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RESEARCH ARTICLE

Endophenotyping social cognition in the broader autism phenotype

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Abstract

Relatives of individuals with autism spectrum disorder (ASD) may display milder social traits of the broader autism phenotype (BAP) providing potential endophenotypic markers of genetic risk for ASD. We performed a case–control comparison to quantify social cognition and pragmatic language difficulties in the BAP ($n = 25$ cases; $n = 33$ controls) using the Faux Pas test (FPT) and the Goldman-Eisler Cartoon task. Using deep phenotyping we then examined patterns of inheritance of social cognition in two large multiplex families and the spectrum of performance in 32 additional families (159 members; $n = 51$ ASD, $n = 87$ BAP, $n = 21$ unaffected). BAP individuals showed significantly poorer FPT performance and reduced verbal fluency with the absence of a compression effect in social discourse compared to controls. In multiplex families, we observed reduced FPT performance in 89% of autistic family members, 63% of BAP relatives and 50% of unaffected relatives. Across all affected families, there was a graded spectrum of difficulties, with ASD individuals showing the most severe FPT difficulties, followed by the BAP and unaffected relatives compared to community controls. We conclude that relatives of probands show an inherited pattern of graded difficulties in social cognition with atypical *faux pas* detection in social discourse providing a novel candidate endophenotype for ASD.

Lay Summary

Relatives of individuals with autism spectrum disorder (ASD) may display milder but qualitatively similar traits known as the broader autism phenotype (BAP). Current knowledge of the BAP is limited and methods to assess traits are not well established. This study aimed to characterize the BAP based on objective measures of social skills. This can allow the identification of BAP traits that indicate genetic risk for ASD in families with many individuals with ASD or the BAP. We studied recognition of socially inappropriate behavior and language (a *faux pas*) as our objective measure of social cognition, and verbal fluency in social conversation as our objective measure of language pragmatics in 25 individuals with the BAP compared to 33 neurotypical participants. Individuals with the BAP showed atypical social cognition with reduced ability to recognize a *faux pas*, as well as altered language pragmatics with decreased verbal fluency. We then examined social cognition in 34 families (159 members) with ASD and the BAP. Across all families, autistic individuals showed the weakest *faux pas* recognition, followed by those with the BAP and relatives without autistic traits compared to community controls. This inherited pattern of graded difficulties in social cognition suggests that atypical *faux pas* recognition may be a marker of genetic risk for ASD. This may facilitate studies investigating the genetic causes of ASD by providing researchers with objective markers of the BAP to better understand neurodivergence in this population.

KEYWORDS
autism spectrum disorder, behavioral genetics, broader autism phenotype, language pragmatics, social cognition

INTRODUCTION

Autism spectrum disorders (ASDs) are characterized by atypical social communication and interaction, and restricted or repetitive behaviors and interests (American Psychiatric Association, 2013). Although more than 100 high-confidence genes have been associated with ASD (Satterstrom et al., 2020), the genetic etiology for more than 75% of cases remains unknown (Bourgeron, 2015; Fernandez & Scherer, 2017; Tammimies et al., 2015). The majority of genetically unsolved cases likely follow complex inheritance with multifactorial genetic and environmental interactions (Berg & Geschwind, 2012; Cannon & Keller, 2006; Lord et al., 2020). Emerging evidence supports the cumulative effect of multiple common genetic variants that are individually of small impact but when aggregated may contribute to substantial liability for ASD (Gaugler et al., 2014; Weiner et al., 2017).

Evidence from family studies suggest a recurrence risk of 3%–18% in siblings of probands (Grønborg et al., 2013; Ozonoff et al., 2011; Sandin et al., 2014). A milder phenotype known as the broader autism phenotype (BAP) characterized by traits that are qualitatively similar to ASD, can be observed in 12%–40% of first-degree relatives who do not meet criteria for an ASD diagnosis (Bolton et al., 1994; Gamliel et al., 2009; Georgiades et al., 2013; Messinger et al., 2013; Rubenstein & Chawla, 2018; Sasson et al., 2013), compared to 2%–9% in the general population (Bora et al., 2017; Constantino & Todd, 2005; Gökçen et al., 2014; Robinson et al., 2011). The BAP may facilitate genetic investigations of ASD in family studies through the identification of individuals with milder trait expression and fewer genetic variants. However, BAP traits are subtle to detect and thus, require more precise methods for accurate identification and characterization as their milder expression is unlikely to significantly impair daily functioning (Bishop et al., 2004). Current diagnostic criteria for ASD encompass a wide range of clinical presentations and severity (Mottron & Bzdok, 2020), but do not include the BAP as these traits are continuously distributed in the general population and not pathognomonic of ASD (Abu-Akel et al., 2019; Constantino & Todd, 2005).

Assessment of the BAP and endophenotype traits

Key challenges in research investigating the BAP are the lack of standardized criteria or an objective reference standard for assessment, and significant heterogeneity in methodological approaches and measurement tools (Volkmar et al., 2014). A systematic review of studies investigating the BAP in parents of probands identified substantial differences in assessment methods across studies that utilized eight different instruments and a wide range of sample sizes (Rubenstein & Chawla, 2018). The estimated proportion of parental BAP differed widely across studies, ranging from 2.6% to 80%. Methodological heterogeneity in measurement and classification likely contributed to the large variance in reported estimates, with poor replicability of findings and risk of misclassification bias associated with the choice of informant and instrument (Volkmar et al., 2014; Rubenstein & Chawla, 2018).

The majority of available tools used to assess the BAP are based on self or informant reports, such as the Social Responsiveness Scale-2 (Bruni, 2014; Constantino, 2011), Broad Autism Phenotype Questionnaire (Hurley et al., 2007) and Autism Spectrum Quotient (Baron-Cohen et al., 2001). Evidence suggests that a potential bias of self or informant reports may be present in raters positive for the BAP, who were more likely to over- or under-report associated traits or provide discordant responses (Rubenstein & Chawla, 2018). For instance, males with the BAP were found to underestimate the severity of BAP traits in themselves relative to spousal informant ratings, suggesting a psychological blind-spot in self-reported BAP traits in males (Sasson et al., 2013). Another study reported informant discrepancies in mothers with the BAP who were more likely to overestimate ASD in their children, with a significant discordance between clinician observations and maternal ratings compared to ratings from mothers without the BAP (Rubenstein et al., 2017). These findings are consistent with previous work showing that informant ratings of family members may be biased by social and communication traits in the rater (Crocetti et al., 2016; Deoliveira et al., 2005).

Self-reported and informant biases may be mitigated by clinician-based interviews and ratings of the BAP, such as the Family History Interview (Bolton et al., 1994), Modified Personality Assessment Schedule (Piven et al., 1997), Broader Phenotype Autism Symptom Scale (Dawson et al., 2007) and the Broader Autism Phenotype Interview (BAPI) (Trevis et al., 2020). To address any clinician rating biases, studies typically use more than one clinician to allow inter-rater reliability estimates to be determined. However, the most objective assessment of the BAP is obtained when it includes direct measures of an individual's behavior or cognitive performance, such as the use of psychometrically-validated neuropsychological tests. These methods often involve high costs and time for staff training in test administration to achieve required reliability. Moreover, most tests have been primarily developed to identify ASD or language impairment rather than the BAP and their utility in measuring milder traits requires further study (for a comprehensive review of current available methods, see Volkmar et al., 2014; Lyall, 2023; Rubenstein & Chawla, 2018).

There is therefore a need for more precise socio-cognitive, behavioral and linguistic methods to

phenotype the BAP. In particular, achieving improved detection of more granular features of the BAP and accuracy of case ascertainment is likely to facilitate genetic investigations through the identification of potential endophenotypic markers (Gould & Gottesman, 2006; Persico & Sacco, 2014). Endophenotypes are heritable quantitative traits associated with disease liability that can be observed in both affected and unaffected individuals as a marker of genetic vulnerability (Beauchaine & Constantino, 2017). Endophenotypic traits are observed in family members of probands at a higher rate than the general population and provide an index of disease liability that varies quantitatively in individuals with a higher genetic risk burden (Gottesman & Gould, 2003). Specific BAP traits in relatives of ASD probands could therefore constitute candidate endophenotypes that are more frequently expressed in members of affected families (Nayar et al., 2020; Piven, 1999; Ronald et al., 2011; Sandin et al., 2014; Trevis et al., 2020; Woodbury-Smith et al., 2018).

The majority of unsolved cases in ASD likely involve complex inheritance with oligogenic or polygenic contributions from multiple classes of genetic variants (Bourgeron, 2015; Tammimies et al., 2015; Warrier et al., 2022; Weiner et al., 2017). However, substantial heterogeneity in phenotypic expression has limited the identification of underlying genetic aetiologies and their role in trait expression in ASD (Warrier et al., 2022). As intermediate phenotypes positioned between genotype and behavior that are thought to involve less complex genetic determinants (Gottesman & Gould, 2003; Gould & Gottesman, 2006; Kendler & Neale, 2010), the identification of familial BAP endophenotypes may facilitate genotype–phenotype investigations. First, by delineating the link between complex and heterogeneous phenotypes and putative genetic mechanisms in ASD (Persico & Sacco, 2014), and second by improving the accuracy of case ascertainment and clinical subgrouping of probands and relatives with milder traits in family studies of gene discovery in ASD (Cannon & Keller, 2006; Flint & Munafò, 2007; Gottesman & Gould, 2003).

Using a clinician-based interview, we previously identified and validated four novel BAP endophenotypes in two large multiplex families with multiple affected members with ASD or the BAP (Trevis et al., 2020). Our deep phenotyping approach involved detailed characterization and assessment of BAP trait clusters and more granular ascertainment of individual traits. This identified the four distinct BAP endophenotypes summarized in Table 1, namely "Socially Unaware", "Pedantic", "Aloof" and "Obsessive". Of these, the first two contain multiple traits relating to theory of mind and pragmatic language ability. This aligns with early work on the familial aggregation of ASD-related traits in affected families showing that first-degree family members of probands with ASD may display mild reductions in socio-communicative ability and the production of language in social discourse (Bolton et al., 1994; Landa et al., 1992). The present study builds on our prior work, with the goal of determining objective measures of social cognition and pragmatic language ability in individuals with the BAP to identify familial BAP endophenotypes.

Socio-communicative abilities in the BAP

Difficulties communicating in a social context may involve pragmatic language difficulties in the use and understanding of language as well as other non-verbal cues that convey social, emotional and communicative meanings (Bosco et al., 2018; Levinson, 1983; Parsons et al., 2017; Prutting & Kirchner, 1987). In autistic individuals, pragmatic language difficulties may include atypical timing and intonation of fluent social discourse and inappropriate utterances (Shriberg et al., 2001). Milder atypical pragmatic features may be observed in family members of probands as disinhibited social comments and awkward self-expression. Conversational turn-taking may be disrupted by overly detailed speech and an increased number of pauses, leading to decreased verbal fluency (Bolton et al., 1994; Landa et al., 1992).

Alongside pragmatic language difficulties there may be a failure to accurately identify and incorporate socially relevant contextual cues in social communication, such as the detection of *faux pas*. The latter occurs when a verbal or non-verbal action during social discourse results in a clear violation of tacit social rules that are generally assumed to be implicitly understood and obeyed. Committed acts of *faux pas* are typically unintended, and often evoke negative responses due to undesirable social consequences when such rules are violated (Baron-Cohen et al., 1999). Successful detection of *faux pas* thus depends on an appreciation of implicit social rules, the socio-emotional consequences when such rules are violated, and the understanding that knowledge states between the speaker and listener could differ. Related difficulties in social cognition and advanced theory-of-mind (ToM) abilities in the attribution of mental states to the self and others in the prediction and understanding of behavior (Premack & Woodruff, 2010) have been reported in individuals with high-functioning ASD (HFA), who show reduced ability to detect and interpret *faux pas* compared to controls (Baron-Cohen et al., 1999; Zalla et al., 2009).

Atypical verbal and paralinguistic aspects of social communication may thus serve as candidate endophenotypes of the BAP, capturing milder forms of reduced social cognition and pragmatic language difficulties pertinent to the interpretation of social situations and contextual cues in social discourse. Although ToM and pragmatic language abilities are likely to be correlated in both typical and atypical development, including ASD, evidence from several studies suggests that pragmatic difficulties are not completely explained by ToM. Specific components of pragmatic language remain preserved independently of ToM deficits, warranting further

TABLE 1 Broader autism phenotype (BAP) endophenotypes and associated traits.

BAP endophenotype	Description	Associated traits
Socially unaware	Poor self-regulation and reciprocity in conversation	• Reduced capacity for clear narrative • Difficulty answering open ended questions • Making inappropriate or awkward comments either on history or during assessments • Tangential pragmatic style • Tendency to monologue rather than participate in reciprocal conversation • Tendency to anger easily • Reduced quantity of verbal output
Pedantic	Self-focused and technical in interactions	• An unusual or awkward greeting style • Unusual eye gaze • Speech has limited variation in tone • Unusual speech volume • Precise articulation and language • Terse pragmatic style • Overly technical language • Narcissistic personality style • Focus on technicalities or minutiae • Fastidious regarding personal appearance • Self-perception incongruent with views of others
Aloof	Difficulties relating to other's emotions and expressing own emotions	• Aloof personality style • Difficult or limited interpersonal relationships • Reduced emotional empathy • A limited capacity to develop rapport with assessors • Reduced affection • Awkward social interactions • Opinionated in conversation • Reduced cognitive empathy • Little appreciation of humor
Obsessive	Regimented approach to life and tendency to ruminate	• Hobby or interest of unusual intensity, or restricted range of interests relative to peers • Large collections or hoarding of items • Fastidious cleaning • Preference for structure in activities of daily living • Recurrent thoughts that are not distressing • Excessive worry

Note: Trevis et al. (2020).

investigation through the use of distinct empirical tasks (Bambini et al., 2016; Bosco et al., 2018; Laghi et al., 2014; Parola et al., 2018). While difficulties in ToM and pragmatic language are commonly identified in autistic individuals, the measurement and detection of milder expression of both features in the BAP is comparatively more challenging given the current limitations and heterogeneity in methods of assessment and identification in this population.

Thus, in the present study, we first aimed to identify objective measures to quantify social cognition and pragmatic language difficulties in individuals with the BAP. In particular, we used two established tasks to assess the recognition of *faux pas* (Faux Pas test; FPT) (Baron-Cohen et al., 1999) and verbal fluency production (Goldman-Eisler Cartoon Task) (Goldman-Eisler, 1968) in social discourse. We hypothesized that individuals with the BAP would show reduced *faux pas* recognition and verbal fluency performance compared to controls recruited from the wider community. We then investigated the utility of *faux pas* recognition as an endophenotypic marker by examining patterns of inheritance in two large families with many affected individuals who were a priori classified with ASD or the BAP. Finally, we investigated the spectrum of *faux pas* recognition in family members with the BAP or ASD and their unaffected relatives in an independent sample of 32 simplex and multiplex families to examine the diagnostic utility of the FPT.

METHODS

Participants

Case-control cohort

Participants comprised a well-characterized group of 25 individuals with the BAP and 33 neurotypical controls matched on age, sex, and FSIQ (Table 2). Individuals with the BAP were recruited from our previous study

TABLE 2 Characteristics of participants with the broader autism phenotype (BAP) and unaffected controls.

	Group	
	BAP	**Controls**
N	25 (16 females)	33 (17 females)
Age (Years)		
Mean (SD)	52.44 (17.20)	50.09 (18.52)
Range	16–80	18–83
Full scale IQ		
Mean (SD)	107.21 (17.32)	114.44 (11.97)
Range	70–133	88–135

Note: Individuals with the BAP performed within normal limits on the standardized measures of cognition and behavior, including executive and adaptive functioning (Supplementary Table 1).

characterizing large multiplex families to identify genetic variants for ASD (Fanjul-Fernández et al., 2021; Trevis et al., 2020). In brief, BAP status in relatives of individuals with ASD was classified using recommended approaches (Bolton et al., 1994; Landa et al., 1992), including administration of the Family History Interview (Bolton et al., 1994) and a purpose-developed semi-structured interview administered by three clinicians with expertise in neurobehavioral conditions (Trevis et al., 2020). Systematic assessment of cognition and behavior was performed using the Wechsler Abbreviated Scale of Intelligence (Weschler, 1999), subtests of the Delis-Kaplan Executive Function System (Delis et al., 2004), the Behavioral Rating Inventory of Executive Function (Gioia et al., 2000), the Adaptive Behavior Assessment System (Harrison & Oakland, 2003), and the Pragmatic Rating Scale (PRS) (Landa et al., 1992), the latter being a clinician-rating tool for assessing social communicative behaviors that violate pragmatic rules (Supplementary Table 1). BAP status was determined by consensus of the three experts following completion of the BAPI and independent review of all data.

Neurotypical controls were recruited from the wider community and screened for a family history of ASD. Four participants in the control group with a positive family history were assessed to be unaffected using the above protocol. All participants were fluent English speakers. Exclusion criteria included a history of neurological or psychiatric conditions. There were no significant differences between the BAP group and controls on age ($t(56) = 0.493$, $p = 0.624$) and FSIQ ($t(38.74) = -1.754$, $p = 0.087$). A Chi-Square Test for Independence (with Yates' correction for continuity) indicated no significant association between sex and BAP status, $\chi^2(1, n = 58) = 0.467$, $p = 0.495$, phi = 0.125.

Large multiplex families

19/25 individuals with the BAP belonged to two large multigenerational families with multiple affected members with an existing or suspected diagnosis of ASD or the BAP (Supplementary Figure 1). Across both families (Family A, $n = 22$; Family B, $n = 27$), we examined FPT performance in affected (ASD: $n = 9$; BAP: $n = 30$) and unaffected relatives ($n = 10$). ASD diagnosis was confirmed using the Autism Diagnostic Observation Schedule—Generic (ADOS-G) (Lord et al., 2000) or the Autism Diagnostic Interview—Revised (ADI-R) (Lord et al., 1997) based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000). BAP or unaffected status in relatives was evaluated based on the rigorous assessment protocol described above (Trevis et al., 2020).

Combined family cohort

In addition to the two large multiplex families, we obtained FPT data from a further 32 families (6 large multiplex families, $n = 32$ members; 26 HFA families, $n = 78$ members) to determine if *faux pas* recognition showed a consistent pattern of effects across independent affected families. Across all 34 families ($n = 159$ members), there were 51 individuals with ASD, 87 with the BAP, and 21 unaffected relatives. Inclusion criteria for the HFA family cohort were a proband with average general intellect (FSIQ ≥90) and their immediate family members (Green et al., 2020). Phenotyping was performed based on the same assessment and evaluation criteria (Green et al., 2020; Trevis et al., 2020) however verbal fluency data was not available.

74/87 individuals with the BAP were previously classified according to the four endophenotypes following deep phenotyping (Table 1). The endophenotyping protocol included the Broader Autism Phenotype Interview (BAPI) (Trevis et al., 2020), a refined version of the semi-structured interview developed to characterize the presence, nature and extent of BAP traits. Interview questions primarily focused on the life story and trajectory of each individual, personal qualities, relationships, social functioning, vocational history, and the developmental and medical history. The BAPI was administered by three experts and participant responses were independently rated with consensus agreement. Endophenotype analysis was performed by a research team member who was not involved in assessments for phenotyping and was blind to BAP status. Proportional scores for each endophenotype cluster were computed by obtaining the sum of all item trait scores within a cluster divided by the maximum total score for that cluster. Endophenotype status was assigned if proportional scores exceeded the cut-off score for each respective endophenotype. Further details on the assessment and scoring procedure for endophenotype classification are reported in (Trevis et al., 2020). All participants provided informed written consent to participate in the study.

Materials and measures

The Faux Pas test

The FPT adapted for adults (Supplementary A) was used to assess the ability to recognize social misunderstandings and violations of social norms in *faux pas* scenarios (Baron-Cohen et al., 1999; Stone et al., 1998). The task comprised four *faux pas* stories and four control stories, and was administered to participants following the approach of Stone et al. (1998). The FPT has good sensitivity in differentiating individuals with high functioning ASD from controls (Baron-Cohen et al., 1999). A higher score on the FPT indicates stronger ability in the identification and understanding of social *faux pas* scenarios, with a FPT score <37 indicating reduced performance (Green et al., 2020). The FPT allows direct measurement of *faux pas* recognition ability and has been previously used to study ToM in ASD and the general population (Atherton & Cross, 2019; Baron-Cohen et al., 1999; Stone et al., 1998; Thiébaut et al., 2016).

The Goldman-Eisler cartoon task

The Goldman-Eisler Cartoon task (Goldman-Eisler, 1968) assesses spontaneous speech production and is sensitive to subtle communication difficulties in clinical populations (Field et al., 2000). The task was administered according to standardized procedures. In brief, discourse production was elicited from the description of an eight frame captionless cartoon, "The Cowboy Story" (Joanette & Goulet, 1990) on three successive trials (cycles) to examine how participants structured their story of the cartoon with repetition (Lillywhite et al., 2010). Previous studies have shown that controls produce increasingly concise narratives on subsequent cycles (known as the "compression effect") as evident from increased verbal fluency compared to individuals with communication impairments (Field et al., 2000; Goldman-Eisler, 1968). The speaking time of each cycle of the Cartoon task was determined from digital audio recordings of each participant. Verbal fluency was calculated based on the word count divided by the total time taken to verbalize the story for each cycle. Filler words were included such as "um", "ah", "er", "uh", as these are employed by speakers to maintain control of a conversation while they are thinking of what to say next (Liu et al., 2006).

Task administration

The FPT and Cartoon task were administered in a quiet location, requiring approximately 30 minutes to complete. Participant responses were video-audio recorded and transcribed verbatim by an investigator blind to BAP status. Additional data was available for individuals with the BAP who were systematically assessed on a rigorous cognitive and behavioral protocol (Supplementary Table 1).

Statistical analyses

Statistical analyses were conducted in SPSS (version 15) and the R environment (R Development Core Team, 2013). Total scores on the FPT violated the assumption of normality and could not be rectified by transformations of the data. The Mann–Whitney U test was used to assess the hypothesis that the BAP group would show reduced recognition of *faux pas* compared to controls. Verbal fluency scores of the Cartoon task required a reflected log10 transformation to fulfill assumptions of normality.

We performed a mixed-design analysis of variance to test the hypothesis that the BAP group would show reduced verbal fluency compared to controls across the three task cycles, with verbal fluency per cycle as the dependent variable. Three individuals with the BAP were excluded from this analysis due to poor quality of audio recordings of their speech output. Across the combined cohort of 34 families, we used a Kruskal-Wallis test to assess the hypothesis that individuals with ASD, the BAP and unaffected relatives would show reduced recognition of *faux pas* compared to community controls without a family history of ASD from the case–control cohort ($n = 29$). Diagnostic utility of the FPT was evaluated following standard methods for evaluating test classifier performance (Altman & Bland, 1994; McGee, 2002).

Power analysis using R package "pwr" (Champely et al., 2018) indicated a minimum total sample size of $n = 52$ for two comparison groups and $n = 66$ for 3 comparison groups required to achieve 80% power for detecting a small to medium effect at a significance criterion of $\alpha = 0.05$. The present study was therefore adequately powered to test the research hypotheses.

RESULTS

Reduced social cognition and pragmatic language ability in the BAP

In the case–control comparison, as hypothesized the BAP group demonstrated significantly reduced recognition of *faux pas* (FPT $Mdn = 34$, $n = 25$) compared to controls ($Mdn = 39$, $n = 33$), $U = 158.5$, $z = -4.013$, $p < 0.001$ (Figure 1a), with greater variability in total FPT scores observed in the BAP group. Individuals with the BAP also failed to demonstrate an increase in verbal fluency over three cycles of the Cartoon task that was observed in the control group (Figure 1b). There was a significant interaction between task cycle and group with

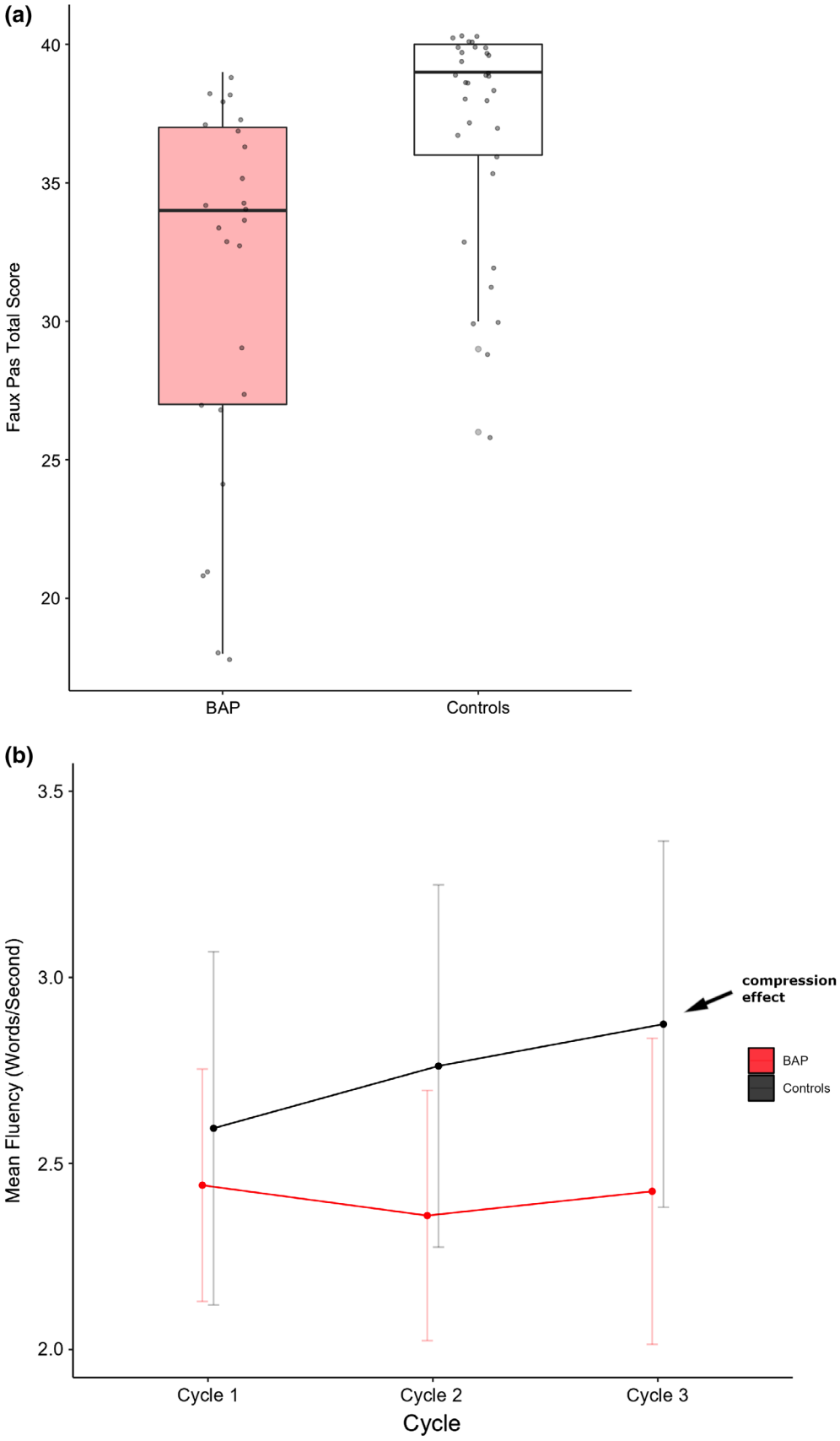

FIGURE 1 Individuals with the BAP demonstrated reduced *faux pas* recognition and verbal fluency during social discourse compared to controls. (a) Boxplots of the median accuracy scores for the Faux Pas test (FPT) for the broader autism phenotype (BAP) and control groups showing decreased recognition of *faux pas* in the BAP group. (b) Mean verbal fluency over the three cycles of the Cartoon task for the BAP and control groups. The BAP group showed reduced verbal fluency and failed to show the compression effect evident from the linear increase in fluency in controls.

the verbal fluency of control participants increasing across each task cycle as expected for the compression effect. In contrast, the verbal fluency of the BAP participants remained consistently low across all three cycles ($\lambda = 0.805$, $F(2, 52) = 6.283$, $p = 0.004$, partial $\eta^2 = 0.195$).

Social cognition inheritance patterns in multiplex families

FPT scores in the two large multiplex families showed a striking pattern of atypical performance consistent with a dominant pattern of inheritance (Figure 2). In Family A ($n = 22$), reduced performance was observed in 3/4 (75%) members with ASD, 9/15 (60%) with the BAP, and 1/3 (33.3%) of unaffected relatives. In Family B ($n = 27$), 5/5 (100%) members with ASD, 10/15 (67%) with the BAP and 4/7 (57%) unaffected relatives demonstrated reduced recognition of *faux pas*.

Inspection of the family pedigrees indicated that reduced FPT performance co-occurred in individuals with the BAP who were previously classified on the four BAP endophenotypes ($n = 74$) (Trevis et al., 2020). In

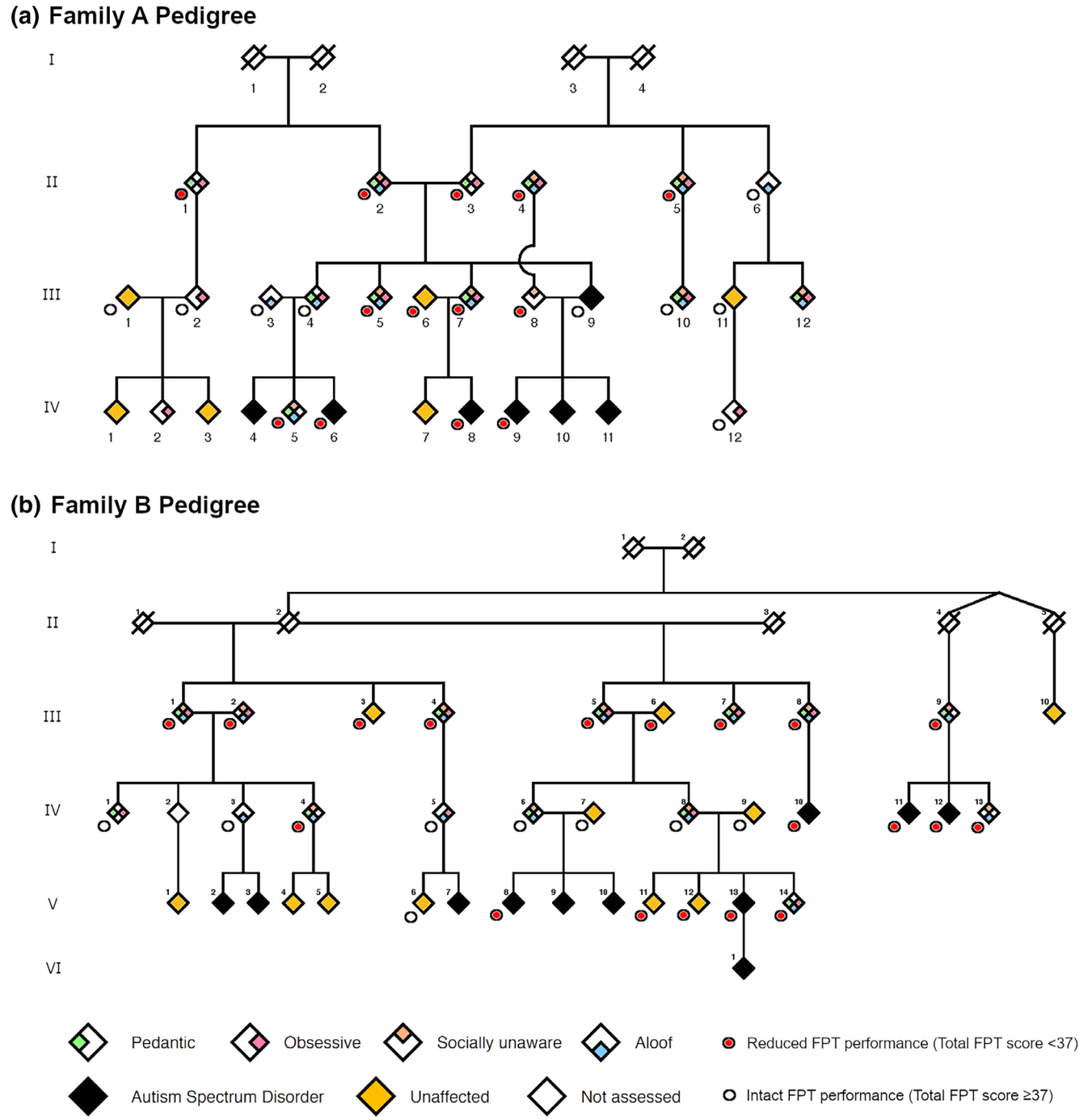

FIGURE 2 *Faux pas* recognition in the large multiplex autism spectrum disorder (ASD) families. Across both families ($n = 49$), Faux Pas test (FPT) performance was reduced in 89% of individuals with ASD (8/9), 63% of those with the BAP (19/30), and 50% of unaffected relatives who did not meet criteria for ASD or the BAP (5/10). Reduced performance is indicated by a red circle.

particular, the FPT scores showed strong sensitivity for all four endophenotypes but poor specificity overall (Supplementary Table 2). The strongest sensitivity of 90.7% (95% CI: 77.9–97.41) was observed for the Socially Unaware endophenotype. Supporting this, in a multiple logistic regression model to predict reduced versus unimpaired FPT performance based on endophenotype class membership, the Socially Unaware endophenotype emerged as the only significant predictor of difficulties in *faux pas* recognition ($z = 2.32$, $p < 0.05$, OR = 5.12, 95% CI: 1.3–20.6) (Supplementary Table 3).

Graded difficulties in social cognition in ASD families

Across the combined family cohort and community controls, there was a significant difference in FPT performance between individuals with ASD, the BAP, and unaffected relatives compared to controls, $H(3) = 37.47$, $p < 0.0001$. As hypothesized, post-hoc pairwise comparisons showed that individuals with ASD ($Mdn = 33$, $n = 51$) demonstrated significantly lower FPT scores compared to controls ($p < 0.0001$). The finding of significantly reduced FPT performance in the BAP group ($Mdn = 34$, $n = 87$, $p < 0.0001$) compared to community controls remained robust. Interestingly, we observed that unaffected relatives of probands similarly demonstrated significantly lower FPT total scores ($Mdn = 35$, $n = 21$) compared to community controls ($Mdn = 39$, $n = 29$), $p < 0.01$ (Figure 3; Supplementary Table 4). There was no significant difference in FSIQ between unaffected relatives ($M = 113.70$, SD = 16.8), family members with the BAP ($M = 110.14$, SD = 12.96) or ASD ($M = 109.62$, SD = 10.41) and community controls ($M = 114.79$, SD = 12.4), $p > 0.05$.

Diagnostic utility of the faux pas test

The FPT demonstrated favorable classifier performance with a sensitivity of 88.2% (95% CI: 76.1–95.6) for ASD and 79.5% for the BAP (95% CI: 69.6–87.4). The FPT achieved a specificity of 79.3% (95% CI: 60.3–92.0) for controls without a family history of ASD. The positive likelihood ratio was 4.26 (95% CI: 2.08–8.76) and 3.84 (95% CI: 1.87–7.90) for ASD and the BAP respectively, suggesting a small to moderate increase in likelihood of affected status given difficulties on the FPT task (McGee, 2002) (Table 3).

DISCUSSION

We found that individuals with the BAP showed marked difficulties in recognizing *faux pas* and decreased verbal fluency in social discourse compared to controls. In two large multiplex families with many affected individuals across multiple generations, we observed poorer recognition of *faux* pas in the majority of ASD and BAP family members and in half the unaffected relatives. These findings were consistent across 32 other affected families with a spectrum of graded difficulties observed in *faux pas* recognition, where ASD individuals were most affected, followed by relatives with the BAP and unaffected relatives compared to community controls. The FPT showed good diagnostic utility as a marker of atypical social cognition including high sensitivity to a broader, Socially Unaware endophenotype, suggesting that poor detection and interpretation of inappropriate social discourse is a core feature of ASD. Combined, these findings provide compelling support for atypical *faux pas* recognition as a novel candidate endophenotype of ASD.

Individuals with the BAP showed a reduced ability to correctly identify or interpret *faux pas* events with poor detection of violations of implicit social rules or the failure to appreciate the socially offensive nature of such behavior. This included the tendency to misinterpret control scenarios as false positive events as well as the attribution of deliberate intent to characters committing *faux pas* rather than appreciating their unintended social nature.

The inability to correctly identify and interpret a *faux pas* may be related to atypical development in advanced theory-of-mind abilities in the attribution of mental states to the self and others necessary to understand and predict behavior based on inferences about underlying emotional and mental states and intentionality (Premack & Woodruff, 2010). As observed in individuals with HFA who show reduced *faux pas* ability (Baron-Cohen et al., 1999; Zalla et al., 2009), individuals with the BAP may display difficulties in the ability to differentiate between the semantic and more abstract pragmatic use of language in social discourse that requires the contextual appreciation of cognitive and emotional states in others (Bishop et al., 2004; Losh & Piven, 2007).

Consistent with this interpretation, reduced FPT performance in the BAP was strongly predicted by the group with higher expression of the socially unaware endophenotype in the present study. This comprises a cluster of traits related to poor self-regulation and reciprocity in conversation, such as making awkward or inappropriate comments, lack of turn-taking or having a tangential language style (Trevis et al., 2020). It is also consistent with the finding of reduced verbal fluency in the BAP due to a failure to adequately compress the social significance of the linguistic narrative over time. The qualitative performance of individuals with the BAP was characterized by longer pauses where no verbal output was present, suggesting an inefficient structuring of fluent social discourse in open-ended situations. This is in line with previous work showing that poorer language-mediated executive functioning ability in the BAP predicted reduced task performance on the FPT, supporting the hypothesis that

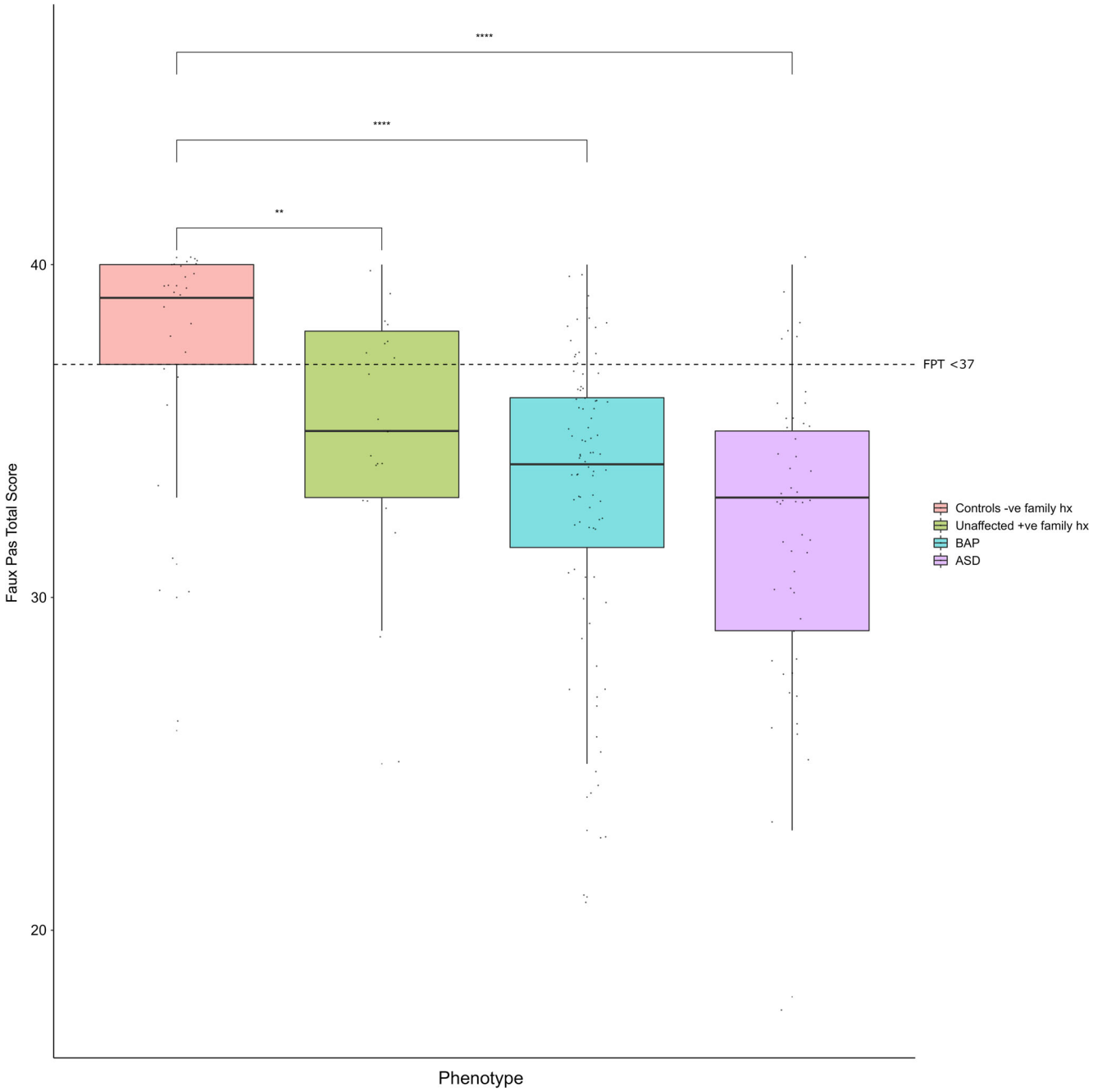

FIGURE 3 The spectrum of Faux Pas test (FPT) performance across the full family cohort. Compared to community controls without a family history of autism spectrum disorder (ASD) (pink), individuals with ASD (purple) showed the poorest recognition of *faux pas*, followed by those with the BAP (blue), and unaffected relatives (green). The median performance of each ASD family group fell below the FPT cut-off score <37. ****$p < 0.0001$, **$p < 0.01$.

higher level theory-of-mind functioning relies on cognitive flexibility and inhibition processes that may be inefficient or mildly reduced in this population (Green et al., 2020).

Together these findings suggest that reduced *faux pas* recognition may be a distinct neurobehavioral marker of atypical social cognition in advanced theory-of-mind that may present in individuals with a higher risk burden for ASD. This was supported by the striking familial aggregation of FPT difficulties that varied according to severity of ASD phenotypes in our combined family cohort. In particular, the *faux* pas endophenotype was expressed at higher levels in at-risk individuals in unaffected relatives of probands, with even greater expression in family members with the BAP or ASD compared to community controls (Cannon & Keller, 2006; Gottesman & Gould, 2003).

Consistent with a liability threshold model, family members of probands may carry a higher risk burden for

TABLE 3 Diagnostic utility of the FPT for ASD and the BAP.

	ASD (95% CI)	BAP (95% CI)
Sensitivity	88.2% (76.1–95.6)	79.5% (69.6–87.4)
Specificity	79.3% (60.3–92.0)	79.3% (60.3–92.0)
LR+	4.26 (2.08–8.76)	3.84 (1.87–7.90)
LR–	0.15 (0.07–0.32)	0.26 (0.16–0.41)
PPV	88.2% (78.5–93.9)	92.11% (85.02–96)
NPV	79.3% (63.86–89.26)	56.10% (44.85–66.76)
Accuracy	85% (75.26–92)	79.49% (71.03–86.39)
Study prevalence	63.75% (52.24–74.21)	75.21% (66.38–82.73)

Abbreviations: ASD, autism spectrum disorder; BAP, broader autism phenotype; CI, confidence interval; FPT, Faux Pas test; LR–, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

ASD that may not result in a diagnosis of ASD but is still sufficient for the expression of milder traits (Berg & Geschwind, 2012; Cannon & Keller, 2006; Gaugler et al., 2014; Geschwind, 2011; Weiner et al., 2017). In heterogeneous populations such as ASD with a high degree of inter- and intra-individual variability, quantitative endophenotypic markers such as *faux pas* recognition may therefore allow dimensional modeling of disease liability in both affected and unaffected individuals for more refined case ascertainment (Almasy & Blangero, 2001; Cannon & Keller, 2006; Lombardo et al., 2019; Pua et al., 2020). Such approaches could mitigate the misclassification of individuals with a higher genetic burden for ASD who express milder traits as "unaffected" controls, improving sample homogeneity and potentially reducing the likelihood of incorrect linkage and genetic variant association outcomes (Fanjul-Fernández et al., 2021; Lombardo et al., 2019).

Atypical *faux pas* recognition as an endophenotypic marker of ASD offers a well-defined neurocognitive target for more precise interrogation of atypical brain structure and function underlying advanced theory-of-mind difficulties in at-risk individuals. Early neuroimaging work supports the predominant role of frontal and medial prefrontal regions in theory-of-mind functioning (Baron-Cohen et al., 1994; Channon & Crawford, 2000; Frith & Frith, 1999; Stone et al., 1998), with emerging evidence implicating atypical cerebro-cerebellar connections in ASD and the role of cerebellar connectivity with frontal, temporo-parietal and limbic networks in social mentalizing processes and the prediction of social behaviors (D'Mello & Stoodley, 2015; Hegarty et al., 2018; Van Overwalle et al., 2019; Van Overwalle & Mariën, 2016). These cortical and subcortical networks have also been linked to reduced *faux pas* performance in other patient groups (Schacher et al., 2006; Yokote et al., 2021). Of note, a recent report of patients with cerebellar atrophy found deficits on advanced theory-of-mind tasks similar to those observed in individuals with ASD, including impaired FPT performance (Clausi et al., 2021). Emerging evidence suggests that the misdetection and misinterpretation of *faux pas* may be linked to weaker executive functioning abilities in language-mediated cognitive flexibility and inhibition in individuals with the BAP (Green et al., 2020).

The present study found a graded pattern of deficits in social cognition in individuals with ASD and the BAP in affected families compared to controls as a candidate endophenotype for ASD. Future investigations should extend this work to identify endophenotypes related to non-social features of ASD in restricted and repetitive behaviors and interests and atypical sensory processing. Behavioral and sensory-motor symptoms are highly prevalent in this population (Leekam et al., 2007) and clinical diagnostic criteria requires the presence of co-occurring features together with reductions in social communication and interaction (American Psychiatric Association, 2013). Given the phenotypic heterogeneity in the clinical presentation of ASD, comprehensive investigation of social and non-social endophenotypes and the relationships between them and distinct endophenotypic markers will be necessary to capture the full spectrum of phenotypic expression (Leekam, 2016; Lenroot & Yeung, 2013).

In line with this view, conventional approaches based on dichotomous case-control classification in neurobiological investigations have typically yielded findings with limited reproducibility (Mottron & Bzdok, 2020; Pua et al., 2017; Tang et al., 2020). Deep phenotyping approaches based on quantitative and more granular endophenotypic markers may thus improve precision in the identification of distinct neurocognitive and neurobiological mechanisms implicated in gene-brain-phenotype pathways in ASD (Beauchaine & Constantino, 2017; Cannon & Keller, 2006; Cannon & Rosso, 2002; Satterstrom et al., 2019). Common and rare variants associated with ASD also confer risk for other neurodevelopmental and neuropsychiatric conditions (Kushima et al., 2018; Marshall, 2020), and the mechanisms of polygenic and pleiotropic effects of genomic risk variants and specific linkage to atypical structure and function at the molecular and brain network levels in the phenotypic expression of ASD are not yet fully understood. This highlights the need for increased precision in phenotyping and genetically-driven stratification methods in case-control studies in idiopathic conditions (Moreau et al., 2021).

One possible limitation of the present study is the confounding influence of the psychosocial environment. Recent work suggests that psychosocial factors including parental education, employment, and socioeconomic status may be associated with increased risk of attention-deficit/hyperactivity disorder (ADHD) (Østergaard et al., 2020). Although adverse psychosocial factors were not found to significantly attenuate disease risk explained by polygenic liability in the same study, the contribution of shared and non-shared environmental influences within affected families nonetheless warrants further investigation (Bölte et al., 2019; Kendler & Neale, 2010; Plomin, 2011). To this end, the study of relatives of

probands with higher genetic liability and shared familial environment may reveal deeper insights into the complex genetic and environmental architecture of heterogeneous neurodevelopmental conditions such as ASD and the spectrum of neurodivergence in the general population. Here, we have demonstrated the utility of detailed examination of granular endophenotypes to facilitate further investigation of putative genotype–phenotype pathways within affected families. Given the limits of self-report and informant-based approaches to assess the BAP, the tasks administered in the present study provide objective and quantifiable measures that allow more refined characterization of this understudied population. Moreover, both tasks require minimal training and are easy to administer. Further investigation of the utility of objective measures in multimodal approaches to assess the BAP is required to achieve improved accuracy and reliability in the classification of milder phenotypes.

CONCLUSION

Individuals with the BAP demonstrated atypical social cognition and language pragmatics compared to community controls in the recognition of *faux pas* and the production of fluent social discourse. Graded deficits in *faux pas* recognition were observed in ASD probands, their relatives with the BAP and unaffected family members providing evidence for a specific endophenotypic marker with strong diagnostic utility. The identification of endophenotypes offers a powerful strategy to improve variant detection in clinical genetic studies of ASD. Disaggregating features of the BAP in family members of probands, who may otherwise be broadly classified as "neurotypical controls", may uncover clinical inheritance patterns relevant to identifying causative genes for ASD. This in turn may aid identification of genes involved in atypical social cognition and associated phenotypes, advancing our understanding of the neurobiological basis of ASD and other neurodevelopmental conditions.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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