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ORIGINAL PAPER

Alpha Asymmetry in Infants at Risk for Autism Spectrum Disorders

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Abstract An emerging focus of research on autism spectrum disorder (ASD) targets the identification of early-developing ASD endophenotypes using infant siblings of affected children. One potential neural endophenotype is resting frontal electroencephalogram (EEG) alpha asymmetry, a metric of hemispheric organization. Here, we examined the development of frontal EEG alpha asymmetry in ASD high-risk and low-risk infant populations. Our findings demonstrate that low and high-risk infants show different patterns of alpha asymmetry at 6 months of age and opposite growth trajectories in asymmetry over the following 12 months. These results support the candidacy of alpha asymmetry as an early neural ASD endophenotype.

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Introduction

Autism spectrum disorder (ASD) forms a heterogeneous neurodevelopmental disorder that typically appears by early childhood (American Psychiatric Association 2013). ASD is characterized behaviorally by impairments in social communication, and repetitive behaviors or restricted interests but is neurobiological in origin. The incidence of ASD in the general population in the United States has recently been estimated to be as high are 1 in 88 (or by estimates, as high as 1 in about 50), making this disorder one of the most prevalent developmental disorders (Kogan et al. 2009; Baio 2012). However, the causes and mechanisms of ASD development are still poorly understood and difficult to study because ASD is a complex disorder that is highly variable at both the genetic and behavioral phenotypic levels (Geschwind 2008; Viding and Blakemore 2007). An emerging focus of ASD research therefore targets the identification of intermediate phenotypes known as endophenotypes that can chart the pathways between the biological and the psychological aspects of these disorders (Viding and Blakemore 2007; Geschwind 2009; Kendler and Neale 2010).

Endophenotypes are biological markers that may exist at any intervening phenotypic level between gene and behavior (Gottesman and Gould 2003). Gottesman and Gould (2003) have identified specific criteria that define endophenotypes. They characterize endophenotypes as heritable markers that co-segregate with the disorder in both the general population and within affected families,

and that consistently and persistently indicate the specific phenotype. Furthermore, endophenotypes are found more frequently in non-affected family members of affected individuals than in the general population, reflecting the effects of genes responsible for the familial risk (heritability) of the disorder. These non-affected family members therefore represent critical populations in which genetic underpinnings of endophenotypes are preserved while the resulting behavioral phenotypes have fewer confounding symptom interactions than those of diagnosed individuals (Zwaigenbaum et al. 2007; Tager-Flusberg 2010). Studies of family members of affected individuals have already been instrumental in identifying candidate endophenotypes in a variety of neuropsychiatric disorders, including ASD (e.g., schizophrenia: Turetsky et al. 2007; bipolar disorder: Hall et al. 2009; depression: Stewart et al. 2010; ASD: Spencer et al. 2012).

Accordingly, many researchers seeking to identify early-developing ASD candidate endophenotypes have focused their attention on infants with an older sibling with the disorder. These infant siblings represent a high-risk cohort with an approximately 20 % chance of receiving an ASD diagnosis (Ozonoff et al. 2011). Even though the majority of high risk infants will not exceed the clinical threshold for an ASD diagnosis, many have been shown to exhibit early subclinical ASD behavioral phenotypes that are also found in infants who do go on to be diagnosed. These differences include social communication impairments and delays in language development (Iverson and Wozniak 2007; Gamliel et al. 2009; Yirmiya et al. 2006), atypical visual disengagement patterns in social contexts and increased interest in non-social stimuli (Ibanez et al. 2008) and reduced positive affect (Cassel et al. 2007; Elsabbagh and Johnson 2007; Rogers 2009; Tager-Flusberg 2010). Several candidate ASD endophenotypes have already been identified in these undiagnosed infant siblings, including differences in head-growth patterns within the first year of life (Redcay and Courchesne 2005), visual orientation differences (Elsabbagh et al. 2009b), event-related-potential (ERP) differences in the neural underpinnings of face processing in 10-month olds (Elsabbagh et al. 2009a; McCleery et al. 2009; Luyster et al. 2011), and differences in the trajectories of resting EEG power across multiple bandwidths (Tierney et al. 2012).

An additional characteristic of neural dynamics that may serve as a potential early ASD endophenotype is hemispheric organization indexed by alpha bandwidth asymmetry. In particular, frontal EEG power measurements for the alpha frequency bandwidth (6–9 Hz) have shown an especially strong, inverse correlation with local neural activity (e.g. higher power values in this band correspond to lower levels of neural electrical activity as measured by PET, Cook et al. 1998; Shagass 1972). Differences in alpha activity between the left and right hemispheres within an individual have therefore been used to study hemispheric asymmetry in neural activity as a metric of frontal lobe organization. A study of older children with ASD by Sutton and colleagues (Sutton et al. 2005) found that children with ASD display atypical patterns of this alpha asymmetry compared to unaffected children. Furthermore, in adults it has been established that this alpha asymmetry marker is partially heritable (Anokhin et al. 2006). Infants at high-risk for ASD with an affected older sibling may thus also experience atypical hemispheric organization during development. However, this alpha asymmetry metric has yet to be evaluated in infancy as a potential early ASD endophenotype.

Importantly, research with typically developing infants has provided evidence that alpha asymmetry changes over the first years of life. For example, Fox and colleagues (Fox et al. 2001, 1994) have shown that typically developing infants display a resting relative right frontal asymmetry (higher activity in the right frontal lobe compared to the left frontal lobe) at 9 months, which subsequently reverses direction to become a relative left frontal asymmetry by 14 months that remains stable through 24 months. Although these results together demonstrate that alpha asymmetry changes during the first 2 years of life, typical developmental trajectories of this alpha asymmetry metric of frontal lobe organization have yet to be thoroughly evaluated across infancy. Charting this developmental course is a secondary aim of the current investigation.

In this present study we sought to evaluate the development of frontal alpha asymmetry in both infants at high-risk for ASD and in low risk infants during the first year and a half of life. Specifically, we examined whether these high and low risk groups differed in their trajectories of alpha asymmetry in order to ascertain the utility of this index as a candidate endophenotype for ASD. Given the significant differences in resting EEG power levels and trajectory in the alpha bandwidth that we previously identified in infants at high-risk for ASD (Tierney et al. 2012), we hypothesized that having an older sibling with ASD would confer familial-risk related differences both in the alpha asymmetry levels and in developmental changes of these asymmetry values within the first 18 months of life. We also hypothesized that the pattern of relative right frontal asymmetry observed in typically developing infants at 9 months of age would be extended back to our earliest time-point at 6 months of age (Fox et al. 2001). Examining alpha asymmetry in a longitudinal sample could therefore extend our current understanding of typically developing alpha asymmetry levels and provide support for this metric as an early ASD candidate endophenotype.

Methods

Participants

Participants were drawn from a sample of infants enrolled in a longitudinal study of the early neurocognitive development of infant siblings of children with ASD. Of the enrolled sample of 168 participants, 146 came in for a study visit, and 126 provided EEG data for 6, 12, and/or 18-month visits. From this number, 108 participants contributed useable data that are reported on in the present study (unusable data were characterized by movement artifact or ambient electrical noise). All infants had a gestational age of at least 36 weeks, had no known prenatal or perinatal complications, and no known genetic disorders (e.g., fragile-X syndrome). Infants were classified as either low- or high-risk for ASD. Infants were designated high-risk ($n = 57$; hereafter referred to as HRA) if they had at least one older sibling with an ASD diagnosis that could not be attributed to a known genetic disorder (i.e., fragile-X syndrome or tuberous sclerosis). All the probands (older siblings) had a confirmed clinical ASD diagnosis that was provided by expert community clinicians. Infants were designated as low-risk ($n = 51$; hereafter referred to as LRC) if they had an older sibling but no first degree relatives diagnosed with ASD.

The two risk groups were well-matched in demographic composition (see Tables 1 and 2 for sample descriptions). The groups were also roughly similar in terms of general cognitive performance (see Table 3). There were no significant differences in standard scores on the Mullen Scales of Early Learning between HRA and LRC infants at 6 months ($t(56) = -0.-70$, $p = 0.485$), however at 12 and 18 months, HRA infants scored statistically lower than the LRC infants (12 months, $t(55) = 2.42$, $p = 0.019$; 18 months $t(30) = 2.54$, $p = 0.017$). However, at both of these latter time points, both groups scored within one standard deviation of the population mean, indicating that neither group was performing below or above the population average.

Table 1 Sample characteristics at each visit for infants at low and high risk for ASD

Targeted ages	Low risk control *n (proportion male)*	High risk autism *n (proportion male)*
6 months	34 (.44 male)	25 (.44 male)
12 months	23 (.48 male)	36 (.50 male)
18 months	11 (.45 male)	24 (.58 male)

Sample sizes are listed for each group at each target age with the proportion of male infants for each sample given in parentheses

EEG Data Acquisition

EEG recording took place in a dimly lit, electrically-shielded, sound-attenuated room. Infants sat on their parent's lap while a research assistant blew bubbles to keep them calm and still during the testing. Continuous EEG was recorded using a 64-channel Geodesic Sensor Net or a 128 HydroCel Sensor Net (EGI, Eugene OR).[1] Prior to recording each session, impedances were checked on-line and were considered acceptable if lower than 50KOhm. EEG data were collected and recorded using NetAmps 200 Amplifiers and NetStation software. The data were amplified, filtered (bandpass 0.1–100.0 Hz), sampled at a frequency of 250 Hz, and online referenced to the Cz electrode. The data were digitized with a 12-bit National Instruments Board (National Instruments, Woburn MA). Two minutes of activity were recorded.

EEG Data Reduction and Analysis

EEG data were first processed offline using NetStation v4.1.2. Data were bandpass filtered 1–50 Hz and re-referenced using an average reference. EEG data were then processed in Matlab 7.6 (Mathworks Inc., Natick, MA) using EEGLAB (Makeig and Delorme 2004) to visually inspect each 2-min EEG segment and select by hand the data free from movement artifact or ambient noise. EEG recordings that did not have a minimum length of 10 s were omitted from further analysis. Power spectral density (psd) for these artifact-free data were calculated in Matlab 7.6 using a 50 % overlapping Hanning window with a frequency resolution of 0.25 Hz. For subsequent examination and analysis, raw psd values were natural log transformed to normalize the 1/f distribution found in raw power spectra of human EEG recordings (Basar 1998). Regions of interest (ROI) were identified in the frontal areas of both the left and right hemispheres corresponding to the F3 and F4 electrodes traditionally used in older EEG studies. Average psd measures were calculated for the ROIs using a subset of 4 electrodes on each hemisphere for the 64-channel net (left hemisphere electrodes: 8, 9, 13, 16; right hemisphere electrodes: 3, 57, 58, 62). A subset of 6 electrodes per hemisphere were then selected for the 128 channel net so that the same scalp area was covered across the two net types (left hemisphere electrodes: 18, 19, 20,

[1] At the start of the project, we used the 64-channel Geodesic Sensor Nets at each testing session, but 2 years into the project, we changed to the 128-channel HydroCell Geodesic Sensor nets. In order to ensure that this equipment change did not influence our results, we assessed whether there were any differences in asymmetry scores between the two nets, but found no statistically significant difference ($t(41) = 0.68$, $p = 0.500$). We also determined that the type of net used was distributed equally across age and risk groups.

Table 2 Family demographic and infant characteristics reported by parents on the infants included in this sample

	Low-risk for autism	High-risk for autism	
Household income[a]	$n = 39$	$n = 48$	$t(85) = -1.11$, $p = 0.269$
	6.87 (2.17)	7.31 (1.12)	
Mother's levels of education[b]	$n = 41$	$n = 50$	$t(89) = 0.58$, $p = 0.564$
	5.85 (1.62)	5.64 (1.84)	
Father's level of education[b]	$n = 41$	$n = 50$	$t(89) = 0.55$, $p = 0.584$
	5.49 (2.12)	5.26 (1.83)	
Mother's age at Infant's birth*	$n = 51$	$n = 57$	$t(106) = -1.89$, $p = 0.062$
	33.44 years (4.30)	35.17 years (5.13)	
Father's Age at Infant's Birth*	$n = 51$	$n = 57$	$t(106) = -2.23$, $p = 0.028$
	35.86 years (5.10)	38.15 years (5.53)	
Infant's birth weight	$n = 51$	$n = 57$	$t(106) = 0.19$, $p = 0.847$
	7.80 lbs (1.03)	7.76 lbs (0.99)	

Data for each index were not available for all subjects; sample sizes are listed for each group on each variable. Mean values are listed with standard deviation in parentheses

[a] Income was reported on a scale of 1–8. (1) < $15,000; (2) $15,000–25,000; (3) $25,000-35,000; (4) $35,000–45,000; (5) $45,000–55,000; (6) $55,000–65,000; (7) $65,000–75,000; (8) > $75,000. [b] Education was reported on a scale of 1–9. (1) some high school; (2) high-school graduate; (3) some college; (4) community college or 2-year degree; (5) 4-year college degree; (6) some graduate school; (7) master's degree (8) doctoral degree; (9) professional degree

Table 3 Mean standard composite scores on the Mullen Scales for Early Learning for the LRC and HRA groups at each age of testing

	Low risk for autism	High risk for autism	
6 months	$n = 33$	$n = 25$	$t(56) = -0.70$, $p = 0.485$
	94.27 (8.98)	96.12 (11.03)	
12 months	$n = 23$	$n = 34$	$t(55) = 2.42$, $p = 0.019$
	111.00 (10.23)	102.70 (14.09)	
18 months	$n = 11$	$n = 21$	$t(30) = 2.54$, $p = 0.017$
	107.1 (12.98)	94.10 (15.26)	

Data were not available for all subjects at all time points; sample sizes are listed for each group at each age of testing when usable EEG data were acquired

23, 24, 27; right hemisphere electrodes: 3, 4, 10, 118, 123, 124).

From the full spectrum data, we narrowed our analysis to the alpha band that has been well-characterized in infants and accordingly, the frequency range of this band was defined as 6–9 Hz (Marshall et al. 2002). The psd values within this range were averaged to produce a band average score for each hemisphere. Asymmetry scores for each infant at each time point were calculated by subtracting the left hemisphere band average from the right hemisphere band average (i.e., right—left score). Consequently, positive scores correspond to higher alpha power in the right hemisphere while negative scores correspond to higher alpha power in the left hemisphere.

We employed multilevel modeling for change (also referred to as hierarchical linear modeling or mixed linear modeling; Singer and Willett 2003) to examine group differences in the development of alpha asymmetry. All statistical analyses were conducted using SAS 9.2 using PROC MIXED and full maximum likelihood estimation. The multilevel model assesses change by estimating two types of parameters that characterize a trajectory, initial status and slope. For this model, we used a compound symmetric error covariance structure such that the residuals were homoscedastic and autocorrelated across time.

Behavioral Assessment

Infants in both groups who reached 18 months of age were assessed for ASD symptoms using the *Autism Diagnostic Observation Scale* (ADOS; Lord et al. 2000), a standardized, semi-structured assessment of early communication, social interaction, and play used by researchers to diagnose ASD. Infants in this study who met cut-off scores for ASD on the ADOS at 18 months were identified as being of concern. In this study, 9 HRA infants met criteria for inclusion in this group (16 % of total HRA sample). As part of a sensitivity analysis, we conducted a follow up analysis in which we removed data from these 9 participants to determine whether the statistical effects changed (see Discussion section for elaboration).

Results

Parameter estimates and associated statistics from this multilevel modeling for change are displayed in Table 4.

Table 4 Estimates of fixed effects from individual growth models in which autism risk predicts initial status and the linear rate of change in asymmetry scores between 6 and 18 months of age

	Full HRA group ($n = 108$)	Reduced HRA group ($n = 99$)
Fixed effects		
Intercept	$\gamma_{00} = -0.095$, $t(106) = -2.11$, $p = 0.038$	$\gamma_{00} = -0.095$, $t(97) = -2.25$, $p = 0.027$
Age (centered)	$\gamma_{10} = 0.014$, $t(43) = 1.89$, $p = 0.066$	$\gamma_{10} = 0.014$, $t(40) = 2.03$, $p = 0.049$
Autism risk	$\gamma_{01} = 0.159$, $t(106) = 2.39$, $p = 0.019$	$\gamma_{01} = 0.152$, $t(97) = 2.37$, $p = 0.020$
Autism risk*age	$\gamma_{11} = -0.022$, $t(43) = -2.17$, $p = 0.036$	$\gamma_{11} = -0.020$, $t(40) = -2.09$, $p = 0.043$
Variance components		
	$\sigma^2 = -0.0031$, $p = 0.709$	$\sigma^2 = -0.0076$, $p = 0.44$
	$\sigma_1 = 0.0656$, $p < 0.001$	$\sigma_1 = 0.080$, $p < 0.0001$

Full HRA group includes all HRA subjects, while the reduced group excludes those HRA subjects who scored high on the 18 month ADOS

Based on this analysis, there was a statistically significant difference in the asymmetry scores between the LRC and the HRA groups at 6 months ($p = 0.019$ such that LRC infants had a more negative asymmetry score (mean = −0.095 μV) than the HRA infants (mean = 0.064 μV). Post hoc GLH tests using the Wald statistic indicated that the average LRC asymmetry score was statistically different from 0 ($\chi^2 = 4.43$; $p = 0.035$), but that the average HRA asymmetry score was not different from 0 ($\chi^2 = 1.71$; $p = 0.191$). These results indicate that at 6 months, LRC infants demonstrate a relative right frontal asymmetry but that the HRA infants show no hemispheric asymmetry in frontal alpha activity.

Furthermore, the slopes of the trajectories for each group were quite different. For the LRC infants, the slope parameter indicated that asymmetry scores demonstrated marginal change of about 0.014 μV per month ($p = 0.065$) over this time period, while there was an age by risk interaction, such that the asymmetry scores for the HRA infants were significantly changing by an additional 0.02 μV per month ($p = 0.036$), but in the opposite direction. So while the LRC infants' scores become less negative on average, the HRA infants' scores become more negative (See Fig. 1a and Table 5 for summary of the sample data). These results indicate that low-risk infants have an average 6-month asymmetry score of −0.095 μV with a subsequent increase of 0.014 μV for every month of age, resulting in an average positive asymmetry score of 0.073 μV at age 18 months. Conversely, high-risk infants have an average asymmetry score of 0.064 μV at 6 months of age and a decrease of -0.0073 μV each subsequent month, resulting in a negative asymmetry score of −0.024 μV at 18 months.

In addition to the differences in 6-month asymmetry and the slope with which they changed, we assessed whether there were detectable differences between the groups at the 12- and 18-month time points. Post hoc GLH tests indicated that the LRC and HRA groups' mean asymmetry scores continued to be different at 12 months ($\chi^2 = 4.72$; $p = 0.030$) but that by 18 months the difference was no longer significant ($\chi^2 = 1.20$; $p = 0.273$). These results suggest that the differences in slope result in a convergence of the levels of asymmetry by 18 months of age. Post hoc tests did not distinguish either the LRC or HRA average asymmetry scores from zero (LRC $\chi^2 = 1.31$; $p = 0.252$; HRA $\chi^2 = 0.26$; $p = 0.608$), suggesting that at 18 months there were no hemispheric differences in alpha power in either group. Importantly, many of the LRC participants (64 %) had positive asymmetry scores at 18 months, although on average they were not different from zero. In contrast, in the HRA group, the majority of infants (65 %) had negative asymmetry scores at this time point. Again, the average for the HRA group was not statistically different from zero; however, these proportions suggest that the distribution of scores for HRA infants was skewed in the opposite direction than it was in the LRC group. Thus, while there did not appear to be any statistically detectable pattern of hemispheric asymmetry at 18 months in either of the groups, the variation within the groups suggests trends toward opposite patterns of organization.

In order to determine whether the trajectory differences between the high and low-risk groups were being driven by a subset of HRA infants who met criteria on the ADOS at 18 months, these analyses were also conducted after removing data from such infants ($n = 9$; see Fig. 1b and Table 5). Multilevel modeling revealed the same effects even after removing the data from these participants (see Table 4). More specifically, all of the group differences in asymmetry scores found in the analysis of the full HRA sample were also present in this reduced sample. These results confirm that the infants who are identified on the ADOS at 18 months as meeting cut-off scores for ASD were not driving the differences in asymmetry changes between the HRA and LRC groups.

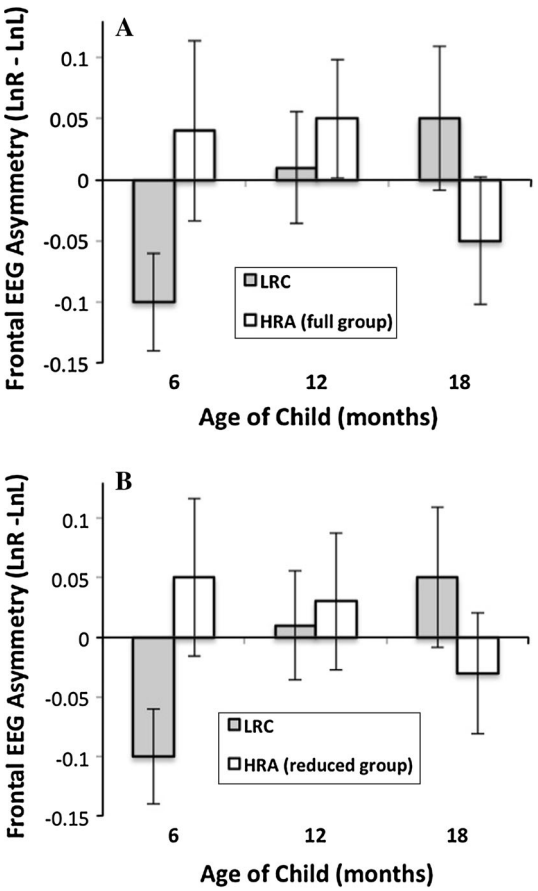

Fig. 1 Sample means with standard errors of alpha asymmetry scores in infants at low and high risk for autism. **a** Comparing low-risk control group (LRC) with full high-risk for autism group. **b** Comparing low-risk control group with HRA group after having removed those infants who met autism criteria on the 18-month ADOS. A positive asymmetry score reflects relative left frontal activation and a negative score reflects relative right frontal activation

Discussion

The results of this study indicate that infants at high-risk for ASD show different developmental trajectories of cortical organization as compared to infants at low-risk. More specifically, high-risk infants demonstrate different hemispheric organization at 6 months of age, as evidenced by their left relative frontal asymmetry, which is in contrast to the low-risk infants' right relative frontal asymmetry. This finding along with recent work from our group on activity in other EEG frequency bands together demonstrate that robust neural differences in high-risk infants are detectable at 6 months of age before behavioral differences emerge (Tierney et al. 2012; Tager-Flusberg 2010). Thus, differences in neural processing as measured by spectral characteristics of the EEG may represent some of the earliest candidates for endophenotypes associated with ASD.

Moreover, this initial difference in asymmetry for high-risk infants follows a subsequent trajectory that proceeds in the opposite direction of the one found for low-risk children. While low-risk children follow a developmental pattern of initial relative right frontal asymmetry toward relative left frontal asymmetry, high-risk children show an initial relative left frontal asymmetry that shifts rightward. Asymmetry measurements at 18 months do not show differences between the groups; however, if the trends continue past this age point, we predict fully reversed patterns of hemispheric organization for these two groups in infancy. These findings suggest that hemispheric organization follows a very different developmental progression in the high-risk infants. Additionally, the trajectory of hemispheric asymmetry development that we observed in the low-risk infants is consistent with patterns in typically developing children reported in Fox et al. (2001). According to their findings, typically developing children demonstrate relative right frontal asymmetry at age 9 months which then shifts to a relative left frontal asymmetry by 14 and 24 months. Our data from the low risk control infants are largely consistent with these findings and provide evidence that these patterns of asymmetry are detectable even earlier, at 6 months of age.

It is important to point out that we observed the same atypical patterns of change in asymmetry in the high-risk group even after we removed data from infants who were flagged for concern on the 18 month ADOS. This indicates that patterns we detected are not driven by a subsample of the high-risk cohort who eventually meet criteria for autism, but rather these effects are characteristic of the group more generally as compared to the patterns of the typically developing infants. Whether such a difference reflects too few infants flagged by the ADOS to detect a significant

Table 5 Mean asymmetry scores with standard deviations for infants at low and high risk for ASD at each target age

Targeted ages	Low risk control mean (SD)	High risk autism (full group) mean (SD)	High risk autism (reduced group) mean (SD)
6 months	−0.10 (0.23)	0.04 (0.37)	0.05 (0.32)
12 months	0.01 (0.22)	0.05 (0.29)	0.03 (0.30)
18 months	0.05 (0.20)	−0.05 (0.26)	−0.03 (0.21)

Full HRA group includes all HRA subjects, while the reduced group excludes those HRA subjects who scored high on the 18 month ADOS

difference between groups or, rather, that our measure of EEG asymmetry truly reflects a candidate endophenotype of the disorder (see Gottesman and Gould 2003) but is not *predictive* of the disorder will only be known as our study continues and we increase our sample size.

In summary, this developmental analysis of hemispheric asymmetry in infants high-risk for ASD illuminates both typical and atypical trajectories of brain development over the first 18 months of life. We found that the high-risk population exhibits atypical neural organization at 6 months of age and that these atypicalities may persist beyond infancy as a candidate endophenotype for ASD. Although this study could only assess asymmetry trajectories until 18 months, future analyses may address this limitation and establish asymmetry trajectories over longer developmental periods through childhood. Additionally, this asymmetry measure has previously been associated with general behavioral functions such as temperament (Davidson 1993; Sutton and Davidson 1997) in typically developing populations. Given that reactive, irritable temperament profiles with low levels of positive affect have been documented in infants who go on to develop an ASD (Zwaigenbaum et al. 2005; Bryson et al. 2007), future prospective studies with larger samples of infants that receive ASD diagnoses can assess how such early atypical EEG development relates to temperament and whether these neural-cognitive associations predict ASD outcomes. Recent evidence indicates that patterns of temperament are related both to risk for ASD as well as symptom severity in those infants who develop ASD (Garon et al. 2009). If alpha asymmetry is an equally strong predictor of variation in temperament, it may also serve as an important indicator of later ASD outcome.

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