Archival Report

Subcortical Brain and Behavior Phenotypes Differentiate Infants With Autism Versus Language Delay


ABSTRACT

BACKGROUND: Younger siblings of children with autism spectrum disorder (ASD) are themselves at increased risk for ASD and other developmental concerns. It is unclear if infants who display developmental concerns, but are unaffected by ASD, share similar or dissimilar behavioral and brain phenotypes to infants with ASD. Most individuals with ASD exhibit heterogeneous difficulties with language, and their receptive-expressive language profiles are often atypical. Yet, little is known about the neurobiology that contributes to these language difficulties.

METHODS: In this study, we used behavioral assessments and structural magnetic resonance imaging to investigate early brain structures and associations with later language skills. High-risk infants who were later diagnosed with ASD \( (n = 86) \) were compared with high-risk infants who showed signs of early language delay \( (n = 41) \) as well as with high- and low-risk infants who did not have ASD or language delay \( (n = 255 \text{ and } 143, \text{ respectively}) \).

RESULTS: Results indicated that diminished language skills were evident at 12 months in infants with ASD and infants with early language delay. At 24 months of age, only the infants with ASD displayed atypical receptive-expressive language profiles. Associations between 12-month subcortical volumes and 24-month language skills were moderated by group status, indicating disordinal brain-behavior associations among infants with ASD and infants with language delay.

CONCLUSIONS: These results suggest that there are different brain mechanisms influencing language development in infants with ASD and infants with language delay, and that the two groups likely experience unique sets of genetic and environmental risk factors.

Keywords: ASD, Brain, Infancy, Language delay, Language profile, Subcortical structure

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In the first 2 years of life, the brain undergoes dynamic changes that are influenced by genetic and environmental factors. In infants later diagnosed with autism spectrum disorder (ASD), aberrant brain development is apparent during the first year of life, well before the defining features are exhibited \( (1–5) \). Delayed language onset is often the first warning sign for ASD, and the majority of affected individuals exhibit difficulties in speech production, speech comprehension, and/or pragmatic language \( (6) \). Patterns of brain development contributing to early language difficulties in ASD have yet to be fully examined during infancy.

Language Development in Children With ASD

The latter half of the first year, and the second year of life encompass a time of rapidly expanding language skills for typically developing children. This peak period of language acquisition is more variable in ASD. Many children with ASD show delays in early milestones such as onset of babbling and first-word acquisition \( (7–9) \). Delays in language are evident at the group level around 12 months of age and become more pronounced by 24 months of age \( (10,11) \). Difficulties in semantic and pragmatic language, and atypical receptive-expressive language profiles also emerge as language skills develop \( (6,12) \). Early language deficits persist for a substantial proportion of children with ASD. About 29% of school-age children with ASD display minimal language and another 24% produce words but not sentences \( (13,14) \). Also, unaffected siblings of children with ASD demonstrate higher rates of language delay \( (7,15) \) and lower language scores \( (16–21) \) than infants with no familial risk for ASD.

Typically developing children generally understand considerably more language than they can produce \( (22) \), a pattern termed a “receptive advantage.” This discrepancy reflects that
Language comprehension is an important prerequisite for production. Several studies have shown that children with ASD, in contrast to those with other neurodevelopmental disorders, do not consistently display this normative profile (12). Late talkers, children with specific language impairment (SLI), children with Down syndrome, and children with general developmental delay all tend to have deficits in language, but their language profiles follow the normative trend (23–25).

Subcortical Neurobiology of Language

Most previous language neurobiology research has involved participants who are past the period of early language development. The few studies to date involving infants and toddlers have shown that the inferior frontal gyrus and superior temporal gyrus (26,27), the amygdala (28), and the splenium of the corpus callosum (29) may be integral to language acquisition. The current study investigates an often-overlooked aspect of language neurobiology: the role of subcortical structures.

To date, there are no published data pertaining to subcortical development and language skills in infants at risk for ASD. However, research at later ages in both typical and atypical development suggests several targets for investigation, including the amygdala, thalamus, and caudate nucleus. These structures were selected a priori for analyses in the current research because they had the strongest evidence for a role in the development of early language skills, or had been implicated in language or social cognition more broadly in ASD.

In children with ASD, amygdala volumes have been both positively and negatively associated with language and communication skills (30–32). In typically developing infants the amygdala has been negatively associated with language scores later in life (28). To date, the amygdala’s role in language is not clear. For decades, lesion studies have implicated the thalamus in processes that support language (33). This structure is thought to influence language development by acting as a hub for information via specific alerting responses. In this model, the thalamus directs certain salient forms of information while inhibiting others, gating information to the cortex and striatum (34). Atypical thalamus volumes have been reported in ASD, and thalamic tracts have been shown to be associated with social affect (35,36). The caudate nucleus has been proposed to be a major region associated with language control, impacting the selection and inhibition of language through a cortico-subcortical loop that connects the caudate to the prefrontal cortex (37,38). Atypical caudate nucleus size has been reported in individuals with SLI and their unaffected siblings; however, caudate size was only significantly correlated with phonological processing in the SLI group (39–41).

These results suggest that caudate size may be a heritable risk factor for SLI, but additional risk factors are necessary for the disorder to be penetrant. Likewise, determining familial or disorder-specific risk factors in subgroups of infants at high risk for ASD may improve the specificity of early identification efforts and investigations of causal pathways (42). For a review of neurobiological language disorder studies, see Krishnan et al. (43) and Mayes et al. (44).

The current study utilizes a high-risk family design in which younger siblings of children with ASD are prospectively studied. Using language skills and brain-behavior phenotypes, we aimed to tease apart disorder-specific effects from those attributed to familial risk. The current study had two main objectives: 1) to chart the development of language skills in high-risk infants later diagnosed with ASD and high-risk infants who showed signs of early language delay and 2) to determine if the subcortical neurobiology of language and brain-behavior associations differed between high-risk infants with ASD and high-risk infants with language delay. Given the previous literature showing brain changes preceding behavioral changes in ASD (1,3,45), we focused on 12-month subcortical volumes and 24-month language skills.

METHODS AND MATERIALS

Participants

This study includes data from 382 infants at high familial risk for ASD and 143 at low familial risk for ASD collected across four clinical data sites (University of North Carolina at Chapel Hill, University of Washington, Children’s Hospital of Philadelphia, and Washington University in St. Louis). Parents provided written informed consent prior to participating in this study. The institutional review board at each site approved the study procedures. See the Supplement for full inclusion/exclusion criteria.

Procedures

Infants and their families participated in clinic visits at 6, 12, and 24 months of age and were scanned using magnetic resonance imaging (MRI) at 12 months of age. Assessments at 24 months included the Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview-Revised (46,47). Clinical-best estimate diagnoses were made by experienced, licensed clinicians using DSM-IV-TR criteria for ASD or pervasive developmental disorder, not otherwise specified. See Estes et al. (10) for a full description of the assessment and diagnostic procedures.

Clinical Measures

Infant cognitive development was measured using the Mullen Scales of Early Learning (MSEL) (48) at 6, 12, and 24 months of age. The MSEL is widely used and normed for children from birth to 68 months of age. Verbal developmental quotients (VDQs) were calculated from the receptive and expressive subscales, and nonverbal developmental quotients (NVDQs) were calculated from the visual reception and fine motor subscales. MSEL receptive advantage scores were computed by creating a receptive-expressive age equivalent difference score (11). A greater receptive advantage would be reflected in a positive mean difference. These scores are agnostic to overall level of language skills (e.g., it is possible to have a positive receptive advantage score and have language skills in the normative or delayed range). Reports from nonclinical comparison samples using the MSEL in this early age range have consistently shown the trend of above-average receptive scores when concurrently compared with expressive scores; hence, in this instance a positive receptive advantage score, and not a score of zero, may reflect the “normative” profile (16,18,49,50).

Infant functional language development was assessed with the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) (51) at 6, 12, and 24 months. The VABS-II is a
semistructured parent interview, and the communication standard score provides an index of a child’s expressive and receptive functional language skills. The ADOS is a semistructured observational play assessment of social interaction, communication, and repetitive behaviors (47). Module 1 or 2 was administered for all participants at 24 months of age, and conventional scoring algorithms were applied (52).

**Diagnostic Classification**

At 24 months of age, infants were assessed for ASD and language delay and classified into the following groups:

**High risk diagnosed with ASD (HR-ASD) group:** Based on clinical best estimate, 86 high-risk infants met criteria for ASD.

**High risk with signs of language delay (HR-LD) group:**

The criteria for this group (n = 41) were 1) high risk, 2) not meeting criteria for ASD, and 3) a t score < 35 (1.5 SDs below the mean) on the MSEL receptive language or expressive language subscales, or both, in accordance with standard measures (16,53). A general cognitive delay (i.e., MSEL NVDQ ≥2 SDs below the mean) would have grounds for exclusion from this group; however, none of the infants met this criterion.

**High risk-negative (HR-Neg) and low risk-negative (LR-Neg) groups:** Infants who were unaffected by ASD and language delay were separated into two groups based on their familial risk status (HR-Neg: n = 255; LR-Neg: n = 143).

**MRI Acquisition and Processing**

Pediatric imaging was completed during natural sleep at each clinical site using identical Siemens TIM Trio 3T scanners (Siemens Corp., Erlangen, Germany). T1- and T2-weighted scans (1 mm³ voxels) were acquired. A full description of the MRI acquisition, image preprocessing, and segmentation of subcortical structures can be found in the Supplement. See also Hazlett et al. (1) for a description of the acquisition and processing procedures. Supplemental Figure S1 shows the results of the segmentation of subcortical structures of interest: bilateral thalamus, amygdala, and caudate.

**RESULTS**

**Participant Characteristics**

Data were available for 525 infants who completed at least two behavioral visits and had a 24-month diagnostic evaluation. Full demographic information is available in Table 1. See the Supplement for analyses related to participant characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR-ASD</th>
<th>HR-LD</th>
<th>HR-Neg</th>
<th>LR-Neg</th>
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<tr>
<td>Brain × Behavior Sample, n</td>
<td>46</td>
<td>29</td>
<td>189</td>
<td>104</td>
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<tr>
<td>Longitudinal Sample, n</td>
<td>86</td>
<td>41</td>
<td>255</td>
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<tr>
<td>Longitudinal Visit Complement</td>
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<td></td>
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<tr>
<td>6-, 12-, and 24-mo visit, n</td>
<td>61</td>
<td>35</td>
<td>192</td>
<td>125</td>
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<tr>
<td>6- and 12-mo visit, n</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>6- and 24-mo visit, n</td>
<td>8</td>
<td>3</td>
<td>13</td>
<td>11</td>
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<tr>
<td>12- and 24-mo visit, n</td>
<td>16</td>
<td>3</td>
<td>50</td>
<td>7</td>
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<td>24-mo visit, n</td>
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<td>Age at 6-Mo Visit, Mo, Mean (SD)</td>
<td>6.49 (0.64)</td>
<td>6.63 (0.83)</td>
<td>6.57 (0.65)</td>
<td>6.71 (0.84)</td>
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<td>Age at 12-Mo Visit, Mo, Mean (SD)</td>
<td>12.68 (0.69)</td>
<td>12.69 (0.62)</td>
<td>12.56 (0.62)</td>
<td>12.64 (0.74)</td>
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<td>Age at 24-Mo Visit, Mo, Mean (SD)</td>
<td>24.75 (1.41)</td>
<td>24.87 (0.80)</td>
<td>24.73 (1.01)</td>
<td>24.70 (0.99)</td>
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<td>Male, %</td>
<td>77</td>
<td>65</td>
<td>54</td>
<td>58</td>
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<tr>
<td>24-Mo MSEL ELC, Mean (SD)</td>
<td>80.60 (17.67)</td>
<td>80.90 (9.56)</td>
<td>106.03 (13.70)</td>
<td>112.01 (13.80)</td>
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<tr>
<td>24-Mo MSEL NVDQ, Mean (SD)</td>
<td>87.80 (12.95)</td>
<td>91.72 (9.08)</td>
<td>103.60 (12.84)</td>
<td>109.14 (13.13)</td>
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<td>24-Mo ADOS Severity Score, Mean (SD)</td>
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<td>1.70 (0.96)</td>
<td>1.58 (1.00)</td>
<td>1.44 (0.95)</td>
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ADOS, Autism Diagnostic Observation Schedule; ELC, Early Learning Composite Standard Score; HR-ASD, high risk diagnosed with autism spectrum disorder; HR-LD, high risk with signs of language delay; HR-Neg, high risk negative; LR-Neg, low risk negative; MSEL, Mullen Scales of Early Learning; NVDQ, nonverbal developmental quotient.
Development of Language Skills

The development of language skills was measured using generalized linear mixed model with maternal education, clinical site, MSEL NVDQ, and sex of the infant as covariates (see the Supplement for full statistical analysis plan and model building strategy). Supplemental Tables S1 and S2 contain least squares means and fixed effects results for all language models. Supplemental Figure S3 displays individual trajectories for language measures.

Longitudinal trajectories from 6 to 24 months of age showed significant group differences in MSEL VDQ ($F_{3,399} = 52.38$, $q < .0001$; Figure 1A). At 6 months of age, the groups did not differ on MSEL VDQ ($F_{3,409} = 1.56$, $q = .332$). At 12 months of age the groups did differ significantly ($F_{3,451} = 12.21$, $q < .0001$). Follow-up pairwise comparisons revealed the HR-ASD group scored lower than the HR-Neg ($t_{451} = -4.84$, $q < .0001$) and LR-Neg ($t_{451} = -5.74$, $q < .0001$) groups. The HR-LD group also scored lower than the HR-Neg ($t_{451} = -2.62$, $q = .009$) and LR-Neg ($t_{451} = -3.62$, $q < .0003$) groups. Finally, the HR-Neg group scored lower than the LR-Neg group ($t_{451} = -2.14$, $q = .032$). The remaining pairwise comparisons were not significant.

At 24 months of age the group differences expanded ($F_{3,473} = 57.67$, $q < .0001$). Pairwise comparisons showed the HR-ASD groups scoring lower than the HR-Neg ($t_{473} = -10.60$, $q < .0001$) and LR-Neg ($t_{473} = -9.82$, $q < .0001$) groups. The HR-LD group also scored lower than the HR-Neg ($t_{473} = -9.43$, $q < .0001$) and LR-Neg ($t_{473} = -9.04$, $q < .0001$) groups. Longitudinal results for the MSEL expressive language and receptive language $t$ scores are available in Supplemental Tables S1 and S2.

To corroborate the MSEL findings (an examiner-based assessment), we conducted follow-up analyses by examining communication standard scores from the VABS-II (a parent report). Results followed the same pattern as the MSEL VDQ: at 6 months of age the VABS communication scores were not significantly different across groups, at 12 months of age the HR-ASD and HR-LD groups scored significantly lower than the HR-Neg and LR-Neg groups, and at 24 months of age these group differences were more pronounced (Supplemental Tables S1 and S2, Supplemental Figure S2).

Development of Language Profiles

To examine the development of language profiles we utilized receptive advantage scores (receptive advantage score = MSEL receptive age equivalent − MSEL expressive age equivalent). Longitudinal trajectories from 6 to 24 months of age showed significant group differences in language profiles ($F_{3,397} = 4.25$, $q = .005$; Figure 1B). At 6 and 12 months of age the groups did not significantly differ ($F_{3,407} = 1.32$, $q = .332$; and $F_{3,450} = 1.91$, $q = .127$, respectively). At 24-months the groups differed significantly ($F_{3,473} = 4.31$, $q = .005$). The HR-ASD group had lower receptive advantage scores (indicating an atypical language profile) than the HR-Neg ($t_{473} = -3.41$, $q = .0007$) and LR-Neg ($t_{473} = -3.28$, $q = .001$) groups. The HR-ASD also scored lower than the HR-LD group; however, this result did not survive multiple comparison corrections ($t_{473} = -2.13$, $p = .033$, $q = .067$). The HR-LD group did not differ from HR-Neg ($t_{473} = -0.40$, $q = .689$) and LR-Neg ($t_{473} = -0.57$, $q = .568$) infants on receptive advantage scores.

Figure 1. Language skills are delayed at 12 months of age in infants that are high risk diagnosed with autism spectrum disorder (HR-ASD) and high risk with signs of language delay (HR-LD), and delays were more evident at 24 months of age. Receptive and expressive language profiles differ at 24 months of age. (A) Mullen Scales of Early Learning verbal developmental quotient (VDQ) from 6 to 24 months of age. (B) Receptive advantage scores from 6 to 24 months of age. The dotted gray line represents a receptive advantage score of zero. Contrast legend is as follows: (a) HR-ASD, (b) HR-LD, (c) high risk negative (HR-Neg), and (d) low risk negative (LR-Neg). Lines represent least-squares means, which are adjusted for covariates in the model (maternal education, clinical site, Mullen Scales of Early Learning nonverbal developmental quotient, and sex of the infant). Error bars = ±1 SEM. *HR-ASD and HR-LD comparison was not significant after controlling for multiple comparisons.

$q = .689$ and LR-Neg ($t_{473} = -0.57$, $q = .568$) infants on receptive advantage scores.

Subcortical Associations With Later Language Skills

MRI data at 12 months of age were available for 368 infants (70% of the larger behavioral dataset). Group ns were as follows: HR-ASD, n = 46; HR-LD, n = 29; HR-Neg, n = 189; LR-Neg, n = 104. Using cross-sectional generalized linear mixed models, we aimed to investigate how the sizes of the amygdala, thalamus, and caudate were related to the later language outcomes of high-risk infants (covariates included
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clinical site, MSEL NVDQ, sex of the infant, and total cerebral volume [TCV]; see the Supplement for full analysis plan and model building strategy). Given a lack of laterality (Supplemental Table S3), the left and right substructure volumes were summed to create a total volume of each substructure.

The main aim for these analyses was to determine if the HR-ASD and HR-LD groups have similar or dissimilar brain-behavior phenotypes by testing the difference in the effect of one specific planned contrast, HR-ASD versus HR-LD. Full fixed effects and tests of simple slopes can be found in Table 2.

First, we examined brain-behavior associations between 12-month subcortical volumes and 24-month language skills (MSEL VDQ) in HR-ASD and HR-LD infants. The HR-ASD and HR-LD groups significantly differed in their associations between MSEL VDQ and thalamus volume ($t_{350} = -2.11, \rho = .035$; Supplemental Figure S4A) and amygdala volume ($t_{350} = -2.50, \rho = .012$; Supplemental Figure S4B). The two groups did not differ in their association between caudate volume and MSEL VDQ ($t_{350} = -1.85, \rho = .065$; Figure S4C).

Subcortical Associations With Later Language Profiles

Next, we examined brain-behavior associations between subcortical volumes and later receptive advantage scores. The HR-ASD and HR-LD groups significantly differed in their associations between receptive advantage scores and thalamus volume ($t_{350} = -3.66, \rho = .003$; Figure 2A), amygdala volume ($t_{350} = -2.57, \rho = .010$, Figure 2B), and caudate volume ($t_{350} = -2.26, \rho = .024$, Figure 2C).

Follow-up Analyses Comparing ASD Infants With and Without Language Delay to the Language Delay Group

Finally, we examined whether language delay infants without ASD (HR-LD, $n = 29$) had different brain-behavior associations than HR-ASD infants who also met criteria for language delay (ASD-LD+, $n = 28$) or ASD peers without language delay (ASD-LD−, $n = 16$). Based on our previous results, this exploratory analysis focused on the association between thalamus volume at 12 months of age and receptive advantage score at 24 months of age, as these measures provided the strongest support for distinct phenotypes for the HR-ASD and HR-LD groups.

The association between thalamus volume and receptive advantage score differed across the three groups, group × thalamus ($F_{2,60} = 5.50, \rho = .006$). Fixed effects for TCV, site, and thalamus volume were not significant ($\rho > .409$). However, the fixed effects were significant for group ($F_{2,60} = 6.37, \rho = .003$, sex of the infant ($F_{2,60} = 5.44, \rho = .023$), MSEL NVDQ ($F_{2,60} = 6.35, \rho = .014$), and age at MRI ($F_{2,60} = 4.36, \rho = .041$). The contrast between ASD-LD+ and ASD-LD− indicated that the two ASD groups did not significantly differ in their brain-behavior association ($t_{60} = -0.47, \rho = .637$). Both ASD groups differed significantly in their brain-behavior association when compared with the HR-LD group (ASD-LD+ vs. HR-LD ($t_{60} = -3.18, \rho = .002$), ASD-LD− vs. HR-LD ($t_{60} = -2.10, \rho = .040$). Tests of effects within each group revealed a negative association between thalamus volume and receptive advantage score for the HR-LD group ($t_{60} = -2.33, \rho = .023$, $q = .069$) that did not survive false discovery rate correction. The association between thalamus volume and receptive

Table 2. Tests of Fixed Effects and Tests of Simple Slopes for Brain-Behavior Analyses

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<thead>
<tr>
<th>Response Variable</th>
<th>Predictor Variable</th>
<th>Receptive Advantage Score</th>
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<tr>
<td></td>
<td>Thalamus</td>
<td>Amygdala</td>
</tr>
<tr>
<td></td>
<td>F  p/q</td>
<td>F  p/q</td>
</tr>
<tr>
<td>Sex of Infant</td>
<td>2.21 .138</td>
<td>1.55 .214</td>
</tr>
<tr>
<td>MSEL NVDQ</td>
<td>120.64 .0001</td>
<td>123.42 .0001</td>
</tr>
<tr>
<td>Site</td>
<td>1.64 .179</td>
<td>1.62 .184</td>
</tr>
<tr>
<td>Age</td>
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<td>0.03 .871</td>
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<tr>
<td>TCV</td>
<td>1.06 .303</td>
<td>2.41 .121</td>
</tr>
<tr>
<td>Subcortical Volume</td>
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<td>0.13 .718</td>
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<tr>
<td>Group</td>
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<td>4.51 .004</td>
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<tr>
<td>Subcortical × Group</td>
<td>2.21 .087</td>
<td>2.79 .080(^b)</td>
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<tr>
<td>Tests of Group Effect</td>
<td>t  q</td>
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<tr>
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<tr>
<td>HR-LD</td>
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<tr>
<td>HR-Neg</td>
<td>0.17 .865</td>
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<tr>
<td>LR-Neg</td>
<td>0.61 .726</td>
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</table>

HR-ASD, high risk diagnosed with autism spectrum disorder; HR-LD high risk with signs of language delay; HR-Neg, high risk negative; LR-Neg, low risk negative; MSEL, Mullen Scales of Early Learning; NVDQ, nonverbal developmental quotient; TCV, total cerebral volume.

\(^a\)Uncorrected $p$ value < .05.

\(^b\) $q$ value < .05.
DISCUSSION

The overarching goal of the current study was to determine if examining infant language development and brain-behavior associations could detect distinct phenotypes in subgroups of infants at high familial risk for ASD. We examined language profiles in infants who were later diagnosed with ASD, infants who went on to show signs of early language delay, and infants who were at low and high familial risk for ASD without ASD or language delay. We also explored whether associations between brain development in the first year of life and later language skills were similar or distinct in high-risk infants with ASD and high-risk infants with signs of early language delay.

Our results supported three conclusions. First, trajectories of language development diverged over time across groups; groups did not differ in language skills at 6 months of age, whereas at 12 months of age the HR-ASD and HR-LD groups were scoring lower than their LR-Neg and HR-Neg peers, with further divergence by 24 months of age. The HR-ASD and HR-LD groups did not differ from one another at any time point on available language measures. These results are aligned with previous reports showing differences in language skills emerging around 12 months of age in infants who go on to have ASD (10). Using a larger sample, we also confirmed previous results showing that infants who present with language delay at 24 months first display delayed skills at, or soon after, their first birthday (54). More generally, our results highlight the increased vulnerabilities in families with a history of ASD. In this sample, 17% of high-risk infants went on to have ASD themselves, and an additional 11% demonstrated signs of early language delay but not ASD. Recent community sample studies have suggested that early language skills are correlated with school-age vocabulary and literacy; however, the relationship is insufficiently strong to predict individual outcomes from infant data (55). School-age children with a family history of ASD have higher-than-expected rates of impairment, including difficulties in speech and language (56); thus, early language delays in high-risk infants may herald these school-age difficulties, but this link remains to be determined.

Our second conclusion is that at 24 months of age the ASD group displayed language profiles that either were balanced or represented an expressive-advantage (e.g., better expressive than receptive skills). All other groups showed a profile of receptive advantage (e.g., better receptive than expressive skills), consistent with previous reports for typically developing children in this age range tested with the same instrument (16,18,49). The current language delay group showed delayed language skills, but their language profiles, while varied, did not differ from their low- and high-risk peers. This pattern of results for the HR-LD group is also similar to previous work in SLI, general developmental delay, and Down syndrome (23,24), where language is delayed but language profiles are intact.
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When contrasting the language profiles of the ASD and language delay groups, results suggest that atypical language profiles are not a familial effect, but are more reflective of a disorder-specific effect for ASD.

Our last conclusion is that high-risk infants who go on to have ASD show distinct brain-behavior associations when compared with high-risk infants with early language delay. Specifically, associations between subcortical structures at 12 months of age and 24-month language skills differed in ASD and language delay infants. For example, ASD and language delay infants differed in their association between the thalamus and language profile, such that for language delay infants, the smaller the volume of the thalamus, the larger the receptive advantage score (i.e., a more normative language profile). Similar patterns were found for the caudate nucleus and amygdala. The negative association between caudate nucleus volume and language profile is in line with previous research on SLI showing that a smaller caudate was associated with better language skills (40). Amygdala volume has been both positively and negatively associated with language and communications skills (30–32); here we find that HR-LD infants with smaller amygdala volumes had more normative language profiles. We recently reported that early brain overgrowth was associated with later ASD diagnosis and social deficits (1). It is possible that for infants with a genetic liability for ASD, inhibited overgrowth is protective for later ASD, and the negative association between language profile and subcortical volume in high-risk infants showing signs of language delay reflects this subgroup’s susceptibility to alterations in brain development. In the current study, we reported similar patterns of association across multiple structures, which could be a result of examining the brain as the behavior (e.g., language) is emerging. The theory of interactive specialization predicts that “developmental change in cognitive skills or behavior will be accompanied by widespread changes across multiple regions” (57). If our findings are situated within this framework we would expect interconnected brain structures to show similar brain-behavior patterns.

We found that high-risk infants showing signs of language delay are distinct from those who develop ASD in both their behavioral trajectories and brain-behavior associations. With respect to brain-behavior results, the overall pattern of association when comparing ASD and LD groups was disordinal in nature, suggesting that the two groups display distinct brain-behavior associations across selected subcortical structures. The behavioral phenotype of these two groups was also distinct. The ASD group showed delayed language skills and atypical language profiles, whereas the language delay group showed delayed language skills but language profiles that did not differ from their typically developing peers. In our exploratory analyses, we found that ASD infants with language delay displayed brain-behavior phenotypes that were indistinguishable from ASD infants without language delay, and all ASD infants (with and without language delay), differed from language delay infants (without ASD). These results suggest that a negative association between subcortical volume and language profile is a disorder-specific effect for language delay.

This study highlights the brain and behavioral heterogeneity among those with increased familial liability to ASD. Our ASD and language delay groups shared comorbid language delay and familial liability for ASD; however, the two groups displayed qualitatively different brain and behavioral profiles, suggesting that the language delay infants exhibit a distinct phenotype, and not merely an intermediate ASD phenotype. These results suggest that different brain mechanisms influence behavioral development in ASD and language delay infants, and that the two groups likely experience unique sets of genetic and environmental risk factors. To take steps toward understanding the causal developmental pathways to pathophysiology, we must, in part, utilize family studies to outline disorder-specific effects and familial effects (42). Such an approach has the potential to move forward efforts to identify subgroups based on biological and behavioral phenotypes agnostic to diagnostic criteria, and take important steps toward a personalized medicine approach to ASD treatment.

Given that there is variability in predicting later outcome from early language skills (58), and that some infants will first meet criteria for ASD at or after 3 years of age (59,60), future efforts should include follow-up assessment at school age. Such follow-up assessments should include children with LD in the absence of familial risk of ASD, as the generalizability of findings to this group is unknown. Studies examining the genetic overlap between ASD and SLI have been mixed, and the two groups have been shown to have distinct behavioral phenotypes, suggesting that distinct genetic and environmental factors contribute to the developmental course of language delay depending on whether there is associated ASD risk (61). It is possible that subcortical structures not examined in the current study are relevant for early language neurobiology; for example, enlargement of the putamen and nucleus accumbens has been reported in adults with developmental language impairment (62). Hence, future efforts may also benefit from taking a more comprehensive approach to regional analyses.

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