement in implementation. The heterogeneity of this study sample, however, should strengthen the credibility of the study, as participating clinicians varied in gender, age, seniority, and discipline. Another limitation is the lack of information regarding clinicians' years of experience in treating patients with ED and those with comorbid autism and ED. Future studies should explore whether clinicians' experience influences the acceptability of the PEACE pathway.

5 Conclusion

The PEACE Pathway has potential benefits for clinicians' approach with patients and service-wide knowledge and awareness of autism, while also bringing practical challenges. Future areas of improvement are highlighted for PEACE resources as well as in the national support system for autistic individuals. This study provides initial evidence for the feasibility and acceptability of the PEACE Pathway, and warrants future studies to investigate patient experience on the pathway.

Data availability statement

Anonymised interview data can be provided upon request to the corresponding author.

Ethics statement

The studies involving humans were approved by King's College Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZL: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. CH-H: Formal Analysis, Writing – review & editing. SB: Supervision, Writing – review & editing. KT: Supervision, Writing – review & editing.

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Conflict of interest

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

The reviewer MS declared a shared affiliation with the authors ZL, SB, KT to the handling editor at the time of review.

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Altered cytokine and chemokine profile linked to autoantibody and pathogen reactivity in mothers of autistic children

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Maternal autoimmunity, and more specifically, the production of specific maternal autoantibodies, has been associated with altered offspring neurodevelopment. Maternal autoantibody-related (MAR) autism is a subtype of autism that is linked to gestational exposure to certain combinations of autoantibodies to proteins known to be important for fetal neurodevelopment. We wanted to address whether mothers with autism-specific patterns of autoantibodies have a skewed cytokine and chemokine profile during an immune response to infection. To do so, we examined a subset of mothers from the Early Markers for Autism (EMA) study who either produced known patterns of MAR autoantibodies (MAR+) or did not (MAR-). We compared the cytokine/chemokine profiles of MAR+ and MAR- mothers in the context of positive immunoglobulin G (IgG) reactivity to several viral and parasitic agents. We observed that MAR+ mothers have a higher level of proinflammatory cytokine interferon-gamma regardless of IgG status. Additionally, when comparing MAR+ and MAR- mothers in the context of the different pathogens, MAR+ mothers consistently had increases in multiple proinflammatory cytokines and chemokines.

KEYWORDS

cytokine, chemokine, autoantibody, autism, autoimmunity

Introduction

Several identified maternal factors increase offspring's risk of neurodevelopmental disorders, including autism. Among these include maternal obesity (1), maternal immune activation (MIA) (2, 3), infection during pregnancy, and maternal autoimmunity and immune dysregulation (4, 5). In particular, the production of specific maternal autoantibodies (ABs) is associated with a subtype of autism known as maternal autoantibody-related (MAR) autism. These ABs target proteins in the brain and the periphery that are known to be important for proper neurodevelopment (6, 7). The eight proteins are collapsin response mediator proteins 1 and 2 (CRMP1/2), neuron-specific enolase (NSE), lactate dehydrogenase A and B (LDHA/B), stress-induced phosphoprotein 1 (STIP1), guanine deaminase (GDA), and Y-box binding protein 1 (YBOX-1) (6–8). The passage of maternal IgG to the fetus is an essential protective mechanism during pregnancy (9, 10). Thus, it is believed that the MAR ABs are also able to cross the placenta, where they can interact with their targets in the fetal compartment, leading to the observed autism pathology (11, 12).

Clinical studies have shown that only specific patterns of MAR ABs are highly associated with an autism outcome; these AB patterns include CRMP1+GDA, CRMP1+CRMP2, CRMP2 +STIP1, CRMP1+STIP1, GDA+YBOX1, STIP1+NSE, and LDHA/B+YBOX1 (13, 14). Moreover, these investigations have revealed that the offspring of mothers with MAR have higher ADOS scores, indicating more severe symptoms. Additionally, specific MAR patterns are associated with more severe clinical outcomes, with maternal ABs to CRMP1+CRMP2 being linked to more severe developmental delay (13, 15). Preclinical studies using rodent models that replicate the clinical MAR AB exposure have identified several behavioral and neurological implications of AB exposure. More specifically, rodent offspring gestationally exposed to a combination of LDHA/B+CRMP1+STIP1, the first clinically observed MAR pattern (7), displayed decreases in social behavior and increases in species-specific anxiety behaviors (11, 16). In addition, we observed AB deposition in the early postnatal brains of these offspring and volumetric changes in several brain regions implicated in ASD pathology (11).

While it remains unclear what triggers some women to produce ABs to these proteins, skewing of the maternal cytokines and chemokines in mothers who produce MAR ABs has been documented (McLellan et al., Manuscript Accepted). Thus, these mothers could have an underlying immune dysregulation, increasing their susceptibility to loss of self-tolerance. Here, we sought to determine if mothers with circulating MAR-specific patterns of ABs during pregnancy also have skewed cytokine and chemokine profiles when mounting an immune response to viral and parasitic agents. To do so, we used participants from the Early Markers for Autism (EMA) study who were exposed to and had detectable immunoglobulin G (IgG) levels to either cytomegalovirus (CMV), Epstein-Barr virus (EBV), influenza type A (Flu-A), varicella-zoster virus (VZV), herpes-simplex I virus (HSV), toxoplasma gondii (TOXO), or who tested positive for c-reactive protein (CRP) between 15 and 19 weeks gestation. We then examined the differential immune response to pathogen exposure between mothers with MAR-specific ABs and those without by assessing their mid-gestational cytokines and chemokines levels. Understanding the level of the cytokine/chemokine response to pathogens in mothers who are positive for MAR ABs will provide additional information regarding the potential mechanistic foundation underlying the autoimmunity noted in these mothers, which can increase the risk of autism in their children.

Methods

Participants

All participants were enrolled in the EMA study (17). Expanded details on the study population have been previously published (18, 19). Mothers were eligible for inclusion in EMA if they participated in the prenatal expanded alpha-fetoprotein screening program (XAFP) and delivered a live-born infant between July 2000 and September 2003. The original study was comprised of three groups: children with autism (n=486), children with developmental delay (DD) but not autism (n=174), and general population controls (n=397) and their respective mothers. The California Department of Developmental Services assessed children with autism and DD, and their diagnostic status was validated by a blinded clinician using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. From the original EMA participants, we first identified all MAR+ mothers, being those with at least one of the MAR autism-specific patterns of ABs, including CRMP1+GDA, CRMP1+CRMP2, CRMP2+STIP1, CRMP1+STIP1, GDA+YBOX1, STIP1+NSE, and LDHA/B+YBOX1, who had a child with autism (n=37). We then selected a subset for MAR- mothers, those that did not have a MAR autism-specific AB pattern, who had a child with autism (n=37) matching them on maternal age, race/ethnicity, and birthplace to MAR+ mothers. MAR+ and MAR mothers were then tested for reactivity to CMV, EBV, Flu-A, VZV, HSV, TOXO, or CRP using the same mid-gestational blood sample. MAR+ mothers of children who were initially diagnosed with DD and were then reevaluated and determined to have autism were not included (n=6). The institutional review boards of the California Health and Human Services Agency and Kaiser Permanente Northern California approved all study procedures.

Sample collection

Maternal samples were collected between 15 and 19 weeks of gestation as part of routine prenatal XFAP screening. Samples were collected in serum separator tubes by obstetrical care providers and underwent XFAP testing. Leftover specimens were shipped on dry ice to our laboratory and stored at -80°C before use in maternal autoantibody, IgG against pathogenic antigens, and cytokine/chemokine measurement assays. Expanded details have been previously described (19).

Measurement of maternal autoantibodies

The presence of maternal ABs to our proteins of interest, CRMP1/2, STIP1, LDHA/B, NSE, YBOX1 and GDA, in this study population, was detected by enzyme-linked immunosorbent assay (ELISA) as previously published (13). Briefly, microtiter plates were coated with antigen (2-3µg/µl as optimized for each protein) diluted in carbonate coating buffer (pH 9.6) and incubated overnight at 4°C. The following day, diluted plasma samples were tested in duplicate. For colorimetric detection, a secondary antibody (goat anti-human IgG-HRP (Kirkegaard & Perry Laboratories, Inc., Gaithersburg, MA)) was used, followed by the addition of BD optEIA liquid substrate for ELISA (BD Biosciences, San Jose, CA). Following incubation, the reaction was stopped with 2N HCl. Absorbance was measured at 450-595 nm using an iMark Microplate Absorbance Reader (Biorad, Hercules, CA, USA). Expanded assay details have been previously described (13).

Detection of IgG against pathogenic antigens and auto-antigens

Maternal IgG to each agent was measured using solid-phase immunoassay (ELISA) as previously described (20). IgG levels were expressed as µg/ml, and results were not corrected for total protein. CRP levels were measured using the High Sensitivity Human C-Reactive protein kit (IBL America, Minneapolis, Minnesota). Further details have been previously described (21–23).

Measurement of maternal cytokines and chemokines

The cytokine and chemokine measurements were performed as originally published (19). Mid-gestational serum concentrations of 22 cytokines and chemokines were measured using a Millipore Multiples bead-based kit (Milliplex MAP Human Cytokine/Chemokine Kit; Millipore, Billerica, MA, USA). Further details on assay methods are in the original study publication (19).

Statistical analysis

Before analysis, all cytokine/chemokine data were natural log-transformed. Descriptive statistics were used to summarize the clinical and socio-demographic variables and the cytokine/chemokine concentrations. Differences between MAR groups were assessed via Chi-square tests for categorical socio-demographic variables and exact Wilcoxon rank-sum tests for continuous socio-demographic variables and IgG values. Multiple linear regression models were used to evaluate the effect of MAR status on cytokine and chemokine levels in mothers with IgG reactivity to at least one of the agents tested. Separate models were run for each cytokine/chemokine with the MAR status (MAR+ or MAR-) as the primary predictor and including maternal race and ethnicity as covariates. In secondary analyses, we restricted the samples to the MAR+ and MAR- mothers who tested positive for that specific infectious agent. We examined each infectious agent separately and evaluated unadjusted MAR+ vs. MAR- differences in each cytokine and chemokine levels using exact Wilcoxon rank-sum tests.

For each analysis, we used false discovery rate (FDR) correction for multiple comparisons to help mitigate the risk of Type I error. We also present the raw *p*-values to provide initial insights into potential associations or differences without adjustments.

Summaries of maternal cytokines, including the mean values and upper and lower quartiles for MAR+ and MAR- mothers and for MAR+ and MAR- mothers in each IgG reactivity group, are shown in Supplementary Tables 1-8.

Results

Differences in IgG reactivity based on MAR AB status

Upon initial assessment of IgG reactivity to infectious agents based on MAR AB status, we identified a higher percentage of MAR + mothers that had reactivity to CRP, EBV, HSV, and Influenza-A than MAR- mothers. Additionally, MAR+ mothers had significantly higher mean toxoplasmosis IgG levels than MAR- mothers (Table 1).

Cytokine and chemokine profiles in MAR+ and MAR- mothers

We first wanted to determine if, in this sample population, there were differences between the MAR+ and MAR- mothers irrespective of IgG reactivity to any of the infectious agents. When comparing these two groups, we found that MAR+ mothers had higher pro-inflammatory cytokine interferon-gamma levels (IFNγ) levels (Table 2). However, this result did not survive multiple comparison adjustments.

Cytokine and chemokine profiles in MAR+ and MAR- mothers with IgG reactivity to infectious agents

We next wanted to determine if, in the mothers who had IgG antibodies to either CMV, EBV, HSV, Flu-A, TOXO, VZV, or had positive CRP reactivity, there was a difference in the cytokines/chemokines levels in those that were MAR+ compared to those who were MAR-. To do so, we compared only the MAR+ and MAR- mothers who had positive reactivity to each agent (Table 3).

Overall, MAR+ mothers had higher levels of cytokines and chemokines in the presence of reactivity to pathogenic agents. Eotaxin (CCL11) was significantly higher in MAR+ mothers compared to MAR- mothers in the presence of reactivity to CMV, Flu-A, and CRP. IFNγ was significantly higher in MAR+ mothers versus MAR- mothers in the presence of reactivity to EBV,

TABLE 1 Demographic information on study participants who were a subset of mothers from the original Early Markers for Autism (EMA) study.

Characteristic	MAR+ (n=37)	MAR- (n=37)	*p*-value[a]
Maternal Birth Country, n (%)			1.00
US	6 (16%)	6 (16%)	
Mexico	13 (35%)	13 (35%)	
Other	18 (49%)	18 (49%)	
Maternal Race, n (%)			0.93
Caucasian	22 (60%)	22 (60%)	
Asian	10 (27%)	9 (24%)	
Other	5 (13%)	6 (16)	
Maternal Ethnicity, n (%)			1.00
Hispanic	11 (30%)	11 (30%)	
Non-Hispanic	26 (70%)	26 (70%)	
Maternal Age (years), mean (SD)	29.2 (5.3)	29.7 (6.3)	0.95
Maternal Weight at Blood Draw (lbs), mean (SD)	156.8 (45.9)	149.4 (39.6)	0.62
Gestational Age at Blood Draw (days), mean (SD)	117.3 (8.0)	119.3 (8.8)	0.35
IgG Value, mean (SD)			
Cytomegalovirus[b]	0.81 (0.49)	0.65 (0.55)	0.15
Epstein-Barr Virus[c]	0.41 (0.25)	0.37 (0.28)	0.18
Herpes Simplex Virus	2.11 (1.23)	1.75 (1.33)	0.17
Influenza A[c]	1.04 (0.33)	0.88 (0.32)	0.054
Varicella-Zoster Virus	1.94 (0.49)	1.87 (0.63)	0.80
Toxoplasmosis[d]	0.29 (0.49)	0.22 (0.35)	**0.047**
C-Reactive Protein[c]	1.30 (0.89)	1.43 (0.82)	0.31

MAR+, mothers with MAR-autism specific patterns of autoantibodies; MAR-, mothers without autoantibodies to any of our tested antigens; SD, standard deviation.
[a]Group differences were assessed using chi-square tests for categorical variables and exact Wilcoxon rank-sum test for continuous variables.
Data missing for: -; [b]2 mothers in the MAR- group; [c]1 mother in the MAR- group; [d]1 mother in the MAR+ group and 2 in MAR-.
Bolding indicates IgG values for which the group differences significantly differed from 0 (p<0.05 without correcting for multiple comparisons).

Flu-A, and HSV. MAR+ mothers who were reactive to Flu-A and CRP also had significantly higher levels of the T-cell-stimulating cytokine IL-2 than MAR- mothers. In addition, MAR+ mothers with reactivity to EBV had significantly higher levels of the T-helper type II (Th2) cytokine IL-13 compared to MAR- mothers with EBV reactivity. There were no statistically significant differences between MAR+ and MAR- mothers with reactivity to VZV. Due to the small sample size (n=3 per group), differences between MAR+ and MAR- mothers with reactivity to toxoplasmosis were not assessed. When we adjusted for maternal race and ethnicity, MAR+ mothers with reactivity to EBV showed significantly higher levels of eotaxin (p=0.007), MAR+ mothers with reactivity to VZV had higher IL-1Ra (p=0.03), and MAR+ mothers with reactivity to CRP had higher IL-12p40 (p=0.04) compared to MAR- mothers. After controlling for multiple comparisons, only IFNγ remained significantly different (FDR adjusted p=0.04) between MAR+ and MAR- who also had reactivity to EBV.

TABLE 2 Adjusted cytokine and chemokine differences between MAR+ and MAR- mothers.

Cytokine/Chemokine	MAR+ versus MAR-		
	Estimate	SE	*p*-value
Eotaxin	0.35	0.39	0.38
GM-CSF	0.34	0.62	0.59
IFNγ	0.79	0.35	**0.03**
IL-2	0.56	0.40	0.16
IL-4	-0.12	0.19	0.56
IL-6	0.62	0.54	0.25
IL-7	-0.05	0.30	0.87
IL-8	0.23	0.40	0.56
IL-10	0.43	0.47	0.36
IL-13	0.20	0.54	0.71
IL-17	0.30	0.57	0.60
IL-12p40	0.56	0.50	0.27
IL-12p70	0.36	0.38	0.35
IL-1α	0.49	0.48	0.32
IL-1β	0.63	0.58	0.28
IL-1Ra	0.59	0.32	0.07
IP-10	0.02	0.19	0.93
MCP-1	0.05	0.20	0.82
MIP-1α	0.14	0.60	0.81
MIP-1β	0.43	0.36	0.24
TNFα	0.27	0.27	0.33
sIL-2Ra	0.12	0.33	0.73

MAR+, mothers with MAR-autism specific patterns of autoantibodies; MAR-, mothers without autoantibodies to any of our tested antigens; SE, standard error.
[a,b]Estimates represent adjusted differences between cytokines/chemokines concentrations between MAR+ mothers (n=37) and MAR-mothers (n=37) from multiple linear regression models fitted to natural log-transformed neonatal cytokine/chemokine concentrations. The models included a term for maternal MAR status and were adjusted for maternal race and ethnicity.
Bolding indicates cytokines/chemokines for which the adjusted group differences significantly differed from 0 (p<0.05 without correcting for multiple comparisons).

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TABLE 3 Cytokine and chemokine differences between MAR+ versus MAR- mothers who had positive reactivity to CMV, EBV, Flu-A, VZV, HSV, or a positive CRP test.

Cytokine/ Chemokine	CMV Positive MAR+ n=12 MAR- n=10			EBV Positive MAR+ n=9 MAR- n=7			Flu-A Positive MAR+ n=14 MAR- n=7			VZV Positive MAR+ n=18 MAR- n=18			HSV Positive MAR+ n=26 MAR- n=21			CRP Positive MAR+ n=10 MAR- n=12		
	Est.	SE	*p*	Est.	SE	*p*	Est	SE	*p*	Est.	SE	*p*	Est.	SE	*p*	Est.	SE	*p*
Eotaxin	1.50	0.57	**0.02**	0.31	0.65	0.64	2.13	0.67	**0.005**	0.22	0.51	0.66	0.03	0.52	0.96	1.69	0.74	**0.03**
GM-CSF	0.83	1.45	0.57	0.52	1.49	0.73	0.99	1.21	0.43	0.55	0.91	0.55	0.17	0.80	0.84	0.65	1.34	0.63
IFNγ	0.35	0.43	0.42	1.16	0.30	**0.002***	1.54	0.64	**0.03**	0.17	0.50	0.74	1.08	0.42	**0.01**	0.40	0.72	0.58
IL-2	0.85	0.67	0.22	-0.13	0.63	0.84	1.84	0.88	**0.05**	0.52	0.65	0.42	0.55	0.52	0.30	1.88	0.74	**0.02**
IL-4	-0.02	0.29	0.94	-0.11	0.43	0.80	0.35	0.33	0.30	-0.09	0.24	0.73	-0.20	0.23	0.37	0.04	0.33	0.90
IL-6	-0.30	1.02	0.77	1.40	1.25	0.28	0.24	1.07	0.82	0.15	0.73	0.84	0.67	0.77	0.39	0.05	0.96	0.96
IL-7	0.28	0.42	0.51	0.18	0.61	0.77	0.15	0.48	0.75	-0.22	0.50	0.66	-0.03	0.43	0.95	0.35	0.56	0.54
IL-8	-0.07	0.52	0.89	0.64	0.97	0.52	-0.09	0.84	0.91	-0.63	0.54	0.25	0.48	0.53	0.36	0.46	0.58	0.44
IL-10	0.66	1.21	0.59	0.75	1.36	0.59	0.40	0.95	0.68	0.29	0.63	0.65	0.34	0.64	0.60	0.01	0.76	0.99
IL-13	0.45	1.00	0.66	2.49	1.03	**0.03**	0.20	0.98	0.84	-0.10	0.74	0.90	-0.19	0.66	0.77	1.10	1.02	0.29
IL-17	0.54	0.95	0.58	0.78	1.17	0.51	2.22	1.08	0.055	-0.06	0.80	0.94	0.31	0.69	0.65	0.32	1.06	0.77
IL-12p40	0.77	1.01	0.46	0.90	0.79	0.28	0.52	1.07	0.63	0.15	0.76	0.85	0.43	0.67	0.53	2.08	1.03	0.06
IL-12p70	-0.09	0.73	0.91	0.06	0.68	0.94	0.51	0.91	0.58	0.39	0.62	0.54	0.06	0.50	0.91	0.76	0.85	0.38
IL-1α	0.43	0.84	0.62	0.86	0.99	0.40	0.31	0.79	0.70	-0.13	0.63	0.84	0.08	0.58	0.89	0.66	0.88	0.47
IL-1β	0.20	1.23	0.88	0.43	1.42	0.77	0.35	1.22	0.77	0.19	0.76	0.80	0.95	0.86	0.28	-0.06	0.91	0.95
IL-1Ra	0.74	0.62	0.25	0.81	0.76	0.30	0.32	0.55	0.57	0.87	0.44	0.06	0.55	0.43	0.20	0.74	0.54	0.18
IP-10	0.12	0.32	0.72	-0.05	0.23	0.83	-0.19	0.47	0.69	0.22	0.32	0.50	0.12	0.25	0.63	0.35	0.41	0.39
MCP-1	0.10	0.42	0.82	0.19	0.48	0.69	0.09	0.41	0.83	-0.01	0.29	0.97	0.03	0.30	0.93	-0.46	0.32	0.17
MIP-1α	-0.11	1.13	0.92	0.50	1.62	0.76	0.86	1.11	0.45	0.15	0.77	0.85	0.40	0.86	0.64	0.27	0.95	0.78
MIP-1β	0.05	0.75	0.95	0.31	0.92	0.74	1.16	0.67	0.10	0.59	0.42	0.16	0.57	0.53	0.29	0.79	0.45	0.09
TNFα	0.09	0.56	0.87	0.06	0.72	0.93	0.46	0.45	0.32	0.15	0.34	0.66	0.16	0.41	0.70	-0.13	0.41	0.75
sIL-2RA	-0.03	0.91	0.97	0.31	1.01	0.76	0.12	0.79	0.88	-0.19	0.57	0.74	0.32	0.41	0.44	0.37	0.45	0.42

Bolding indicates significant cytokines/chemokines for which the group differences significantly differed from 0 ($p<0.05$ without correcting for multiple comparisons).
MAR+, mothers with MAR-autism specific patterns of autoantibodies; MAR-, mothers without autoantibodies to any of our tested antigens; CMV, Cytomegalovirus; EBV, Epstein-Barr virus; Flu-A, Influenza A virus; VZV, Varicella-Zoster virus; HSV, Herpes Simplex Virus; CRP, C-reactive protein; SE, standard error.
*Group differences remained significant after correcting for multiple comparisons using false discovery rate.

Discussion

Maternal ABs to CRMP1/2, STIP1, LDHA/B, Y-BOX1, GDA, and NSE have been linked to a subtype of autism known as MAR autism (6–8). More specifically, certain MAR-AB patterns have been shown to be highly associated with an autism outcome (13, 14). It is unclear whether some women are susceptible to the production of these ABs due to underlying immune dysregulation or if their autoimmune status is inherently associated with changes in other arms of the immune system, such as cytokine and chemokine production. In addition to autoantibodies, excessive activation of the maternal immune system during pregnancy has frequently been associated with an increased risk of offspring development of autism (2, 3). Thus, understanding the immune status in the context of infection in mothers with MAR+ ABs provides valuable insight into the immune dysregulation that could underlie the loss of self-tolerance, resulting in the production of MAR-ABs.

Understanding the maternal gestational immune status in the context of infection for mothers with MAR+ ABs provides valuable insight into the immune dysregulation that could underlie the loss of self-tolerance. Herein, we used this strategy to examine a subpopulation of participants enrolled in the EMA study to determine if MAR+ mothers had changes in their cytokine/chemokine profile when they also had IgG reactivity to infectious agents or tested positive for C-reactive protein when compared to those mothers who had the same infection status but were MAR-.

Regardless of IgG reactivity, MAR+ mothers had higher levels of the proinflammatory cytokine IFNγ, suggesting an underlying inflammatory state in these mothers. Co-stimulatory activity, which the presence of inflammatory cytokines can induce, is necessary for the adaptive immune system to respond to antigens and, therefore,

generate antibodies. In the absence of co-stimulation, immune tolerance is induced (24). Thus, an underlying inflammatory state could predispose MAR+ mothers to their autoimmune state.

When we considered MAR+ mothers with IgG reactivity to different infectious agents, including EBV, HSV, and Flu-A, we noted an increase in serum levels of several proinflammatory cytokines, including IFNγ. For example, MAR+ mothers with IgG reactivity to CMV and Flu-A also had increased levels of the proinflammatory chemokine eotaxin. While important for recruiting eosinophils and T cells to sites of infection, excess eotaxin has been associated with allergic and autoimmune diseases, suggesting negative implications, such as increased risk for autoimmune-related health consequences, for MAR+ mothers (25, 26). Further, higher levels of neonatal eotaxin in newborn bloodspots have been previously associated with an increased risk of autism (18). Interestingly, IL-13 was higher in MAR+ mothers with IgG reactivity for EBV. IL-13 functions to promote proliferation of B cells and regulate eosinophilic inflammation. However, previous studies have shown that IL-13 production is induced in B cells early during EBV infection via the EBV protein Zta, contributing to the proliferation of EBV-infected B cells (27). This could suggest that MAR+ mothers may have more dramatic effects of EBV-associated immune dysregulation. In addition to their AB status, higher levels of inflammation in mothers during gestation can also have lasting impacts on their offspring. Therefore, we also assessed differences in CRP reactivity between MAR+ and MAR- mothers. MAR+ mothers, who had elevated CRP levels, which is used as a marker of inflammation, had significantly higher levels of the proinflammatory Th-1 cytokine IL-2 and eotaxin than CRP+ MAR- mothers.

Taken together, these data indicate that MAR+ mothers are susceptible to higher levels of inflammation during the response to infectious agents and in the absence of infection. Additionally, dysregulation in key cytokines/chemokines in the context of infection suggests a suboptimal immune response, which may predispose MAR+ mothers to a loss of self-tolerance and reactivity to MAR-ABs.

Our analyses should be considered in light of several study limitations. First, as we only measured the mothers' maternal cytokines/chemokines and IgG status at one mid-gestational timepoint, we do not have insight into how the cytokines/chemokines may have changed throughout pregnancy. Second, the infectious agents against which we assessed reactivity can remain latent in the body. Therefore, IgG reactivity for these agents can only indicate infection at some time but will not indicate if there is an active infection during pregnancy. In addition, as pregnancy is a unique immune state in which particular responses may be dampened, IgG levels during pregnancy could differ from pre- to post-pregnancy. However, this is less likely given that the immune response during pregnancy skews toward antibody production and away from a cellular response (28). Third, as this analysis only included 37 MAR + and 37 MAR- mothers and only some had IgG reactivity to the different infectious agents, our sample size in these comparisons was very small. Due to the modest sample size in our study, the statistical power was limited, and we elected to present both raw *p*-values and the results after corrections for multiple comparisons, offering a comprehensive view of the statistical analysis. As a result, it is important to exercise caution when interpreting *p*-values that are not adjusted for multiple comparisons, as they may lead to an increased risk of Type I errors. Thus, our findings in this preliminary study should be regarded as tentative. However, given the potential for broader clinical implications, we hope they suggest possible directions for future targeted research studies. A larger study would likely yield more robust results and be adequately powered to examine associations in the presence of multiple confounders and covariates. Future studies to address how MAR AB production is related to the response to active infection in a larger sample cohort will help to address the overall immune state of mothers possessing these autism-specific ABs. Finally, as we only considered mothers of children who were later diagnosed with autism, we cannot assess how the maternal levels of cytokines/chemokines in the context of IgG reactivity to infectious agents impacts offspring neurodevelopment. This latter aspect will be important to evaluate in future studies. This study provides an exciting hypothesis-generating set of preliminary data that will contribute to future studies addressing the interactions between autoimmunity and the impacts of infection during pregnancy.

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 humans were approved by Institutional Review Board at Kaiser Permanente, the State Committee for the Protection of Human Subjects, and the Institutional Review Board at University of California, Davis. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because we used only banked samples that were exempt from informed consent.

Author contributions

JM: Conceptualization, Formal analysis, Writing – original draft. LC: Conceptualization, Funding acquisition, Investigation, Resources, Writing – review & editing. AI: Formal analysis, Validation, Writing – review & editing. CY: Data curation, Methodology, Writing – review & editing. PA: Writing – review & editing. RY: Data curation, Methodology, Writing – review & editing, Resources. JV: Conceptualization, Data curation, Funding acquisition, Resources, Writing – review & editing.

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Conflict of interest

Author JW has patents issued for the ELISA technology used to screen for MAR ABs and has founded a UC Davis startup company to develop the technology for commercial use.

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1348092/full#supplementary-material

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Head circumference growth in children with Autism Spectrum Disorder: trend and clinical correlates in the first five years of life

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Background: Macrocephaly is described in almost 15% of children with Autism Spectrum Disorder (ASD). Relationships between head growth trajectories and clinical findings in ASD children show a high degree of variability, highlighting the complex heterogeneity of the disorder.

Objectives: The aim of this study was to measure differences of the early growth trajectory of head circumference (HC) in children with ASD and macrocephaly compared to ASD normocephalic children, examining clinical correlates in the two groups of patients.

Methods: HC data were collected from birth to 5 years of age in a sample of children with a confirmed diagnosis of ASD. Participants were classified into two groups: ASD macrocephaly (ASD-M, Z-scores ≥1.88 in at least two consecutive HC measurements), and ASD non-macrocephaly (ASD-N). Based on the distribution of HC measurements (Z-scores), five age groups were identified for the longitudinal study. Developmental and behavioral characteristics of the ASD-M children compared to the ASD-N group were compared by using standardized scores.

Results: 20,8% of the children sample met criteria for macrocephaly. HC values became indicative of macrocephaly in the ASD-M group at the age range from 1 to 6 months, and persisted thereafter throughout the first five years of age. ASD-M children showed significantly higher developmental quotients of Griffiths III B and D subscales compared to ASD-N group. No significant differences in the severity of ASD symptoms assessed by ADOS-2 were observed between ASD-M and ASD-N groups.

Conclusion: In this study HC size from birth to 5 years links to accelerated HC growth rate as early as the first 6 months of age in children with ASD and macrocephaly, preceding the onset and diagnosis of ASD. We found that in early childhood, children with ASD-M may exhibit some advantages in language and social communication and emotional skills without differences in autism severity,

when compared with age-matched normocephalic ASD children. Longitudinal analyses are required to catch-up prospectively possible relationships between head size as proxy measure of brain development and neuro-developmental and behavioral features in children with ASD.

KEYWORDS

Autism Spectrum Disorder, macrocephaly, head circumference, head growth trajectory, neurodevelopment, endophenotype

1 Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by social communication impairment and restricted, repetitive and stereotyped patterns of behaviors, interests or activities (1). The rising global prevalence rate of ASD (2) and the complexity of the ASD etiology, clinical features and developmental trajectories, have prompted intensive research to identify specific biological markers and endophenotypes for earlier diagnosis and treatment (3–5). Accelerated head growth associated with brain enlargement is a commonly reported biological feature of ASD, affecting 14%–34% of patients (4, 6–10). Head circumference (HC) is an accurate, rapid, and inexpensive tool used by research as a proxy measure of brain growth in the assessment of children with ASD (11).

Macrocephaly (or macrocrania) is clinically defined as an abnormally large head with an occipitofrontal circumference (OFC) greater than the 97th percentile.

A higher frequency of head overgrowth has been reported in children with ASD compared to typically developing children (TD) at varying age ranges, emphasizing a certain variability HC with respect to gender and age in ASD subjects (5). The abnormal head growth trajectory starts early in postnatal life and continues until at least 5 years of age (12). Early cerebral overgrowth in children with ASD may be followed by volumetric regression throughout the childhood (13). However, a recent longitudinal study showed the persistence of brain enlargement from early to late childhood in a subset of patients with ASD compared to age and sex-matched control subjects. This finding was correlated with a greater increase in white matter volume and a slower decrease in grey matter volume over time in ASD patients (14). Neuroimaging studies described a generalized enlargement of frontal, temporal and parietal lobes, involving both gray and white matter (15) or mainly limited to the frontal lobe gray matter (13, 16).

Altogether, previous findings have generally been interpreted as reflecting excessive neurogenesis/neuronal proliferation and inappropriate synaptic pruning, which may underlie the increased brain size in patient subsets with ASD (17, 18). These neuropathological abnormalities would also result in cortical surface area overgrowth (19), especially in cortical areas related to sensory information processing (middle occipital cortex) in children at high risk for ASD than in those at low or no risk for ASD. Thus over-expansion of cortical surface area and related head size increase may represent an early event in a cascade leading to brain overgrowth and emerging ASD symptoms (20), supporting identification of children at risk of ASD with or without a history of regression (8, 10, 21).

The timing of HC increase in children with ASD and its relationship to the appearance of behavioral symptoms is unclear so far. Overall, the results of studies are inconsistent regarding age, gender and intelligence quotient (IQ) effects on the HC growth rate and the relationship of macrocephaly to the clinical features of ASD and their severity (8, 22–24).

Clinical variables have been explored in order to identify meaningful subgroups that may share common genetic underpinning (8). Macrocephaly has been described as a clinical indicator of genetic subtypes of ASD. Historically, mutations in the gene phosphatase and tensin homolog (PTEN) were detected in a subset of individuals with large head and ASD (25).

Dysregulation of brain developmental processes due to multiple genomic variations in genes involved in cell proliferation (e.g., PTEN, mTOR pathway), chromatin remodeling (e.g., chromodomain helicase DNA binding protein 8, CHD8), protein transcription and translation and biological adhesion (WNT pathway) has been associated with ASD and macrocephaly (26–30), in order to provide elucidation of genotype–phenotype correlations and new insights into different subtypes of ASD. Approximately 17–20% of children with ASD and macrocephaly have pathogenic PTEN mutations (27) showing a distinct neurobehavioral phenotype with cognitive impairment extended to adaptive behavior, sensory deficits, repetitive behavior and decreased memory function (31–33).

In the effort to correlate different patterns of brain growth during development with the heterogeneous neurodevelopment trajectories of ASD in different subsets of affected individuals, the need for longitudinal analyses has been highlighted to carry out meaningful phenotyping (12, 22).

The present study was undertaken to assess longitudinal changes in head circumference by cross-sectional analyses in a

sample of ASD children, with the aim of detecting significant differences in the growth trajectory of head circumference in children with macrocephaly compared to normocephalic children, in the first five years of life. We foresee that this study may identify a possible endophenotype of ASD associated with macrocephaly examining clinical correlates in the two groups of patients.

2 Materials and methods

2.1 Study design

This cross-sectional study was performed in two phases. In the first one, HC measurements were collected from birth to 5 years of age in a sample of children with ASD consecutively observed during the study period. In the second phase, we compared ASD children with macrocephaly (ASD-M) and normocephalic children (ASD-N) using neurodevelopmental and neurobehavioral assessment tools.

Data used for this study were collected from the clinical files and obtained as part of clinical protocols for patients with ASD. The study was approved by the local Ethics Committee of Catania University Hospital. All procedures performed in the present study were in accordance with the 1964 Declaration of Helsinki and its later amendments (2013). Written informed consent was obtained from both parents of each participant.

2.1.1 Participants and data collection procedure

At study entry, 79 subjects were recruited, between October 2022 and July 2023, from a clinical population with ASD, diagnosed at the Child Neurology and Psychiatry Unit, Department of Clinical and Experimental Medicine, University of Catania. Longitudinal auxological data (HC, height and weight) were collected from birth to 5 years of age using medical records from the Child Neurology and Psychiatry Unit. Data on gestational age at birth were also collected.

The Inclusion criteria were as follows: 1) a clinical diagnosis of ASD according to DSM-5 criteria and all testing measures, including the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2); 2) age at study time ≤ 5 years; 3) at least 3 HC measurements in the time period between 0 and 5 years of age.

Exclusion criteria included: 1) general overgrowth (head circumference, height and weight >97th percentile/>2 standard deviations, SD); 2) presence of microcephaly (head circumference <3rd percentile/<-2 SD); 3) lack of repeated measures of HC in the first five years of age.

All HC data refer to measurements obtained manually, using a non-stretchable tape measure placed over the maximum fronto-occipital head circumference.

HC, body length and weight measures at birth were converted into percentiles using the Italian Neonatal Study (INeS) charts, promoted by the Italian Society of Neonatology.

The Growth4 Software was used to calculate percentiles and SD values for each available measurement from the postnatal period to 5 years of age, according to the World Health Organization (WHO) growth charts.

HC measurements were normalized for sex and age by conversion to Z-scores based on the WHO mean values for healthy infants (World Health Organization 2006, Child Growth Standards).

Macrocephaly was defined as a HC greater than the 97th percentile, that is more than 1.88 SD above the normative mean (z score > 1.88) (8, 24, 34).

Participants were classified into two groups: ASD macrocephaly (ASD-M, Z-scores ≥1.88 in at least two consecutive HC measurements), and ASD non-macrocephaly (ASD-N).

Based on the distribution of HC measurements (Z-scores) in the study sample, five age ranges were identified: birth, 1–6 months, 8–18 months, 20–32 months, 33–60 months. In each age range, ASD-M and ASD-N patients were matched for age and sex.

All participants underwent neuropsychiatric assessment and clinical data were compared between the two study groups ASD-M/ASD-N. The clinical diagnosis of ASD was confirmed using the Autism Diagnostic Observation Schedule, second edition (ADOS-2). The Griffiths Scales of Childhood Development - 3rd edition (Griffiths III) was administered in order to assess the psychomotor development.

2.2 Standardized measures

Symptoms of ASD were established using the gold-standard tools for ASD diagnosis: Autism Diagnostic Interview-Revised (ADI-R) (35) and the Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2) (36). The ADOS-2 is a semi-structured, standardized assessment of core deficits in ASD. It contains five modules that are differentiated by children's developmental and language levels. In the present study participants completed the Toddler Module (designed specifically for children 12–30 months old with limited language), the Module 1 (used for children aged from 31 months who do not consistently use phrase speech) or the Module 2 in a minority of children using phrase speech, but who were not verbally fluent. To allow comparisons among different modules, ADOS-2 scores (total score, Social Affect, SA, and Restricted and Repetitive Behaviour, RRB, scores) were converted to respective calibrated severity scores (CSS 1–10 indicating absence to severe autism) (37–39).

An overall measure of children's psychomotor development was provided by the Griffiths III assessment across five subscales (40). Subscale A (Foundations of Learning) assesses the ability of learning; subscale B (Language and Communication) evaluates the development of both receptive and expressive language and social communication abilities; subscale C (Eye and Hand Coordination) assesses visual perception and fine motor skills; subscale D (Personal-Social-Emotional) evaluates child's ability to adapt, personal autonomy and early social and emotional development through items measuring imitation, joint attention, emotional recognition and empathy; subscale E (Gross Motor domains) refers to the child's early development of postural control, gross body coordination, balance and visual-spatial coordination. Subscale raw scores and general development raw

scores are calculated to determine the Developmental Age, Scaled Score and Development Quotient, according to the norm tables.

2.3 Statistical analysis

In the first phase of the study, the one-way ANOVA statistical test was initially applied to compare ages (months) as means (M) and standard deviations (SD) in the five subgroups (age ranges). Analysis of variance (ANOVA) was then performed to find out possible significant differences on HC measurements (z-scores) between the two groups (ASD-M/ASD-N) in each age range.

In the second phase of the study, we used the independent samples t-test to compare the mean scores on each clinical assessment measure between the two groups (ASD-M/ASD-N).

The statistical significance level α was established at 0.05. All statistical tests were performed by using SPSS version 27 (SPSS, Inc., Chicago, IL, USA, IBM, Somers, NY, USA).

3 Results

3.1 Comparison of HC growth in children with ASD in the period from 0 to 5 years of age

Out of an initial sample of 79 subjects with ASD, thirty-four patients were excluded due to the unavailability of repeated HC measurement during the age 0–5 years. Forty-five children with a confirmed diagnosis of ASD (male to female ratio = 5:1; mean age: 4.4 ± 1.1) were included in two groups (ASD-M/ASD-N) based on HC measurements (Z-score). Ten children (20,8%) met criteria for macrocephaly (Z-scores ≥1.88). Routine laboratory analyses, extended metabolic screening and array-CGH analyses yielded normal results. Two patients were diagnosed with germline PTEN mutations (c.697C>T/p.Arg233 and c.62T>G/pPhe21Cys, respectively).

Demographic characteristics in ASD-M/ASD-N groups are reported in Table 1.

TABLE 1 Demographic characteristics in ASD-M/ASD-N groups and in the total sample.

Participants	ASD-M *(N = 10)*	ASD-N *(N = 35)*	Total Sample *(N = 45)*
Years of age (mean ± SD)	4.2 ± 0.8	4.5 ± 1.1	4.4 ± 1.1
Males	7 (70%)	31 (88.6%)	38 (84.4%)
Females	3 (30%)	4 (11.4%)	7 (15.6%)
Pre-term birth	0	3 (8.6%)	3 (6.7%)
At-term birth	10 (100%)	32 (91.4%)	42 (93.3%)

ASD-M, macrocephalic group; ASD-N, normocephalic group; N, number of participants; SD, standard deviation.

At each study interval, the mean age was not significantly different between the two groups ASD-M/ASD-N (birth: $F(37)=2.28$, $p=0.14$; 1–6 months: $F(17)=2.74$, $p=0.12$; 8–18 months: $F(18)=0.92$, $p=0.35$; 20–32 months: $F(23)=2.82$, $p=0.11$; 33–60 months: $F(28)=0.16$, $p=0.69$).

HC Z-score data in the ASD-M group compared to the ASD-N group at each age range are reported in Table 2. At birth HC measurements were in the normal range in both groups. However, mean Z-scores were significantly higher in the ASD-M group than in the ASD-N group ($F=10.2$, $p=0.004$).

We found a significant increase of HC in the ASD-M group compared to the ASD-N group at each age interval (Table 2) suggesting that ASD-M patients showed an excessive HC growth in the study period than ASD-N subjects (Figure 1).

3.2 Neurobehavioral phenotype comparison between ASD-M and ASD-N children

In the second phase of the study, we sought to determine whether and to what extent the developmental and behavioral characteristics of the ASD-M group differed from the ASD-N group, by comparing the mean scores obtained on each clinical assessment tool (Table 3). At the time of assessment, chronological age (CA) (ASD-M mean age: 29.7 ± 9.4 months; ASD-N mean age: 34.6 ± 9.3 months) was not significantly different between the two groups (t=1.4, p=0.08), ruling out that possible clinical differences might be related to different CA in the group comparison.

We first investigated about differences in the severity of autism symptoms by using the ADOS-2 total CSS. No significant differences were found comparing ASD-M children with ASD-N children (SA CSS: $t=0.3$, $p=0.76$; RRB CSS: $t=0.8$, $p=0.81$; CSS TOT: $t=0.2$, $p=0.85$).

As to the developmental profile on the Griffith III scales, the General Development Quotient (GDQ) was below the normal range

TABLE 2 Head circumference z-scores data in ASD-M group compared to ASD-N group at each age interval.

Age (months)	Study groups	Z-score means (± SD)	*F*	*p*
Birth	ASD-M	0.9 (± 0.4)	10.2	0.004*
	ASD-N	-0.02 (± 0.7)		
1–6	ASD-M	1.6 (± 1.3)	8.7	0.009*
	ASD-N	0.2 (± 0.8)		
8–18	ASD-M	1.5 (± 0.8)	5.1	0.036*
	ASD-N	0.6 (± 0.8)		
20–32	ASD-M	2.1 (± 0.7)	21.3	<0.0001*
	ASD-N	0.4 (± 0.9)		
33–60	ASD-M	2.2 (± 0.3)	29.6	<0.0001*
	ASD-N	0.6 (± 0.7)		

ASD-M, macrocephalic group; ASD-N, normocephalic group; N, number of participants; SD, standard deviation.
*$p<0.05$, significant difference.

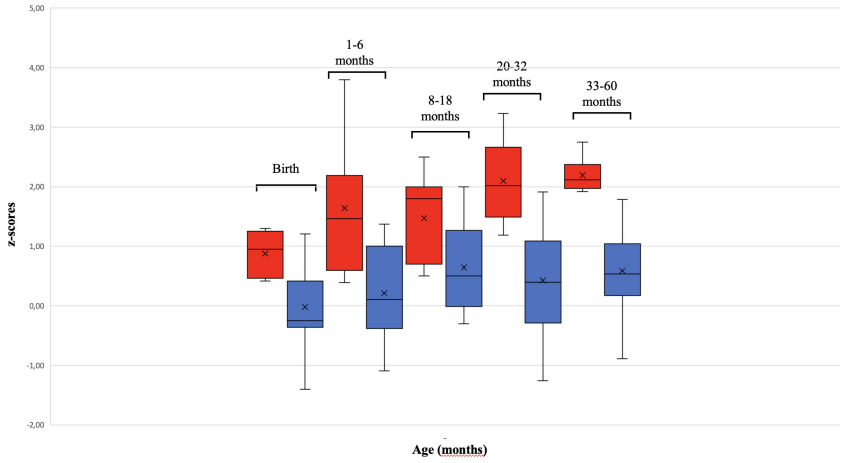

FIGURE 1
Differences in HC growth between ASD-M and ASD-N children from birth to 60 months. The box plot shows that children with Autism Spectrum Disorder and macrocephaly (ASD-M, red) had a more rapid HC growth than ASD normocephalic subjects (ASD-N, blue). The two patients harboring PTEN mutations (outliers) were not included in the HC growth analysis.

in both groups, but was significantly higher in ASD-M children (mean GDQ = 68.2± 18.11) than in the ASD-N group (mean GDQ = 57.03 ± 12.77) (t= 2.16, p=0.02).

Then, development quotients (DQ) on each subscale of the Griffiths III were compared between the ASD-M and ASD-N groups. No significant differences were found for the subscale A (t=0.9, p=0.38), subscale C (t=1.1, p=0.27) and subscale E DQ (t=1.1, p=0.28). ASD-M children scored significantly higher on the subscale B (t=3.4, p=0.0016) and subscale D (t=2.2, p=0.032) than ASD-N children (Table 3).

4 Discussion

The present study aimed to investigate the growth trajectory of HC in a sample of ASD children in the first five years of life. We

TABLE 3 Comparison of the Griffiths III and ADOS-2 scores between ASD-M and ASD-N study groups.

Clinical assessment		Group	Mean (± SD)	t	p
Griffiths III	DQA	ASD-M	77.1 (± 22.5)	0.9	0.38
		ASD-N	70.6 (± 19)		
	DQB	ASD-M	65 (± 17.1)	3.4	0.0016*
		ASD-N	51.9 (± 8.1)		
	DQC	ASD-M	74.3 (± 20.2)	1.1	0.27
		ASD-N	67 (± 17)		
	DQD	ASD-M	70.4 (± 16.7)	2.2	0.032*
		ASD-N	58.4 (± 14.1)		
	DQE	ASD-M	84.6 (± 20.1)	1.1	0.28
		ASD-N	76.5 (± 19.7)		
ADOS-2	SA CSS	ASD-M	7.3 (± 2.3)	0.1	0.45
		ASD-N	7.2 (± 2.5)		
	RRB CSS	ASD-M	6.9 (± 1.9)	0.8	0.22
		ASD-N	6.2 (± 2.7)		
	CSS TOT	ASD-M	7.2 (± 2.4)	1.1	1.14
		ASD-N	7.0 (± 2.3)		

ASD-M, macrocephalic group; ASD-N, normocephalic group; SD, standard deviation; DQA, Subscale A Development Quotient; DQB, subscale B Development Quotient; DQC, subscale C Development Quotient; DQD, subscale D Development Quotient. DQE, subscale E Development Quotient; ADOS-2, Autism Diagnostic Observation Schedule; SA CSS, Social Affect Calibrated Severity Score; RRB CSS, Repetitive and Restrictive Behavior Calibrated Severity Scores; CSS TOT, Calibrated Severity Total Score.

sought to determine whether macrocephaly was correlated with other clinical characteristics in ASD children profiling a possible endophenotype associated with macrocephaly.

Macrocephaly was consistently reported in children with ASD than in neurotypical peers (5, 8, 10, 41), with an overall prevalence rate of 15.7% vs 3%, respectively (4).

In this study 20.8% of the total sample of ASD children developed macrocephaly during the first 5 years of life, a finding consistent with rates reported in the ASD literature (11, 34, 42, 43).

We found that ASD patients with macrocephaly (ASD-M group) presented a significantly larger HC size at birth compared to normocephalic ASD children (ASD-N group), although birth Z-scores were in the normal range in both groups. This result might indicate a possible prenatal brain overgrowth, consistent with observed late-gestational fetal HC overgrowth among children with ASD (44, 45). Most studies reported normal HC at birth in ASD infants (6, 10, 12, 46–48), while a few studies described smaller HC at birth with an overt increase in later months in ASD infants compared to neurotypical children (11, 23).

In the current ASD-M sample, head circumference was found to be consistent with the definition of macrocephaly from the first six months of life ($F=7.7$, $p=0.014$) and persisted thereafter throughout the first five years of age. In line with previous studies, we found that an accelerated HC growth rate is present in the first year of life and precedes the onset and diagnosis in children with autism spectrum disorder (8, 10, 20, 21, 23). Increased rates of head growth in early childhood (13) were mantained until the age of 5 years in children with ASD (12, 46, this study) and were not followed by volumetric regression until at least late childhood (age 11) (14).

Brain size is positively correlated with cognitive function in typically developing individuals, however previous data are inconsistent regarding neurocognitive development in ASD children with macrocephaly (22). Moreover, brain and behavior relationships may develop at different times during development, illustrating the need of longitudinal analyses to achieve meaningful phenotyping. Notably, we found significant differences of ASD-M children compared to the ASD-N group, assessed by the Griffiths III developmental scales.

Increasing evidence suggests the validity of Griffiths III in describing specific developmental profiles in children with ASD. Recently different developmental profiles on the Griffiths III have been detected in children with ASD with respect to children with developmental delay (DD) (49). Griffiths III B and D-subscales, which probe language, social and emotional skills, have been shown to be the most impaired in ASD and the most predictive for ASD risk (49–53). In this regard, we recently developed a novel level-2 ASD screener, the Developmental Autism Early Screening (DAES), by selecting the most predictive Griffiths III B- and D-subscales items for ASD risk in the first three years of age, which may differentiate children with ASD-risk from their peers with DD or with typical development (TD) (53).

In the present study we found that the Griffiths III DQ on the B and D subscale were significantly higher in ASD-M than in ASD-N group. This indicates that at the study time, children with ASD and macrocephaly showed less impairment in language, communication, social and emotional skills compared with age-matched normocephalic ASD children.

An advantage in language development and general IQ measures was reported in ASD patients with macrocephaly (9). Abnormal acceleration of HC in early life was associated with better adaptive functioning and less impairment in social and behavioral domains in macrocephalic children compared to normocephalic children with ASD. This observation led to the hypothesis that the accelerated head growth in early childhood may be a protective reaction in response to pathognomonic neurodevelopmental processes that contribute to ASD (8).

On the other hand, additional studies yielded conflicting results or failed to detect significant differences in the DQ and IQ scores between macrocephalic and normocephalic ASD patients (12, 34, 43). Lower IQ scores might be associated with a history of language and social skills regression in ASD children with macrocephaly (10, 22, 54). In some instances, better non-verbal than verbal performances were correlated with increased head size in ASD patients (41).

These discrepancies in the clinical correlates of HC in ASD may reflect abnormalities in neurodevelopmental trajectories of ASD children whereby different skill domains become increasingly uneven over time (41).

The association between the peculiar neurodevelopmental profile of ASD-M children and the underlying neuroanatomical abnormalities and pathophysiological mechanisms needs to be further investigated. The degree, rate and/or duration of the brain overgrowth may be related to neuroanatomical and clinical outcome of ASD neurophenotypes. An inappropriate synaptic pruning or arborization with increased axon and dendrite number and size produces too many connections in various brain areas (18). The better performance of ASD-M children in language, social and emotional skills might suggest that the brain areas involved in these domains are not directly affected by abnormal growth processes or, alternatively, are more active due to compensatory mechanisms at certain times of neurodevelopment.

Otherwise, we found no significant differences between ASD-M and ASD-N groups in the severity of ASD symptoms assessed by ADOS-2. This result is consistent with other studies that did not identify differences on ADOS (10, 12, 22), ADI-R (24) and CARS (55), used to measure ASD severity in the studied groups of ASD patients with macrocephaly.

There are certain limitations in this study. The sample is relatively small and available measurements of head circumference are not uniform in all considered age ranges. Moreover, we focused on the first 5 years of life. Further investigations are needed to compare the two groups (ASD-M/ASD-N) at older ages, in order to detect differences in head growth and developmental trajectories. A few studies have suggested that the differences between ASD children with macrocephaly and ASD normocephalic children may persist at older ages (7, 56). It is not clear whether a brain size normalization occurs in adolescence: discrepancies between studies might be explained by the age heterogeneity of participants and a selection bias due to the inclusion of more compliant patients with higher IQs in neuroimaging studies (14). Imaging and EEG studies may be

informative to further investigating additional features of the ASD-M endophenotype related to the neuro-behavioral profile. The co-occurrence of temporal EEG abnormalities, regression and macrocephaly has been described in a previous study, in order to define anatomic or pathophysiologic subtypes of ASD, highlighting the crucial role of the temporal region in processing language and social stimuli (57).

5 Conclusions

Alterations in brain organization and developmental trajectory might be strong biological indicators of ASD subtypes that would be associated with different patterns of behavioral symptoms or co-occurring conditions (22). In this study HC measurements from birth to 5 years links to early accelerated HC growth rate as early as the first 6 months of age in children with ASD and macrocephaly, preceding the onset and diagnosis of ASD. This observation concurs with recent findings illustrating that sub-regional brain fetal measurements at 20 weeks and fetal HC at 28 weeks were positively associated with Q-CHAT scores at 18–20 months of age (45). In addition, we demonstrate that in early childhood, children with ASD-M may exhibit some advantages in language and social communication and emotional skills without differences in autism severity, when compared with age-matched normocephalic ASD children. In this regard, we emphasize the need of longitudinal analyses to catch-up prospectively possible relationships between head size as proxy measure of brain development and neuro-developmental and behavioral features. Prospective investigations in larger samples may well consider including *ad-hoc* genetic and technical investigations to understand the precise nature of the association between accelerated head growth in ASD and the clinical phenotype. This future perspective may increase knowledge about clinical outcome and guide the therapeutic choices.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Comitato Etico Locale Catania 1. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

LaC: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. LuC: Conceptualization, Data curation, Methodology, Writing – original draft. LR: Conceptualization, Data curation, Methodology, Writing – original draft. AP: Writing – review & editing. MC: Methodology, Writing – review & editing. RR: Supervision, Writing – review & editing. RB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

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

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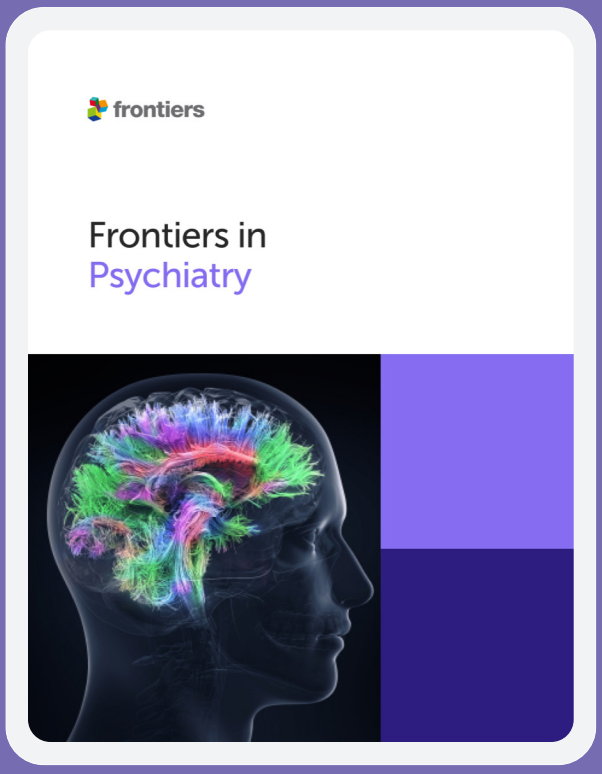

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