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Childhood Academic Performance: A Potential Marker of Genetic Liability to Autism

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Abstract

Autism spectrum disorder (ASD), a heritable neurodevelopmental disorder, confers genetic liability that is often expressed among relatives through subclinical, genetically-meaningful traits, or endophenotypes. For instance, relative to controls, parents of individuals with ASD differ in language-related skills, with differences emerging in childhood. To examine ASD-related endophenotypes, this study investigated developmental academic profiles among clinically unaffected siblings of individuals with ASD (n=29) Lower performance in language-related skills among siblings mirrored previously-reported patterns among parents, which were also associated with greater subclinical ASD-related traits in themselves and their parents, and with greater symptom severity in their sibling with ASD. Findings demonstrated specific phenotypes, derived from standardized academic testing, that may represent childhood indicators of genetic liability to ASD in first-degree relatives.

Keywords

Autism spectrum disorder; endophenotype; language; academics; broad autism phenotype

Introduction

Autism spectrum disorder (ASD) is a genetically-based neurodevelopmental disorder with heritability estimates up to 90% (Abrahams & Geschwind, 2008; Freitag, 2007;

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Ethical Approval. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Study procedures were approved by the Northwestern University Institutional Review Board (IRB).

Informed consent. Informed consent was obtained from all individual participants included in the study. Adult participants provided written consent. Participants under the age of 18 or whose parents maintained guardianship were consented via parent consent and assent.

Conflict of Interest. All authors declare that they have no conflicts of interest.

Gupta & State, 2007; Tick et al., 2016), and multiple high confidence risk genes now identified (Rylaarsdam & Guemez Gamboa, 2019; Schaaf et al., 2020). Substantial etiologic heterogeneity is also evident. While *de novo*, rare, structural, and common genetic variations have all been implicated in the genetic architecture of ASD (de la Torre-Ubieta et al., 2016; De Rubeis et al., 2014; Iossifov et al., 2014; Krumm et al., 2015), most cases of ASD are polygenic, resulting from complex interactions involving multiple genes and environmental factors, with <5% of total genetic liability attributable to single gene causes (Bespalova & Buxbaum, 2003; Betancur, 2011; de la Torre-Ubieta et al., 2016; Gaugler et al., 2014; Ronald et al., 2006; State & Levitt, 2011; Szatmari et al., 2007). Investigating endophenotypes in relatives (i.e., traits that can be measured across the clinical to subclinical spectrum and are more directly linked to genetic contributions (Gottesman & Gould, 2003)), may help to disentangle the genetic complexity of ASD and reveal more homogenous subgroups of families who might be effectively stratified for more targeted studies of etiology and treatment.

A substantial body of literature has identified a constellation of subclinical phenotypes present among a subgroup of clinically unimpaired parents of individuals with ASD which may reflect greater genetic liability to ASD, known as the Broad Autism Phenotype (BAP) (Bailey et al., 1995; Bernier et al., 2012; Bolton et al., 1994; Davidson et al., 2014; Folstein & Rutter, 1977; Losh et al., 2008; Piven, 2001; Piven et al., 1997; Piven & Palmer, 1999; Sasson, Lam, et al., 2013; Simonoff et al., 2008). The BAP encompasses personality features and language abilities that are qualitatively similar to the defining characteristics of ASD but are expressed more subtly and are not associated with functional impairment, such as social reticence or inflexibility, and mild differences in pragmatic (i.e., social) language (Hurley et al., 2007; Landa et al., 1992; Losh et al., 2008, 2009; Piven et al., 1997; Piven & Palmer, 1999). Studies seeking to further characterize the neuropsychological profile of the BAP have reported many traits that mirror those seen in individuals with ASD but are milder in expression, such as differences in social cognitive abilities and language-related skills, that warrant further investigation (Hogan-Brown et al., 2014; Hurley et al., 2007; Losh et al., 2009, 2010; Nayar et al., 2018; Norton & Wolf, 2012; Sasson, Nowlin, et al., 2013; Schmidt et al., 2008).

Subtle differences in language-related skills have been particularly notable in clinically unaffected relatives of individuals with ASD ranging from self and informant reported early language delays or literacy difficulties (Bailey et al., 1998; Folstein et al., 1999) and mechanistic differences in language processing and fluency (Hogan-Brown et al., 2014; Nayar et al., 2018; Schmidt et al., 2008), to more nuanced or complex features of pragmatics, including prosody, and narrative generation abilities (Landa et al., 1992; Lee et al., 2019; Losh et al., 2012; Patel et al., 2019, 2021). Several studies have demonstrated reduced fluency on tasks that tap into broader cognitive and linguistic processes that underly complex language among first-degree relatives (Hogan-Brown et al., 2014; Losh et al., 2010; Nayar et al., 2018; Norton & Wolf, 2012). For instance, a study investigating links between eye movement and speech on a task that involves rapid naming of familiar objects (Rapid Automatized Naming, RAN), found slower naming times, and less fluid eye movement patterns during naming (e.g., frequent refixations to previous items) relative to controls, and associations between such patterns and pragmatic language skills (Nayar et al., 2018).

Prior literature also suggests that speech sound processing is impacted in parents, including phonological processing weaknesses evidenced via difficulties with nonword repetition (Schmidt et al., 2008), as well as diminished encoding of speech sounds and less efficient neural systems of audio-vocal feedback (Patel et al., 2022; Patel et al., 2019; Schmidt et al., 2008). Evidence of such broader linguistic weaknesses in ASD and first degree relatives, including linguistic fluency and speech sound processing, suggests that differences in these foundational skills may have downstream impacts on functional language abilities such as pragmatics, and highlight the importance of conductng broader explorations of language related skills to improve understanding of the mechanistic underpinnings of pragmatic language profiles ASD families.

Deeper explorations of pragmatic phenotypes have also revealed discrepancies from controls in the acoustic characteristics of speech that are similar to those observed in ASD and characterized by differences in intonation, modulation of volume, rate of speech, and stress patterns (Landa et al., 1992; Losh et al., 2012; Patel et al., 2019, 2021). Importantly, emerging evidence of the neural underpinnnings of prosodic differences among individuals with ASD and first degree relatives implicates inefficient encoding of speech sounds, characterized by decreased phase locking to pitch frequencies and reduced timing precision, as well as immature auditory and motor system integration. (Patel et al., 2022; Patel et al., 2019). Pragmatic language difficulties have further been evidenced among parents through subtle differences in narrative generation, characterized by decreased complexity and coherence, with overall narrative quality subject to context variability (Lee et al., 2019). Taken together, these findings suggest that language-related skills broadly reflect a prominent area of impact in the BAP that appear complexly related, warranting further investigation to elucidate language based gene-behavior relationships that may contribute to the characteristic social communication difficulties in ASD (Bolton et al., 1994; Bora et al., 2017; Di Michele et al., 2007; Gokcen et al., 2009; Landa et al., 1992; Ruser et al., 2007; Sung et al., 2005; Szatmari et al., 2000; Whitehouse et al., 2007).

One challenge in efforts to characterize language-related differences as endophenotypic markers among parents of individuals with ASD is that studies have been largely limited to the study of adults, who have been identified only after ASD status has been determined in their child. While critical in understanding how complex language skills can be subtly impacted by genetic liability to ASD, important questions remain concerning the developmental trajectories that might lead to such differences in adulthood. Furthermore, existing studies of parents and siblings are potentially confounded by the bidirectional nature of pragmatic language and social behavior, such that having a child or sibling with ASD might influence the content and quality of the one’s language use and styles of social interaction. In one study, however, archival childhood academic testing records (the Iowa Test of Basic Skills, the same as were used in the present study) were examined as a window into earlier developmental periods when such endophenotypes could be first emerging among individuals who would later go on to have a child with ASD (Losh et al., 2017). Using a longitudinal, retrospective design, this study found subtle differences in childhood academic performance and rates of development, particularly evident in language-related skills, that predicted the presence of BAP features in adulthood, as well as ASD symptom severity in their child with ASD. The language domain of the ITBS was most robust in differentiating ASD parents from controls, with differences emerging at the domain level and across several subtests (i.e., language usage and expression, punctuation, and capitalization), though marginal findings emerged in reading comprehension and applied mathematics among subtests with relatively significant language demands. Relatedly, literacy outcomes are often poor for at least a subgroup of individuals with ASD with reading comprehensions standing out as an area of particular weakness (Davidson & Weismer, 2014; Jones et al., 2009; McIntyre et al., 2017; Nation et al., 2006; Solari et al., 2017). Oral language abilities have been shown to co-occur with reading challenges, and are believed to mediate reading difficulties, suggesting that language skills in ASD may reflect an important foundation for reading development and may additionally impact performance in other domains of academics with reliance on on these skills (e.g., applied mathematics) (Bishop & Snowling, 2004; Catts & Kamhi, 2005; Davidson & Weismer, 2014; McIntyre et al., 2017). While mathematical ability is often thought to be an area of strength among many individuals with ASD, some studies have reported evidence of a high frequency of difficulties in mathematics that were predicted by verbal ability and early language skills (McKernan & Kim, 2021; Oswald et al., 2016). Taken together, these findings suggest that specific profiles of language development may serve as potent childhood markers of genetic liability to ASD with potentially broad contributions to academic functioning, and highlight the importance of research into early patterns of language development in first-degree relatives.

Clinically unaffected siblings of individuals with ASD offer additional insight into the early emergence of ASD endophenotypes. The ASD-sibling literature has provided important evidence that language-related skills (and other domains) are indeed impacted early in development among at least a subgroup of siblings without ASD (Ben-Yizhak et al., 2011; Bishop et al., 2006; Bolton et al., 1994; Constantino et al., 2006; Dalton et al., 2007; Dorris et al., 2004; Fombonne et al., 1997; Hogan-Brown et al., 2014; Oerlemans et al., 2013; Pilowsky et al., 2003; Piven et al., 1997; Ruzich et al., 2016; Shaked et al., 2006; Toth et al., 2007). For instance, subgroups of unaffected adolescent siblings have been reported to display mild deficits in social cognition, demonstrated by greater difficulty with emotion recognition when viewing eyes and faces (Dorris et al., 2004; Oerlemans et al., 2013), and atypical social visual attention patterns (e.g., fewer fixations to the eye region of the face), accompanied by differences in underlying brain activation and structure (Dalton et al., 2007).

Similar to parent studies, there have been particularly compelling findings related to language in siblings, noted both in studies of high risk infants and in studies of schoolage and adolescent siblings. For example, clinically unaffected siblings of individuals with ASD have been shown to exhibit elevated rates of early language delays and differences in social engagement, as early as 14 months (Bailey et al., 1998; Gamliel et al., 2007, 2009; Landa et al., 2012; Lindgren et al., 2009; Minton et al., 1982). One study also found that childhood communication difficulties among school age unaffected siblings were associated with atypical communication abilities in their parents who exhibited traits of the BAP, highlighting important intergenerational associations between the BAP and language difficulties in high risk families (Bishop et al., 2006). Additional differences have been reported that mirror those documented in parents, including difficulties with language fluency, demonstrated by tasks of rapid automatized naming, (Hogan-Brown et al., 2014), pragmatic language abilities, (Ben-Yizhak et al., 2011; Eyuboglu et al., 2018; Toth et al., 2007) and phonological awareness (Charman et al., 2017) have also emerged as areas of relative weakness among some siblings. While this growing body of literature suggests some parallels in the phenotypic expression of genetic liability across generations of families impacted by ASD, the BAP has not yet been clearly defined in siblings and it remains relatively unclear if genetic liability presents in the same way among siblings and parents. Important to also highlight is the inconsistency in language related findings in siblings and parents of individuals with ASD. Several studies have documented no differences in structural language skills such as grammar and syntax, or in receptive vocabulary (Cruz et al., 2013; Levy & Bar-Yuda, 2011; Lindgren et al., 2009; Toth et al., 2007), while others have observed difficulties in assessments tapping these domains (Losh et al., 2017; Taylor et al., 2013; Toth et al., 2007). The use of different methodologies and assessment tools likely plays a role in the variability of findings, however, a more nuanced explanation is that only subgroups of first-degree relatives are exhibiting language-related difficulties, highlighting the importance of examining language patterns in the context of broad autism phenotype characteristics that reflect genetic liability to better detect potentially biologically meaningful patterns. Nevertheless, investigations of key findings from the parent literature are an important next step in characterizing the phenotypic expression of genetic liability across generations, and across developmental stages.

To answer this important question, the present study examined archival childhood academic testing records in siblings of individuals with ASD, parallel to those previously studied in parents of individuals with ASD (Losh et al., 2017). Specifically, childhood academic profiles in unaffected siblings of individuals with ASD across the domains of language, reading, and math were examined in comparison with controls. Familial relationships of academic performance were also explored between siblings and their parents, and also within sibling pairs, along social cognitive and psycholinguistic phenotypes that have been implicated in studies of the BAP in adults. We predicted that unaffected siblings would exhibit similar patterns of differences, primarily in language-related skills, that were previously reported in parents, and that familial associations of academic performance would emerge. Further, we explored potential phenotypic clustering within families by examining siblings' childhood academic profiles in relationship to symptom severity in their sibling with ASD, and features of the BAP in their parents. Together, early indicators of genetic liability to ASD that are evident in academic performance and present across generations may help clarify the developmental expression of the BAP, and how such traits aggregate across generations, in individuals with and without clinical impairment.

Methods

Participants

Participants included 29 clinically unaffected siblings of individuals with ASD (SIBS-A) and 88 typically developing controls without a sibling with ASD. Additionally, 43 parents of individuals with ASD and 23 individuals with ASD were included to evaluate familial relationships between SIBS-A academic performance and clinical behavioral phenotypes.

Every effort was made to include intact families for clinical behavioral assessments; however, direct assessment was not always feasible with children with ASD. As such, the sample included 23 of 29 full familes (i.e., both biological parents, child with ASD, and unaffected sibling), the additional 6 families included an unaffected sibling and both parents. Data from parents of individuals with ASD were included from a previously published report (Losh et al., 2017) to permit analyses of familiality of traits across generations. A small subset of 28 previously studied controls from that study were also included (added to the group of 60 newly ascertained control subjects) to increase power in hierarchical linear models, which are robust in tolerating unbalanced samples and heterogeneity of variances between groups, and perform better with greater overall samples (Maas & Hox, 2005; Snijders, 2005). A subset of participants also completed in person assessments of ASD- and BAP-related phenotypes (20 SIBS-A, 36 controls, 22 ASD, and 43 parents). Participants were recruited in the state of Iowa because of the availability of archival academic assessment records collected from students who attended public school in that state. Many of the families affected by ASD were recruited through the University of Iowa Children's Hospital Autism Center, which serves as the primary center for ASD evaluations and treatment in the state of Iowa. Recruitment materials were distributed to families who had been treated at the center inviting them to participate in the study. Additionally, extensive community-based recruitment efforts across the state of Iowa were employed to increase representativeness of the sample (e.g., schools, clinics, advocacy groups, and attendance at community-based events and festivals).

Inclusionary criteria for SIBS-A and controls included grade school attendance in Iowa and English as a first language. The SIBS-A and parent groups included only individuals who had a sibling or child with a clinical diagnosis of ASD and no family history of a genetically based condition associated with ASD, such as fragile X syndrome or Rett syndrome. Control participants were screened for personal and family history of ASD, related neurodevelopmental disorders, and language or cognitive impairments.

ASD status was confirmed for participants in the ASD group using the Autism Diagnostic Observation Schedule-2 (ADOS-2;Lord et al., 2012) and medical records with ASD status diagnosed based on meeting criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) -IV or −5 criteria (American Psychiatric Association, 2013). For participants in the SIBS-A group, ASD diagnoses were ruled out by administering the ADOS-2 or the Social Responsiveness Scale (SRS;Constantino, 2013), as well as collecting detailed medical histories to screen for history of ASD-related concerns. IQ was measured using the Wechsler Intelligence Scale for Children—Third Edition (WISC-III) or the Wechsler Abbreviated Scale of Intelligence (WASI) (Stano, 2004; Wechsler, 1949). SIBS-A and control groups included comparable numbers of males and females (see Table 1; $p=.66$). There were no significant differences in overall IQ between SIBS-A and controls ($p=.172$), although SIBS-A had a significantly higher mean verbal intelligence quotient (VIQ) compared to controls ($t(31)=2.5$, $p<.05$). Controls were significantly older than SIBS-A at the time of enrollment when in person assessments were completed ($t(114)=-13.077$, $p<.001$), which reflects the inclusion of all control participants in the comparison group who had available archival testing data, as testing records were obtained from childhood at the same age, and thus results reflect group performance during childhood based on grade level. See Table 1 for sample characteristics.

Procedures

Childhood academic testing records were obtained for SIBS-A, parents, and controls from the Iowa Test of Basic Skills (ITBS;Hoover et al., 2001) and its analog used in high school, the Iowa Tests of Educational Development (ITED;Forsyth et al., 2001), described in greater detail below. Procedures were approved by the Northwestern University Institutional Review Board and informed consent was obtained by all participants.

Academic Skill Assessments

The Iowa Test of Basic Skills and Iowa Test of Educational Development.— ITBS (grades K-8) and ITED (grades 9–12) were developed at the University of Iowa and are nationally standardized, norm-referenced tests that have been annually administered in the state of Iowa since the 1950s. Henceforth, both assessments will be referred to collectively as ITBS. These tests evaluate annual performance across the core academic subjects of language, reading and math. Each subject is comprised of subtests as follows: 1) language subtests include spelling, capitalization, punctuation, and language usage and expression; 2) reading subtests include vocabulary and comprehension; and 3) math subtests include concepts, and problem solving. Descriptions of composite scales and subtests are provided in Table 2.

Woodcock Johnson Tests of Achievement.—At the time of enrollment, the WJ-III (Woodcock et al., 2001) was administered to siblings as a measure of stability and consistency of academic skills. The WJ-III is a well validated measure with strong psychometric properties that has been used extensively in research (Woodcock et al., 1990, 2001). Analyses focused on the WJ-III broad reading (Letter–Word Identification, Reading Fluency, Passage Comprehension subtests) and broad mathematics standard scores (Calculations, Math Fluency, as well as the Math Calculation Skills subtests), which were most comparable to skills assessed in the ITBS.

ASD-related phenotypes in siblings and individuals with ASD

Autism Diagnosis and Symptom Severity.—The Autism Diagnostic Observation Schedule-2 (ADOS-2;Lord et al., 2012) was used to verify ASD diagnostic status in the ASD group and a subset (n=16) of the SIBS-A groups. Algorithm scores from the Social Affect and Restricted and Repetitive Behavior domains as well as calibrated overall severity comparison scores were used as measures of symptom severity in correlational analyses (Gotham et al., 2009; Lord et al., 2012).

Pragmatic Language.—Pragmatic language abilities were assessed using the Pragmatic Rating Scale-School Age (PRS-SA;Landa, 2011) or the Pragmatic Rating Scale (PRS;Landa et al., 1992). The PRS-SA is designed to evaluate pragmatic language abilities in children and is rated from semi-structured play and conversation from the ADOS-2 (Lord et al., 2012). For participants older than 18 years at the time of enrollment, the PRS was used. The PRS is coded based on a semi-structured conversational interview in which an examiner asks a series of questions about their childhood, schooling, social relationships, and occupation. Participants' language samples were coded utilizing similar coding schemes tapping key pragmatic skills (e.g., providing appropriately detailed information versus giving overly detailed or insufficient or vague responses; adopting appropriate register and avoiding too candid or personal topics, etc.). Two coders, blind to group classification, independently rated the interactions for pragmatic language features on a three-point scale, with 0 indicating absent, 1 indicating mild, and 2 indicating present. The coders resolved coding discrepancies through discussion in order to reach a consensus. As participants in the sibling group completed either the PRS or the PRS-SA, depending on their age, proportion scores were derived for each task and combined into a single Pragmatic Language score to increase power in analyses.

Social Cognition.—Social cognition was assessed utilizing the adult or adolescent version of the Reading the Mind in the Eyes Test-Revised (Baron-Cohen, Wheelwright, Hill, et al., 2001). During this task, participants were asked to select an adjective that best represents the emotion being conveyed through an image of the eye region of the face. The adolescent version was adapted to include fewer test items and simplified response options to make it more suitable for a younger cohort (Baron-Cohen, Wheelwright, Spong, et al., 2001). Scores are converted into percent correct; thus, higher percentage scores reflect greater performance.

BAP-related phenotypes in parents of individuals with ASD

Personality Traits.—Personality features associated with the BAP (socially aloof and rigid) were assessed using the Modified Personality Assessment Schedule-Revised (MPAS-R;Tyrer, 1988) which has been used extensively in prior studies of the BAP (Losh et al., 2008, 2017; Nayar et al., 2020; Piven et al., 1997). The MPAS is a semi-structured interview that probes for the presence of subtle personality traits that mirror the core social and restricted/repetitive symptoms of ASD. Subject interviews were conducted by trained interviewers, and consensus coded by two independent raters, with coding based on concrete examples of trait endorsement. MPAS data were only collected within the ASD parent group.

Pragmatic Language.—Pragmatic language abilities were assessed in parents using the PRS (Landa et al., 1992), as described above.

Social Cognition.—Social cognition was assessed in parents using the adult version of the Reading the Mind in the Eyes Test-Revised (Baron-Cohen, Wheelwright, Hill, et al., 2001), as described above.

Data Analysis

The data analytic plan followed that employed in a prior study of the ITBS in parents of individuals with ASD (Losh et al., 2017), using hierarchical linear models to determine estimates of academic skills and development over time (HLM;Raudenbush & Bryk, 2002; Singer et al., 2003). HLM was employed to account for repeated measures that cluster within participants (i.e., individual participants' academic scores from multiple grades) and as a more conservative approach for comparing performance across multiple academic domains (Gelman et al., 2012). Estimations of both fixed effects (i.e., parameters for the sample as a whole) and random effects (i.e., parameters for participants at the individual level) were derived. This method of analysis allowed for comparison of academic performance and rates of development across groups in the test composites of language, reading and math, as well as the subtests associated with each domain. Each model included group (SIBS-A versus controls), grade, and the interaction between group and grade as predictors of academic performance. Random effects produce values for individual performance at each grade level (represented as the intercept) and individual growth over time (represented as the slope). Individual state-normed grade equivalent scores from all grades where data were available for each participant (ranging K-12) were commited to hierarchical linear models. On average, each participant contributed data from seven grade time points. The data were centered at third grade to account for sparser data at the earliest and latest grades. As such, group effects are interpreted as differences between groups at the third-grade time point. In an effort to to detect potentially subtle group effects in this unique set of data, marginal effets are reported in the results pertaining to academic performance, and should be interpreted with caution. Although the SIBS-A group demonstrated significantly higher mean VIQ at the time of enrollment, VIQ was not included as a covariate in analyses due to collinearity of intelligence and academic performance (Mayes et al., 2009), and to mirror previously discussed analyses conducted in parents (Losh et al., 2017). Additionally, given that the SIBS-A group exhibited a *higher* mean IQ and VIQ, this was deemed a more conservative approach, given our hypothesis that the SIBS-A group will exhibit lower childhood ITBS performance relative to controls.

Random effects were extracted from the HLM for correlational analyses, including (1) associations between academic performance among SIBS-A and expression of ASD-related phenotypes (i.e., ASD symptoms, pragmatic language, social cognition) in themselves, and their clinically affected siblings with ASD, and (2) associations between the SIBS-A group's academic performance profiles and BAP-related phenotypes in their parents (i.e., personality features of the BAP, pragmatic language, and social cognition), and (3) familial relationships of academic performance between the SIBS-A and ASD parent groups. All correlational analyses with ASD parent groups were conducted with mothers and fathers separately in order evaluate potential patterns of lineality. Given the large number of subtests comprising each composite score, and that we did not have specific predictions about how performance across the subtests of the three composite scores might interrelate across siblings and parents, analyses focused more specifically on parent-child relationships within the same composite score or subtest only (e.g., child and parent language usage and expression subtest performance and rate of development were examined, but cross subtest or cross domain relationships were not examined). Finally, associations between siblings' academic performance on the ITBS and their academic achievement on the WJ-III at the time of enrollment were explored to assess the stability and consistency of academic achievement over time.

Results

Developmental Academic Performance.

Results of the HLM models revealed no main effects for group (SIBS-A and control) in performance or rates of development on the ITBS composite scores, though a marginal effect was evident in the language composite, with SIBS-A's performance trending lower relative to controls ($t(449) = 1.79$, $p = 0.07$, see Table 3, Figure 1). Significant group effects were evident in capitalization ($t(311) = 2.17$, $p <. 05$) and language usage and expression subtests ($t(324) = 2.65$, $p < .01$) within the language domain, such that the SIBS-A group demonstrated lower performance than controls. No group effects emerged in subtest performance in the domains of reading or math (see Table 4, Figure 1). Results revealed no significant group effects in rates of development across composite scores or subtests of the ITBS; however, a marginal group effect emerged on the language usage and expression subtest ($t(324) = 2.65$, $p = .055$; see Table 4), characterized by slower development in the SIBS-A group relative to controls.

Current Standardized Measure of Academic Achievement.—The SIBS-A group performed in the average range relative to established norms on both the reading and math domains of the WJ-III at the time of enrollment, though significant variability was observed across participants (broad math M=97.38, SD=23.93, broad reading M=96.46, SD=15.11). Among SIBS-A, increased achievement on the broad reading score and broad math indices on the WJ-III were significantly associated with better performance on the ITBS across all composite scales and subtests in the domains of language, reading, and math (ps <.05), with the exception of the capitalization subtest of the ITBS, which was significantly associated with WJ-III broad math score, but only marginally associated with broad reading scores ($p = .06$). All associations are presented in Table 5.

Correlations with ASD-related phenotypes in siblings of individuals with ASD

Pragmatic Language.—No significant associations emerged between childhood academic performance and pragmatic language abilities within the SIBS-A group (rs< |.42|, *p*s > .12).

Social Cognition.—Within the SIBS-A group, lower performance on the language usage and expression subtest, overall reading performance, and performance on the reading comprehension subtest were associaited with poorer social cognition ($r(16) = .53$, $p < .05$; $r(20) = .45$, $p < .05$; $r(20) = .50$, $p < .05$, respectively; see Figure 2).

Correlations with ASD-related phenotypes in siblings and individuals with ASD

ASD Symptom Severity.—A slower rate of development in the capitalization, and language usage and expression subtests among the SIBS-A group was associated with increased symptom severity in the social affect domain in the ASD group ($r(14) = -.54$, $p <.05$; $r(14) = -.57$, $p < .05$) No significant associations emerged with overall severity scores or in the restricted and repetitive behavior domain.

Pragmatic Language.—No significant associations emerged between childhood academic performance within the SIBS-A group and pragmatic language abilities in the ASD group (rs< |.53|, *p*s > .10).

Social Cognition.—A slower rate of development among SIBS-A in language and math, and in the reading vocabulary and math problem solving subtests was significiantly associated wth poorer social cognitive abilities in the ASD group ($r(8) = .79$, $p < .05$; $r(9) = .71$, $p < .05$; $r(9) = .67$, $p < .05$; $r(9) = .78$, $p < .05$, respectively).

Correlations with BAP-related phenotypes in parents of individuals with ASD

Personality Features of the BAP.—Different patterns of association were observed between mothers' and fathers' BAP traits and siblings' ITBS performance. In mothers, rigid personality style was associated with a slower rate of development in language in the SIBS-A group, and with slower development in the capitalization, and language usage and expression subtests specifically ($r(15) = -.60$, $p < .05$; $r(14) = -.80$, $p < .01$; $r(14) = -.72$, $p < .01$, respectively; see Figure 2). Social aloofness among mothers was also associated with slower rates of development in the capitalization and language usage and expression subtests in the SIBS-A group ($r(14) = -.62$, $p < .05$; $r(14) = -.54$, $p < .05$, respectively; see Figure 2).

Among fathers, rigid personality style was associated with a *faster* rate of development in reading overall and the reading comprehension subtest in the SIBS-A group ($r(16) = .55$, $p <.05$; $r(16) = .67$, $p <.01$, respectively), as well *better* performance across math subtests of concepts and problem solving ($r(17) = .50$, $p < .05$; $r(17) = .50$, $p < .05$, respectively). There were no significant associations with the socially aloof dimension of the BAP in fathers; however, a marginal positive association emerged with social aloofness and faster rates of development in reading vocabulary ($r(16)$, $p = .06$).

Pragmatic Language.—No associations emerged between pragmatic language abilities in mothers or fathers and academic performance or rate of development on the ITBS in the SIBS-A group (*p*s > .10)

Social Cognition.—Examining parent-specific associations revealed a marginal association between lower social cognitive abilities in mothers and a slower rate of development in capitalization in their children from the SIBS-A group ($r(14) = .53$, $p = .051$). No associations emerged between fathers' social cognition and rate of development or academic performance in the SIBS-A group (rs< |.47|, *ps* >.12).

Parent-Child Relationships in Academic Performance

Parent-child associations of ITBS performance revealed significant positive correlations in the language domain for mothers, and in the math domain for fathers. Specifically, mothers' performance and rate of development on the usage and expression subtest were positively correlated with their child's performance and rate of development on this same subtest ($r(13) = .60$, $p <.05$; $r(12) = .60$, $p <.05$, respectively). Fathers' rate of development in the math composite and on the problem solving subtest were positively associated with their child's performance on those tests ($r(9) = .67$, $p < .05$; $r(13) = .64$, p

< .05, respectively). Conversely, in reading, significant positive correlations were evident in both mother-child and father-child dyads. Mothers' overall reading and vocabulary performances were positively correlated with their child's rate of development in reading overall and vocabulary ($r(13) = .52$, $p < .05$; r(13) = .54, p <.05, respectively). Father's overall reading performance and rate of development were associated with their childs rate of development in reading overall ($r(9) = .69$, $p < .01$; $r(9) = .65$, $p < .05$, respectively). In reading comprehension, fathers' performance was associated with their child's performance and rate of development on that subtest ($r(9) = .52$, $p < .05$; $r(9) = .71$, $p < .05$, respectively)

Discussion

This study investigated patterns of developmental academic performance among siblings of individuals with ASD across the domains of language, reading, and math, making use of archival, longitudinal data available from childhood. Findings revealed differences primarily in language-related skills, mirroring findings from parallel data previously reported among parents (Losh et al., 2017), and suggesting overlapping developmental language performance patterns across generations of first-degree relatives of individuals with ASD. Further, lower performance on these language subtests among siblings was associated with increased ASD severity in affected siblings, and the presence of BAP personality features in parents, with different patterns of parent-child asosciations in mothers and fathers. This familial clustering of phenotypes may point toward language development profiles in siblings as an important childhood phenotypic marker of genetic liability to ASD.

Consistent with prior literature documenting differences in pragmatic language and broader language skills among first-degree relatives of individuals with ASD, siblings of individuals with ASD demonstrated lower performances relative to controls in overall language performance, and specifically in the capitalization and language usage and expression subtests of the ITBS, as well as a slower rate of development on the language usage and expression subtest. Both of these subtests tap complex grammatical language skills, including correct usage of verbs, distinguishing pronouns, modifiers, word choice, and agreement and require the testee to integrate information across utterances to make inferences on the communicative intent and meaning of passages to differentiate statements from questions and identify pauses and mark pauses or breaks. The language and usage subtest also assess understanding of discourse organization, clarity, and appropriateness of expression. In sum, performance on these subtests reflect a more complex integration of language skills, including foundational structural language abilities as well as tapping more nuanced components of pragmatics to make inferences and determine appropriate language usage, consistent with higher-level functional language skills that are often seriously impacted in ASD. It is notable that such differences were evident among siblings of individuals with ASD in spite of siblings' higher mean verbal intelligence scores, and no differences were detected in reading or math skills. This finding suggests specific and subtle differences in language usage among ASD siblings that IQ assessments, which primarily query vocabulary knowledge, are not able to detect. It is also striking that differences between groups only emerged in such assessments examining functional language, despite the reliance on other additional academic skills, such as literacy abilities, where differences were not observed. Together with findings that these same subtests of capitalization and usage and expression were also relatively delayed in childhood for parents of individuals with ASD (Losh et al., 2017), these findings suggest specific language-related skills tapped by these subtests are impacted by genetic liability to ASD. Across both studies, differences in performance were subtle, and first-degree relatives of individuals with ASD were still on average performing above grade level, which is consistent with prior evidence suggesting that features of the BAP are subclinical in nature, not associated with functional impairment, and only observed in a subset of individuals.

Differences in pragmatic language and social cognitive abilities have been consistently implicated in the BAP (Ben-Yizhak et al., 2011; Di Michele et al., 2007; Hurley et al., 2007; R. Landa et al., 1992; Losh et al., 2009; Losh & Piven, 2007; Sasson, Nowlin, et al., 2013; Yirmiya et al., 2006), and such measures were used here to evaluate links between early academic performance and BAP-associated traits within siblings. Indeed, findings revealed links between childhood language usage and expression and social cognitive abilities, suggesting that this subtest in particular may tap skills that are influenced by increased genetic liability for ASD in early development.These findings are consistent with Losh *et al.*'s earlier report of academic developmental in parents (Losh et al., 2017), which also identified important relationships between academic trajectories and ASD endophenotypes in adulthood among parents, where patterns of childhood academic performance predicted the presence of social and language features of the BAP and social cognitive abilities. Further, in both studies relationships emerged with the rate at which language skills developed in parents and siblings and the degree of ASD symptom severity in their family member with a clinical diagnosis of ASD. Identifying such phenotypic markers in childhood, evident in both siblings and parents, sheds light on the childhood emergence of ASD endophenotypes that may serve as a precursor to adult BAP presentations. These findings contribute to extensive literature characterizing ASD endophenotypes among first-degree relatives. Importantly, these results are also consistent with prior genetic studies of ASD that have identified several risk loci that are associated with language phenotypes in individuals with ASD and their family members, spanning the subclinical to clinical spectrum, and overlapping with other language-related disorders (Alarcón et al., 2008; Bartlett et al., 2014; Nayar et al., 2020).

Furthermore, the present study identified key associations that suggest differential parent-child relationships for mothers and fathers, where only mothers' BAP characteristics and childhood language abilities were related to siblings' language abilities. Indeed, a growing body of literature has suggested that the presence and quality of ASD endophenotypes differ among mothers and fathers, as do relationships between parent endophenotypes and their child's clinical behavioral presentation (Flippin & Watson, 2018; Hasegawa et al., 2015; Losh et al., 2010; Nayar et al., 2020; S. Patel et al., 2022; Seidman et al., 2012). Consistent with the results reported here, several studies have found BAP traits in mothers, but not fathers, to be linked to child language abilities in individuals with ASD (Flippin & Watson, 2018; Hasegawa et al., 2015; Nayar et al., 2018, 2020). Similarly, we identified that in mothers, both of the core personality features that comprise the BAP (social aloofness and rigidity) were robustly associated with slower development of language abilities in their clinically unaffected child. Conversely, rigid personality style among fathers was associated with a faster rate of development in math and reading. A recent study exploring the interrelationships between polygenic risk, traits of the BAP, and ASD symptom expression among ASD families also reported strikingly similar results, where mothers, but not fathers, who evidenced increased ASD polygenic risk scores also exhibited greater pragmatic language difficulties associated with the BAP (Nayar et al., 2020). Furthermore, they found that maternal pragmatic language ability was related to severity of social communication impairment in their child with ASD, whereas in fathers, more rigid personality styles were associated with increased restricted and repetitive behaviors in their child.

Similarly distinct patterns were also evident in parent-child relationships of academic performance on the ITBS. Mothers' childhood language ability was associated with their child's language ability and fathers' childhood math ability was associated with their child's math ability. Previous work suggests that ASD may be more common among children whose fathers are mathematicians, physicists, and scientists, and that mathematicians themselves score higher on scales measuring autistic traits, which may explain father-child relationships in childhood math ability, as well as relationships between child math ability and rigid personality features in fathers (Baron-Cohen, 1998; Baron-Cohen, Wheelwright, Skinner, et al., 2001). Together, these findings demonstrate a pattern of lineality consistent with stronger heritability for ASD-related language traits from mothers, and restricted and repetitive behaviors or rigid phenotypes from fathers. Consistent with prior work, these findings inform understanding of the intergenerational transmission of ASD related phenotypes, and provide evidence for differential transmission among mothers and fathers and familial clustering of ASD-related traits. Such co-aggregation of key phenotypes among family members and across generations may be particularly informative for understanding the genetic etiology of ASD, as they may represent phenotypes that could be used to define more genetically homogenous subgroups of families, and guide genetic analyses that incorporate phenotypes on family members.

In sum, the results of this study add to findings in parents suggesting that patterns of academic language development among first-degree relatives of individuals in ASD may be important to study for clues into the genetic etiology and heritability of ASD. Given their standardized nature, and widespread administration, academic achievement tests may be particularly fruitful for extracting key phenotypes to help guide ASD genetic studies and to disaggregate the complex ASD phenotype into genetically meaningful traits that can be more directly investigated across affected and unaffected individuals. This approach has the potential to identify more genetically homogenous subgroups of families and may help to elucidate the underlying pathogenesis of ASD as well as contribute to the understanding of biological mechanisms underlying language that cross diagnostic boundaries.

Limitations and Future Directions

An important consideration in interpreting findings concerns the generalizability of these findings to more diverse populations, and the potential implications of environmental factors on the presented results. Although every effort was made to include a representative sample of participants (e.g., recruiting over an extended period of time, through widespread venues in both rural and metropolitan areas) academic testing records were nonetheless available only on residents of Iowa, who were mostly Caucasian. Socio-economic factors and access to educational resources are undoubtedly related to academic achievement outcomes (see Sirin, 2005 for review). It will be important that future studies investigating academic performance, and in particular studies investigating potential genetic contributions, characterize these relationships thoroughly.

Furthermore, it is possible that siblings' language development is impacted by virtue of having a sibling with ASD, where communication interactions with both parents and a clinically affected sibling may be shaped in ways that influence a child's language and academic development. The role of parenting style is also important to consider, particularly when interpreting parent-child correlations that appear to suggest specific patterns of lineality, with language-related traits in siblings cosegregating with BAP traits in mother-child dyads and math-related skills more associated with the BAP in father-child dyads. It could be that mothers are interacting more frequently with their children, thus contributing more to early language development. Importantly, however, research suggests that maternal and paternal language interactions contribute comparably to language development in their children, which suggests that mother-child language associations observed here may in fact be capturing genetic contributions (Pancsofar et al., 2010; Pancsofar & Vernon-Feagans, 2006). Furthermore, such striking similarities in profiles observed among siblings and those previously documented among parents (where their academic performance was measured in childhood, prior to having a child with ASD), are suggestive of a biological basis. That is, the similar childhood patterns observed among both parents and siblings may suggest that this trend in academic performance is not attributable solely to such environmental influences, but instead reflective of heritable factors conferring ASD-genetic risk that contribute to the developmental trajectory of language-related skills. Although environmental influences are important considerations, it is noteworthy that a large-scale study examining polygenic scores for ASD among individuals with ASD and their parents highlighted divergent sex-related patterns in associations with ASD traits, and in particular matrilineal pragmatic language abilities. Together with findings from the current study, these results suggest that traits related to ASD may be sex-linked among clinically unaffected relatives as well. Taken together, it would additionally be worthwhile to further investigate sex differences at the child level in larger samples, to evaluate whether the heritability of traits differs in mothers and fathers with male and female children.

Additionally, whereas associations between childhood academic performance and a current standardized measure of academic achievement at the time of enrollment suggest consistency of academic performance over time, ITBS data were sparser at upper and lower time points, and longitudinal findings should therefore be verified in larger samples in younger and older school-age groups in particular. Such analyses would also offer an opportunity to assess academic trajectories using growth curve analyses to evaluate for nonlinear developmental patterns. It is important to also note that both sibling and control groups in this study performed well above average on standardized assessments of IQ, which may explain why both groups performed above grade level expectation across domains of the ITBS. Replication of these analyses in a more representative sample with regard to overall IQ will be important to more accurately characterize how developmental trajectories may deviate from controls in unaffected siblings of individuals with ASD.

Conclusions

In conclusion, this study identified patterns of relatively lower performance and slower development in language-related skills among clinically unaffected siblings of individuals with ASD that mirror those previously documented among parents, and that were associated with more severe ASD symptomatology in siblings with ASD, and the presence of the BAP in parents, and mothers in particular. Findings add to existing literature that has documented patterns of lineality consistent with maternal inheritance for a constellation of language-related features. Taken together, these findings may contribute to a potential developmental language profile that can be studied for insights into the genetic transmission of ASD, and using standardized academic testing records that could be studied in population-based samples.

Abbreviations:

ASD	autism spectrum disorder
ADOS-2	Autism Diagnostic Observation Schedule, 2nd Edition
BAP	Broad Autism Phenotype
ITBS	The Iowa Test of Basic Skills and Iowa Test of Educational Development
PRS-SA	Pragmatic Rating Scale-School Age
PRS	Pragmatic Rating Scale

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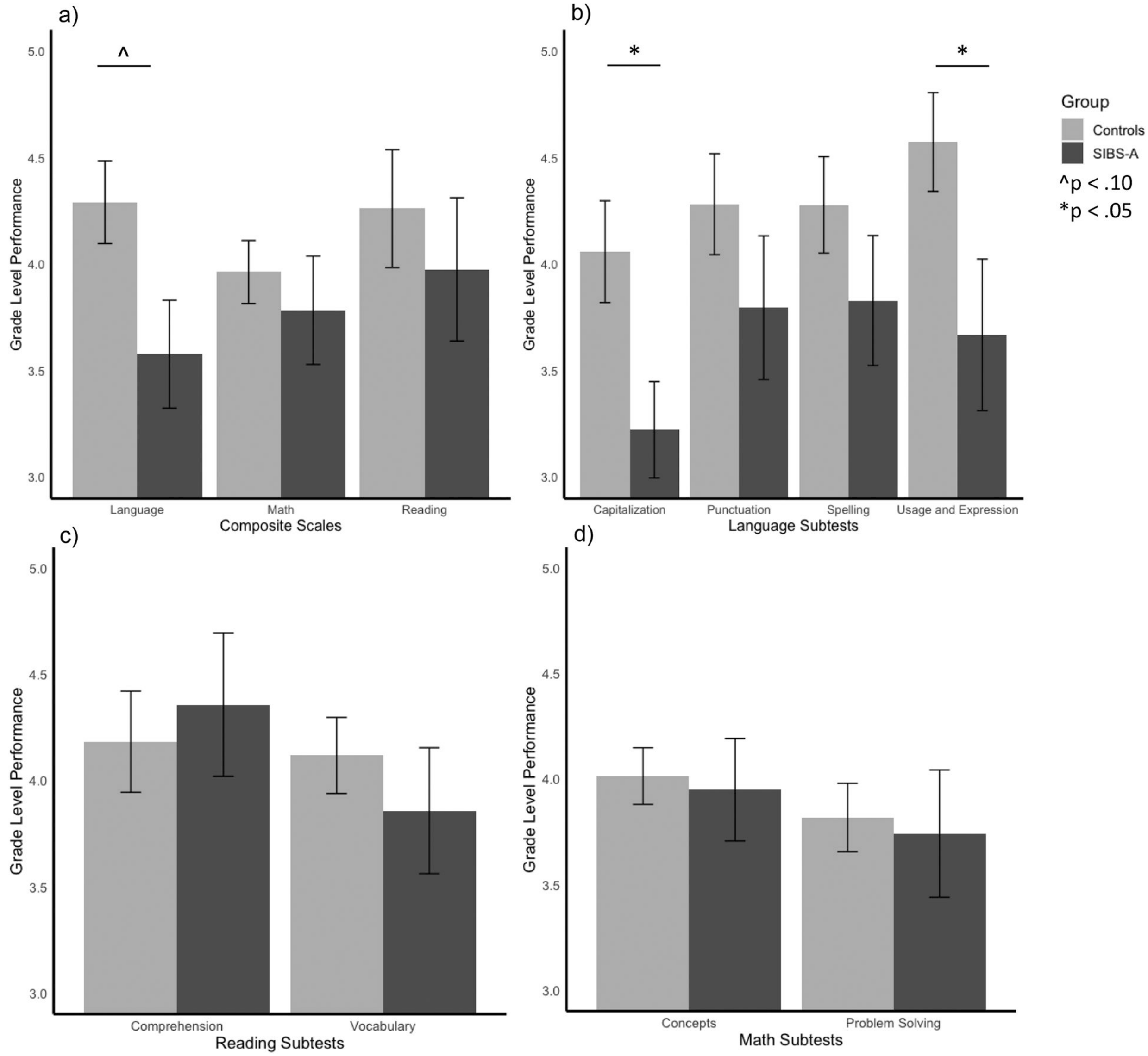

Figure 1.

Estimated grade 3 performance across domains and subtests among SIBS-A and controls. Groups did not differ across composite scores, though the SIBS-A group trended lower than controls in the language composite (a, p=.07). The SIBS-A group performed significantly lower than controls on the capitalization and language usage and expression Subtests ($p < .05$, $p < .01$, respectively) within the language domain (b), but no differences emerged on reading or math subtests (c, d).

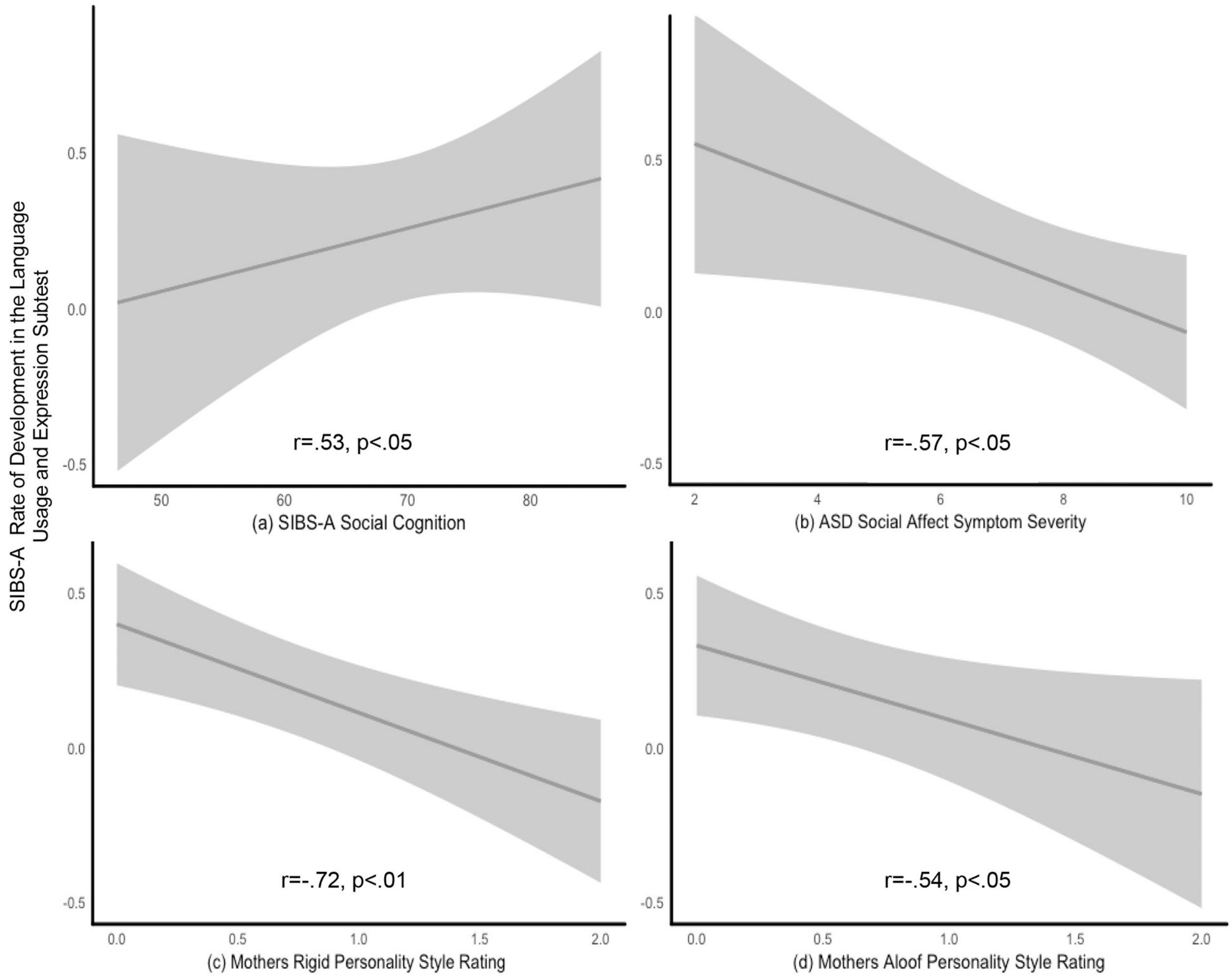

Figure 2.

Associations between SIBS-A language development and clinicial-behavioral features. Patterns of childhood development on the ITBS language usage and expression subtest among siblings of individuals with ASD are associated with ASD and BAP phenotypes in themselves, their parents, their sibling with ASD. A slower rate of development on this subtest in ASD siblings was significantly associated with (a) poorer performance on a task of social cognition (b) increased social affect symptom severity on the ADOS-2 in their clinically affected sibling, and (c) increased rigid and (d) aloof personality styles in their mothers. The grey shaded area represents the 95% confidence interval.

Table 1:

Participant Characteristics

	SIBS-A	Controls	ASD	ASD-parents
N	29	88	23	43
Sex (M:F)	17:12	57:31	23:0	21:22
Age at Enrollment	17.15 (6.37)***	43.41 (15.71)	14.70 (5.56)	46.20 (7.02)
IQ	118.71 (11.60)	113.37 (12.51)	99.85 (17.43)	113.85 (9.38)
VIQ	121.29 (13.30)*	110.42 (13.89)	99 .00(22.50)	113.46 (8.86)
PIQ	113.57 (12.78)	112.8 (14.74)	95.77 (21.89)	111.06 (11.76)
ADOS [1]	1.17 (.389)	--	7.55 (2.52)	--
SRS [2]	51.30 (14.54)	--	83.76 (12.97)	--
PRS/PRS-SA [3]	.11 (.07)	--	.37 (.15)	.18 (.11)
MPAS Rigid [4]	--	--	--	.84 (.78)
MPAS Aloof [4]	--	--	--	.72 (.74)
Eyes Task5	69.17 (12.31)	--	60 (13.33)	76.06 (11.30)

Notes: Group comparisons reflect SIBS-A vs. Controls,

*p<.05,

**<p.01,

***p<.001

[1]ADOS Calibrated overall severity scores (range 1–10),

[2]SRS Total T Scores,

[3]Calculated proportions combing PRS or PRS-SA total scores (range 0–1),

[4]MPAS 5-point scale ratings (range 0–2),

[5]Eyes task percentage correct

Table. 2

Description of ITBS composite scales and subtests

Composite Scale	Subtest	Description
Language	Spelling	Identifying words spelled incorrectly from array of choices, assessing phonological and phonemic awareness
	Capitalization	Identifying capitalization errors in a body of text, including recognition of different lexical and syntactic categories denoted by capitalization rules
	Punctuation	Identifying punctuation errors (including under- and over-punctuation) in passages, identifying possessives, plurals, use of contractions, marking of compound and complex sentences, use of ellipsis
	Usage and expression	Identifying grammatical errors in a passage, such as verbs, pronouns, modifiers, agreement, etc., also involving judging discourse organization, clarity, and appropriateness of expression
Reading	Vocabulary	General vocabulary content assessed by matching words with correct pictures and completing sentences with appropriate word
	Reading comprehension	Assesses comprehension of sentences, passages, and stories, including drawing inferences to generalize about material
Math	Concepts	Assesses understanding of number properties, operations, numerical and geometric patterns, and measurement
	Problem solving	Solving word problems and interpreting data from graphs and tables

Table 3.

Fixed effects of grade level and group on ITBS composite scores

Group and Grade comparisons, fixed effects	ITBS Composite Scores		
	Language Estimate (SE)	**Reading Estimate (SE)**	**Math Estimate (SE)**
Intercept	4.04 (0.02)‡	4.29 (0.4)‡	4.2 (0.2)‡
Grade	1.12 (0.04)‡	1.12 (0.04)‡	1.13 (0.04)‡
Group (Controls vs. SIBS-A)	0.72 (0.4)^	0.1 (0.36)	0.14 (0.4)
Grade*Group	−0.12 (0.08)	−0.05 (0.07)	−0.06 (0.08)

Notes: Intercept represents the estimated grade equivalent of ITBS scores at third grade. Estimated values represent the estimated degree of change as a result of the predictor variable (e.g., grade or group). With regard to grade estimates, a score of 1 is interpreted as 1 grade level increase per grade. All Random Effects are significant.

^ $p < .10$,

‡ $p < .001$

Table 4.

Fixed Effects of grade level and group on ITBS subtest performance

	Language				Reading		Math	
Group and Grade comparisons, fixed effects	**Spelling Estimate (SE)**	**Capitalization Estimate (SE)**	**Punctuation Estimate (SE)**	**Usage and Expression Estimate (SE)**	**Vocabulary Estimate (SE)**	**Comprehension Estimate (SE)**	**Concepts Estimate (SE)**	**Problem Solving Estimate (SE)**
Intercept	4.07(0.2)‡	3.49(0.22)‡	4.03(0.21)‡	3.99(0.23)‡	4.19(0.17)‡	4.46(0.22)‡	3.99(0.13)‡	3.96(0.17)‡
Grade	1.11(0.05)‡	1.24(0.08)‡	1.19(0.08)‡	1.28(0.08)‡	1.1(0.04)‡	1.12(0.04)‡	1.19(0.05)‡	1.24(0.06)‡
Group (Controls vs. SIBS-A)	0.31(0.4)	0.96(0.44)*	0.56(0.41)	1.23(0.47)†	−0.08(0.34)	−0.08(0.43)	0.050.26)	−0.13(0.33)
Grade*Group	−0.12(0.1)	−0.16(0.16)	−0.08(0.15)	−0.29(0.15)^	−0.03(0.08)	−0.04(0.09)	−0.11(0.1)	−0.1(0.12)

Notes: Notes: Intercept represents the estimated grade equivalent of ITBS scores at third grade. Estimated values represent the estimated degree of change as a result of the predictor variable (e.g., grade or group). With regard to grade estimates, a score of 1 is interpreted as 1 grade level increase per grade. All Random Effects are significant.

^ $p < .10$

* $p < .05$,

† $p < .01$,

‡ $p < .001$

Table 5.

Pearson's correlations of ITBS scores and WJ-III Broad Reading and Math indices in the SIBS- A group

ITBS	WJ-III Broad Reading	WJ-III Broad Math
	r values	
Language Composite	**.69** *	**.75** **
Spelling	**.70** *	**.74** **
Capitalization	.59^	**.70** *
Punctuation	**.63** *	**.71** **
Usage	**.72** *	**.63** *
Reading Composite	**.78** **	**.73** **
Vocabulary	**.78** **	**.68** *
Reading Comprehension	**.75** **	**.74** **
Math Composite	**.82** **	**.78** **
Concept	**.79** **	**.83** **
Problem Solving	**.80** **	**.74** **

Notes:

^ $p<.1$,

* $p < .05$,

** $p<.01$