The development of lateralized brain oscillations in infancy: what we can learn from autism

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Abstract (English)

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by impaired social and communication skills. Recent studies suggest that these impairments could be caused by atypical lateralization in the brain, where one hemisphere is more active than the other during cognitive processing. A growing body of research indicates that hemisphere specificity is reduced in adults diagnosed with ASD, but more research is needed to understand whether these patterns emerge early in infancy. This study used data from the International Infant EEG Data Integration Platform (EEG-IP); a multi-site cohort study of infants at risk for ASD and age-equivalent controls (London: 7, 14 months; Seattle: 6,12,18 months) to explore developmental trajectories of lateralization. We extracted brain lateralization indices from cortical sources reconstructed from EEG recordings collected while participants watched a video. The study included 92 infants at familial risk for autism (at least one full sibling, with an existing ASD diagnosis) and 91 controls. We found that at twelve months, infants at risk for autism had stronger left-hemisphere lateralization patterns in gamma activity compared to controls. These differences were further accentuated in the superior temporal gyrus (p's < 0.05). The superior temporal gyrus is important for phoneme discrimination and auditory attention and, in some cases, can be considered an important precursor for language learning. Lateralization is a key part of development, and our study can shed light on the developmental differences that can impact various cognitive processes in autism.

Abstract (French)

Le trouble du spectre autistique (TSA) est un trouble neurodéveloppemental caractérisé par une altération des compétences sociales et de communication. Des études récentes suggèrent que ces déficiences pourraient être causées par une latéralisation atypique dans le cerveau, ou par un hémisphère qui est plus actif que l'autre pendant le traitement cognitif. Un nombre croissant de recherches indiquent que la spécificité de l'hémisphère est réduite chez les adultes diagnostiqués avec TSA, mais des recherches supplémentaires sont nécessaires pour comprendre si ces différences émergent tôt dans l'enfance. Cette étude a utilisé les données de International Infant EEG Data Integration Platform (EEG-IP); une étude de cohorte des enfants à risque de TSA (Londres : 7, 14 mois ; Seattle : 6, 12, 18 mois) pour explorer les trajectoires développementales de la latéralisation. Nous avons extrait les indices de latéralisation cérébrale à partir de sources corticales reconstruites à partir d'enregistrements EEG collectés pendant que les participants regardaient une vidéo. L'étude a inclus 92 participants à risque familial d'autisme (au moins un frère ou une sœur avec un diagnostic de TSA) et 91 contrôles. Nous avons constaté qu'à douze mois, les enfants à risque d'autisme présentaient une latéralisation de l'hémisphère gauche plus forte dans l'activité gamma par rapport aux contrôles. Ces différences étaient encore accentuées dans le gyrus temporal supérieur ($p < 0,05$). Le gyrus temporal supérieur est important pour la discrimination des phonèmes et l'attention auditive et, dans certains cas, peut être considéré comme un précurseur important pour l'apprentissage du langage. La latéralisation est un élément clé du développement et notre étude montres comment les différences de développement peuvent avoir un impact sur divers processus cognitifs dans l'autisme.

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I would also like to thank the research teams at the University of Washington and the BASIS team at the University of London for collecting the data used in this study. The following sources of funding that made this project possible are acknowledged: Gabriel Blanco holds a Quebec Autism Research Trainee fellowship from the Transforming Autism Care Consortium (TACC). Finally, I would also like to thank the several individuals that provided me with advice and guidance in various aspects during the completion of this program: Myriam Beauchamp, Jose Blanco, Maribel Gomez, Mikaela Mari Jusi, Jelena Popic, Scott Huberty, Mandy Steiman, Ellie-Anna Minogianis, and Afiqah Jusuf.

Contribution of Authors

Gabriel Blanco Gomez was the lead writer of the manuscript. He contributed to the conceptualization, hypotheses, data analysis, and interpretation of the results. Data collection was carried out by the Basis Team at the University of London and a team led by Sara Jane Webb at the University of Washington. Christian O'Reilly contributed to the conceptualization of the project as well as the data analysis and preprocessing. Mayada Elsabbagh oversaw all aspects of the project.

List of Tables and Figures

Introduction

The idea that the human brain has two hemispheres with differing functions has been around for centuries (Broca, 1861; Kimura & Archibald, 1974; H. Liu et al., 2009; Oades, 1998). For example, the processing of linguistic input is thought to activate regions in the left hemisphere (S. Wang et al., 2019), while the right hemisphere is associated with other higher-order functions such as attention (Russell-Giller et al., 2021; Śmigasiewicz et al., 2017) and visuospatial integration (Gotts et al., 2013). This hemispheric asymmetry emerges early during the first trimester of gestation (Corballis, 2013) and its disruption has been linked to various learning impairments (Cantiani et al., 2019), and neurodevelopmental disorders (Seery et al., 2013). The development of a functionally lateralized brain is key in infancy as it allows children to fully realize their linguistic potential (Spironelli & Angrilli, 2010). Despite this, most studies related to early brain lateralization have focused on clinical populations, leaving a large gap in our understanding of how brain oscillations lateralize. In light of this, our study seeks to fill this gap by first presenting brain lateralization in autism spectrum disorder (ASD) compared to neurotypical controls and then systematically breaking down how these differences can shed light on the development of brain lateralization.

Lateralization in Autism

ASD is a neurodevelopmental condition characterized by a wide range of symptoms, causes, and endotypes (American Psychiatric Association, 2013). Although a diagnosis for ASD can be made as early as 18 months (Ozonoff et al., 2015), research on autism has shown that abnormalities in brain development can start as early as 3 months of age (Wolff et al., 2012). Using electroencephalography (EEG), researchers have found differences in spectral power

across all frequency bands in the EEG spectrum (theta 4-6 Hz; alpha 6-13 Hz; beta 13-30 Hz and gamma 30-50 Hz), with studies reporting that 3-month-old babies at risk for autism have lower spectral power than their neurotypical peers (Huberty et al., 2021; Levin et al., 2017). The biological mechanisms that underlie autism risk and symptomatology are not fully understood but asymmetries in the development of brain hemispheres could be at play. Autistic individuals show brain asymmetries in both structural (D'Mello et al., 2016; Wolff et al., 2012) and functional connectivity (Alaerts et al., 2016). For example, during a listening task, typically developing children exhibited leftward activation, whereas toddlers at familial risk for ASD exhibited rightward activation (Eyler et al., 2012). Similarly, infants at risk for autism have a left-hemisphere bias during face processing, while control groups exhibit right hemisphere dominance (Keehn et al., 2015).

These differences in lateralization can represent a potential biological index for ASD and a possible mechanism underlying the observed symptomatology. Nevertheless, questions remain about how lateralization arises in ASD and a disagreement exists about the directionality of results. A few studies have suggested that autistic individuals have more lateralization relative to controls (Eyler et al., 2012; Gabard-Durnam et al., 2015; Keehn et al., 2015). For instance, Floris et al. (2016) found that autistic children showed extreme rightward lateralization during a finger-tapping paradigm while control participants did not show any dominance of motor networks. Other studies, however, have argued the opposite phenomenon, wherein autistic individuals lack any type of lateralization and their neurotypical counterparts show a clear hemisphere dominance (Rolison et al., 2021; Seery et al., 2013). This inconsistency in lateralization studies can be attributed to variations in task design, neuroimaging methods, regions of interest, age, and most

importantly, a lack of normative studies outlining how lateralization emerges in typical development.

Although a handful of landmark studies have been published regarding lateralization in neurotypical infants (Anaya et al., 2021; Brooker et al., 2017; Emerson et al., 2016; Gartstein et al., 2020; Howarth et al., 2016) they are limited both in spatial specificity and scope. First, these studies have focused exclusively on alpha power (EEG activity within the 6-13 Hz range in adults and 6-9 Hz in infants), excluding lateralization in other frequency bands (i.e., theta, gamma), even though lateralization of higher frequency bands has recently been shown to modulate various cognitive processes (Adam et al., 2020; Benasich et al., 2008; Cartocci et al., 2021; Morillon et al., 2012). Second, they primarily focus on frontal EEG activity given its association with internal behaviors and emotion (Brooker et al., 2017), yet lateralization can be found in various regions across the brain. Thus, considering the functional and anatomical segregation of brain oscillations and its importance on brain specialization, our field would greatly benefit from a detailed and nuanced documentation of the development of lateralization across brain regions, frequency bands, and developmental stages.

In the current study, we focus on the very early developmental period when lateralization patterns emerge (Emerson et al., 2016; J. Liu et al., 2019). Using resting-state EEG recordings, our goal is threefold. First, explored whether there are group differences in lateralization between infants with no known family history of ASD and those who at 24 months are identified as either at-risk with an ASD diagnosis (AR-ASD+), at-risk without an ASD diagnosis (AR-ASD-) or controls. Second, we explored when these group differences emerge (i.e., 6 or 12 months) and how they interact with different frequency ranges on the EEG spectrum (theta, alpha, beta, and gamma). In line with previous research, we hypothesize that children at risk for autism will show

atypical patterns of lateralization as early as 6 months of age. We also hypothesize that autistic infants (AR-ASD+) will show more deviance from controls than at-risk infants who do not develop ASD (Control > AR-ASD- > AR-ASD+). Finally, we aim to present an in-depth examination of the progression of brain lateralization in individual brain regions. One of the drawbacks of using EEG as an imaging tool is a lack of strong spatial resolution. Electrodes measure activity at the level of the scalp and thus fail to account for deeper cortical sources. One solution that has gained traction within the neuroscience community is source estimation, a methodological technique that involves co-registration techniques to offset the low spatial resolution of EEG. In short, source estimation uses MRI-derived information such as skull thickness, tissue conductivity, and anatomical boundaries in conjunction with high-density EEG nets to localize sources of EEG activity (Michel & Brunet, 2019; O'Reilly et al., 2021) In our study, we used this technique to examine lateralization patterns across various regions, advancing our understanding of the lateralization of brain oscillations in development.

Methods

Participants:

This study relied on data from the International Infant EEG Data Integration Platform (EEG-IP), a multi-site pooling of two longitudinal cohorts of infants at risk for autism (van Noordt et al., 2020). Participants in this study were assigned to one of two groups: infants at-risk (AR), defined as those with hereditary risk by virtue of having a sibling with an ASD diagnosis; and controls, defined as infants with no known family history of ASD. All participants were free from known prenatal or postnatal neurological complications or unrelated genetic disorders. Data were collected at two sites as part of independent projects: Birkbeck, the University of London in

the United Kingdom (EEG collected around 7 and 14 months) and Seattle Children's Hospital in the United States (EEG collected around 6, 12, and 18 months). A total of 192 infants were enrolled in this study (AR; n=98 and Control: n=94). Participant statistics and demographics can be found in Table 1.

Table 1. Total number of participants for each group. Number of males are in parentheses.

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Risk Group	Outcome	London	Seattle	Total
At-Risk	ASD	17(11)	12(5)	29(16)
	no-ASD	36(10)	29(23)	65(33)
	unknown	1(0)	2(0)	3(0)
At-Risk Total		54(21)	43(28)	97(49)
Control	ASD	0	3(2)	3(2)
	no-ASD	50(21)	37(21)	87(42)
	unknown	0	5(3)	5(3)
Control Total		50(21)	45(26)	95(47)
Total Across Risk Groups		104(42)	88(54)	192(97)

Clinical assessments were conducted at 24 and 36 months. Diagnosis was ascertained by clinicians and informed, among other criteria, by the Autism Diagnostic Observation Schedule (ADOS). In the Seattle group, ADOS assessments were conducted at 18 months and 24 months but only for the AR group. In the London group, the ADOS was administered to the AR group at 24 months and both the control and AR groups at 36 months. All ADOS scores were calibrated and standardized (Hus & Lord, 2014). In total, 30 participants were diagnosed with ASD to form the AR-ASD+ group. We further excluded one participant from the control group who was later diagnosed with ASD and two participants for whom diagnostic outcomes were missing. Given that EEG was only available at 18 months for the Seattle group, we decided to exclude it completely from these analyses and focus on the 6-7 month and 12–14 month recordings. For simplicity, participants who are 6-7 months old and participants who are 12-14 months old will be referred to as 6 months and 12 months old, respectively.

EEG data acquisition

Resting-state high-density EEG was recorded while participants watched 30-40 second videos, presented in a randomized order. These videos included 1) a woman singing nursery rhymes, 2) bright colored toys moving and/or 3) bright colored toys being manipulated by a human hand (London only). EEG data were acquired using a 128-channel Hydrocell geodesic sensor net and Electrical Geodesics (Eugene, Oregon) Net Station software. To remove any powerline contamination, a 50Hz and a 60Hz notch-filter were applied to the London and Seattle recordings, respectively. EEG was recorded at 500Hz with a vertex reference (channel Cz) and re-referenced to an average reference.

Recordings were standardized and preprocessed with the EEG-IP-L pipeline (Desjardins et al., 2021). Noisy channels and epochs were identified and removed. Independent component analysis was performed, and independent components associated with non-neural sources (e.g., EOG components) were rejected. Annotations for noisy channels, epochs, and independent component classification were reviewed by an expert to confirm the initial classification (Desjardins et al., 2021). EEG recordings that survived artifact rejection were segmented into 1-second non-overlapping epochs and these epochs were used to calculate lateralization indices and for source reconstruction. The mean number of epochs was 168, 192 and 179 for the AR-ASD+, AR-ASD-, and control groups respectively. Six participants were excluded because they had less than 19 epochs, an insufficient number for adequate analysis (Fraschini et al., 2016). In addition, we excluded all participants whose EEG spectral power values were ±3 standard deviations away from the mean. This threshold is consistent with established practice for artifact rejection and corresponds to rejecting values that are more extreme than 99.7% of the Gaussian distribution (Miskovic et al., 2009). This resulted in a total sample size of 179 participants.

Source reconstruction was estimated using an age-appropriate head template (O'Reilly et al., 2021). This template was built from Magnetic Resonance Imaging (MRI) averages and boundary element method (BEM) segmentation of head tissue. It should be noted that all sources were estimated using a 12-month template to avoid systematically confounding the effect of using different templates with the age at the time of EEG recording. To estimate sources, the MNE python package (Gramfort et al., 2013) and the eLORETA inverse operator (Pascual-Marqui et al., 1994) were used, with a $\lambda^2=10^{-4}$. A total of 66 regions of interest (ROIs) were obtained from the original templates based on the Desikan-Killiany parcellation (Desikan et al., 2006). Sources were averaged within each brain region.

EEG Lateralization index

Lateralization was derived from absolute spectral power (SP). SP was computed from the standardized EEG-IP recordings using the *compute_source_psd()* function in MNE-Python (Gramfort et al., 2013). For each recording, the power spectrum was averaged across all 1-second epochs. A lateralization index (LI) was then calculated using the formula LI=(LH − RH)/(LH + RH), where LH and RH are the left-hemisphere and right-hemisphere SP, respectively, for homotopic brain regions (Thut, 2006). LI values were calculated for the following frequency bands: theta 4-6 Hz; alpha 6-13 Hz; beta 13-30 Hz; gamma 30-50 Hz. Values for each frequency band were calculated by averaging the spectral power within each range (e.g., alpha 6-13 Hz).

Statistical Analyses

To analyze the statistical significance of lateralization patterns, we ran a three-way repeated-measures ANOVA using age (6 months, 12 months) and frequency band (theta, alpha,

beta, gamma) as within-subjects factors and outcome (AR-ASD-, Control, AR-ASD+) as between-subject factors. It should be noted that we ran two analyses, one to compare outcomes as between-subject factors and another to compare only the risk groups (AR vs. Control), regardless of the diagnostic outcome. For the second analysis, both AR-ASD- and AR-ASD+ were grouped. Greenhouse-Geisser sphericity corrections were applied to within-subject factors that violated the sphericity assumption. We further examined significant main effects and interactions with paired t-sample tests. Bonferroni corrections were applied to correct for multiple tests. Throughout the analyses, we kept a strict $\alpha = .05$, although marginally significant effects ($0.05 < p < .10$) were also reported. All analyses were done using R 3.6.0 (R Core Team, 2019) and the 'rstatix'packages (v0.7, Kassambara, 2021).

Mixed effects model

A mixed-effects multi-factorial linear regression model was used to assess the effect of risk status, age, brain region, and biological sex on lateralization. Nested random effects were included for each subject. Fixed effects were included for the testing site and biological sex. Two models were included in this study:

1) $LI \sim outcome * age * regions + sex + site$
2) $LI \sim risk * age * region + sex + site$

Model (1) was used to test the interaction of region, age, and outcome group on lateralization. Model (2) was used to test the impact of risk status on lateralization. Statistical analyses were run using various python packages, mainly statsmodels 0.9.0 for linear regression, pandas 1.4.0 for data manipulation, and seaborn 0.11.0 for visualization.

Results

Lateralization differences between diagnostic groups at 12 months

Overall, our analyses showed that all three diagnostic groups (AR-ASD-, Control and AR-ASD+) had similar lateralization values at 6 months of age, but a three-way ANOVA revealed a statistically significant three-way interaction between outcome group, age, and frequency band ($F(2,136 = 4.71, p = <.01)$ as shown in Table 2. Further inspection revealed that at 12 months, the difference between groups' means was statistically significant in the gamma frequency range ($F(2,151) = 3.30, p= 0.04$) but not in the theta, alpha or beta bands, as shown in Figure 1 (A and B). This suggests that higher frequency bands tend to shift towards more lateralization around the 12-month mark for autistic infants. Multiple pairwise comparison tests were then carried out to further assess group differences. Given that the gamma band was the only frequency band that had a significant group interaction, we limited our analysis to gamma band power. We found a statistically significant difference between the AR-ASD+ and AR-ASD- groups (adjusted-p= 0.038), wherein the AR-ASD+ group had a higher mean lateralization value (more-leftward dominance) than the AR-ASD- group. As seen in Figure 1.B, the 12-month-old AR-ASD+ infants had more lateralization in higher frequencies, starting at about 20Hz and peaking at 30+ Hz. Furthermore, the lateralization differences between AR-ASD+ and controls showed a trend towards significance in the gamma range (adjusted-p= 0.09), where once again infants within the AR-ASD+ group had higher lateralization values (more leftward asymmetry) compared to the control group (as shown in Figure 1.B). Thus, as hypothesized, autistic infants showed different lateralization patterns during the first year of life. Lateralization values for each group and timepoint can be found in Table 3.

Table 2. Repeated measures ANOVA with outcome as a between-subjects variable and age and band as within-subject variables.

Effect	Df	Sum Sq	F	p-value	p<0.05
outcome	2.00	116.00	0.48	0.62	
age	1.00	116.00	12.90	0.00	*
band	1.29	149.75	1.82	0.18	
outcome:age	2.00	116.00	0.74	0.48	
outcome:band	2.58	149.75	2.44	0.07	
age:band	1.18	136.78	11.26	0.00	*
outcome:age:band	2.36	136.78	4.71	0.01	*

Table 3. Mean lateralization values for each group and frequency band
Mean lateralization values and standard deviation at each age group (6 months or 12 months) and for each frequency band (Theta, Alpha, Beta, and Gamma). Contrasts are made between the three outcome groups: AR-ASD-, Control, and AR-ASD+.

Descriptive Statistics					
Mean Lateralization at 6 months (sd)					
Group	n	**Theta**	**Alpha**	**Beta**	**Gamma**
Control	72	0.053 (0.049)	0.06 (0.057)	0.048 (0.081)	0.04 (0.094)
AR-ASD+	22	0.051 (0.068)	0.053 (0.07)	0.02 (0.09)	0.012 (0.093)
AR-ASD-	50	0.047 (0.074)	0.064 (0.082)	0.032 (0.093)	0.02 (0.097)
Mean Lateralization at 12 months (sd)					
Group	n	**Theta**	**Alpha**	**Beta**	**Gamma**
Control	73	0.006 (0.07)	0.01 (0.085)	0.012 (0.084)	0.007 (0.088)
AR-ASD+	26	-0.022 (0.057)	-0.018 (0.062)	0.038 (0.091)	0.05 (0.102)
AR-ASD-	55	0.004 (0.058)	0.004 (0.065)	-0.002 (0.071)	-0.003 (0.081)

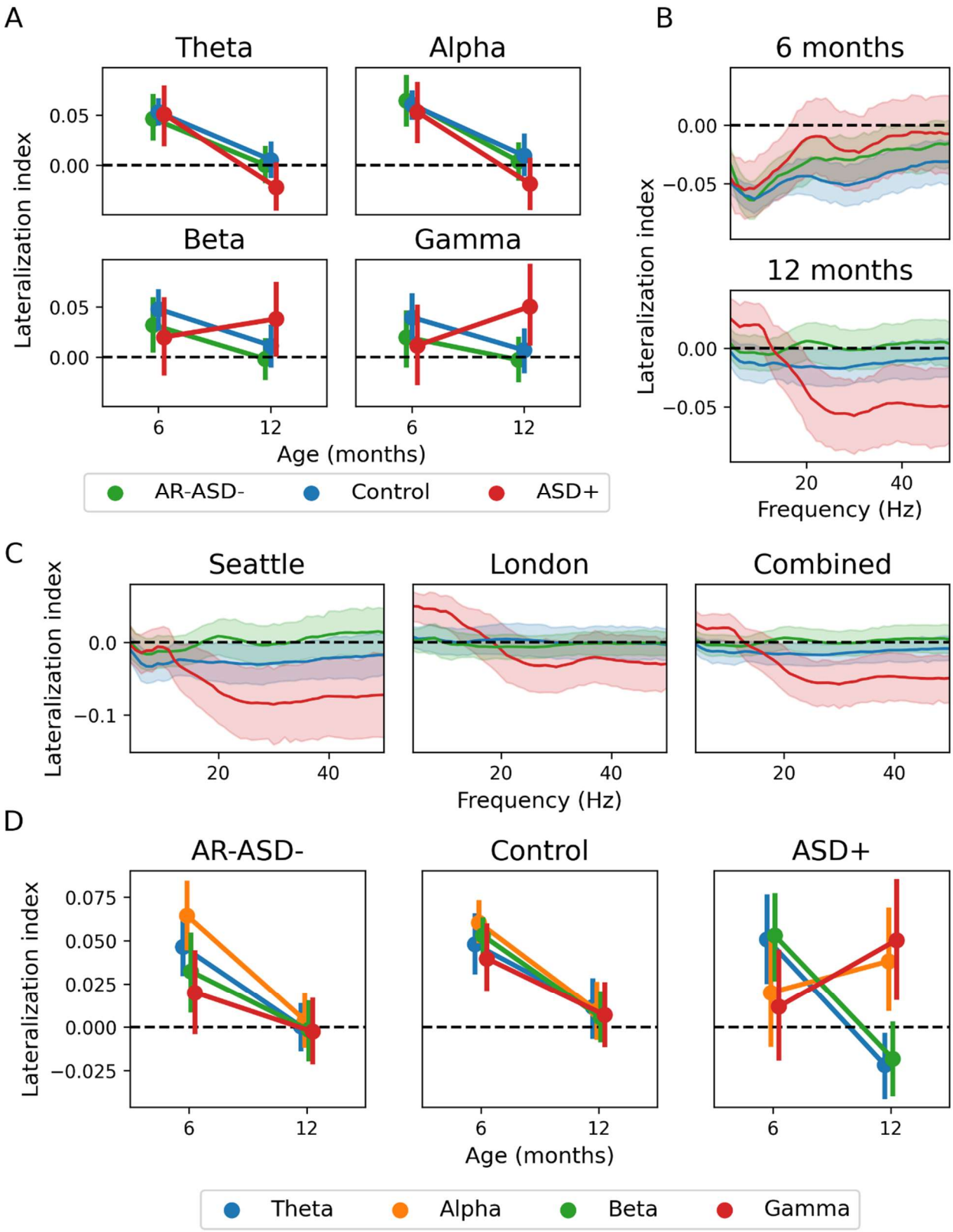
A
Theta
Alpha
Beta
Gamma
Lateralization index
0.05
0.00
6
12
Age (months)
AR-ASD-
Control
ASD+
B
6 months
12 months
0.00
−0.05
20
40
Frequency (Hz)
C
Seattle
London
Combined
0.0
−0.1
D
AR-ASD-
Control
ASD+
0.075
0.050
0.025
0.000
−0.025
Theta
Alpha
Beta
Gamma

Figure 1. **A)** Mean lateralization indices as a function of age (6 months to 12 months) for each frequency band: theta, alpha, beta, and gamma. Contrasts between outcome groups: AR-ASD- (green), Control (blue) and AR-ASD+ (red). Negative values represent right-hemisphere dominance while positive values represent left-hemisphere dominance. **B**) Mean lateralization indices across the EEG frequency spectrum. Cross-sectional analyses for each timepoint: 6 months (top) and 12 months (bottom). The AR-ASD+ group shows right hemisphere lateralization at 12 months of age while the Control and AR-ASD- groups show a lack of lateralization. Confidence intervals were set at 90%, as represented by the shadowed areas. **C**) Site differences in EEG frequency spectrum at 12 months of age. Analyses are presented for each of the testing sites: Seattle (left), London (middle) and both sites combined (right). **D**) Changes in mean lateralization for each outcome group: Control (left), AR-ASD- (center), and AR-ASD+ (right). Analyses are presented for each frequency band. All changes in lateralization between 6 and 12 months of age are significant except for changes in gamma lateralization.

Autism risk and lateralization

We further examined the relationship between risk and the development of lateralization without an emphasis on later diagnosis. We pooled AR-ASD+ and AR-ASD- participants together and conducted a repeated measures ANOVA to examine whether ASD risk was enough to develop differences in lateralization. No significant effects were found between risk status and lateralization at 6 months or 12 months ($p>0.05$). We also found no significant interaction between risk status and lateralization at each of the four frequency bands ($p>0.05$; see Figure 2.A). These findings suggest that lateralization follows the same developmental trajectory in at-risk infants and controls.

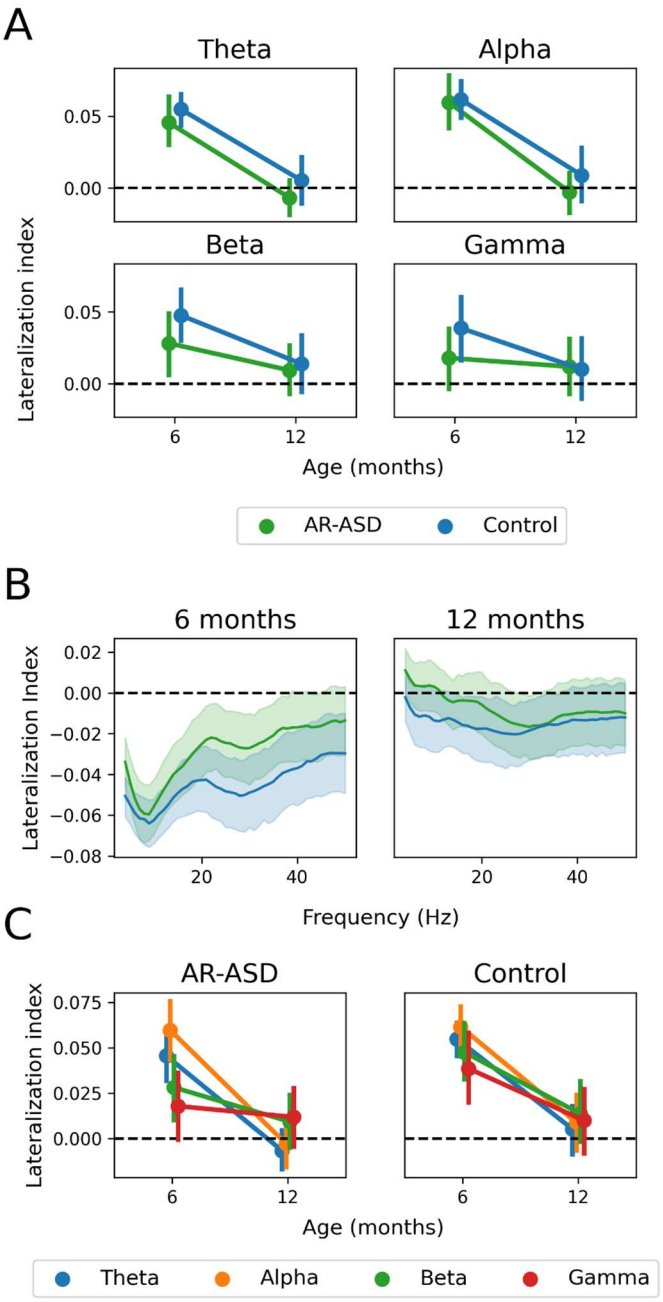

Figure 2. **A)** Mean lateralization indices as a function of age (6 months and 12 months) for each frequency band: theta, alpha, beta, and gamma. Contrasts between risk groups: AR-ASD (green), Control (blue). Negative values represent right-hemisphere dominance while positive values represent left-hemisphere dominance. **B**) Mean lateralization indices across the EEG frequency spectrum. Cross-sectional analyses for each timepoint: 6 months (top) and 12 months (bottom). **C**) Site differences in EEG frequency spectrum at 12 months of age. Analyses are presented for each of the testing sites: Seattle (left), London (middle) and both sites combined (right). **D**) Changes in mean lateralization for each risk group: AR-ASD (left) and Control (center). Analyses are presented for each frequency band.

Gamma lateralization decreases in typically developing infants

Another goal of this study was to examine how lateralization in infants with ASD can highlight key aspects of lateralization during typical development. Given that gamma lateralization was abnormal in the ASD group, we decided to further examine developmental changes of gamma in the control group. A repeated measures ANOVA showed a statistically significant main effect for age ($F(1,116) = 12.90$, $p < 0.001$). Follow-up analyses of age for each group revealed that changes in gamma band lateralization between 6 months and 12 months were statistically significant in the control group ($p = 0.032$) but not in the other two risk groups. In the control group, there was a shift from left hemisphere dominant lateralization toward no lateralization as shown in Figure 1. D. There was no significant difference between time points for infants in the AR-ASD+ group ($p>0.05$) and AR-ASD- group ($p>0.05$) as shown in Figure 1.D. Therefore, all diagnostic groups start with highly lateralized gamma oscillations, but over time, typically developing infants experience a shift in lateralization towards symmetry that is not seen in the other groups, highlighting a critical change towards no lateralization that occurs at 12 months. Further analyses were carried out to understand whether this shift toward no lateralization was due to drastic changes in power within the left hemisphere or the right hemisphere. Post-hoc analyses showed that there was no significant change in gamma power between 6 months and 12 months for the left hemisphere ($p>0.05$) or the right hemisphere ($p>0.05$). However, there was a larger mean decrease in the left hemisphere absolute power (-0.11 units) compared to the mean decrease in the right hemisphere absolute power (-0.08 units), which could explain differences in lateralization. There were also no significant effects or interactions between sex and changes in lateralization ($p>0.05$).

Lateralization across different brain regions

We used source estimation to further break down the development of lateralization in specific brain regions. Using data only from the control group, we calculated lateralization scores for 34 source estimation regions and averaged them across all participants at 6 and 12 months. Z-scores were then calculated for each region and sources were defined as "lateralized" if they were ± 2 SD away from the mean. At 6 months of age, three regions were above the defined threshold, these include the posterior middle frontal gyrus (pMFG), the parahippocampal gyrus (PHG) and the superior temporal gyrus (STG) as shown in Figure 3. At 12 months of age, two other regions were also denoted as lateralized, these include the medial orbitofrontal gyrus (mOFG) and the pars orbitalis subsection of the inferior frontal gyrus (IFG). The top regions for each age group are presented on Table 4. To avoid errors related to multiple comparisons, only these regions were used to test for group differences.

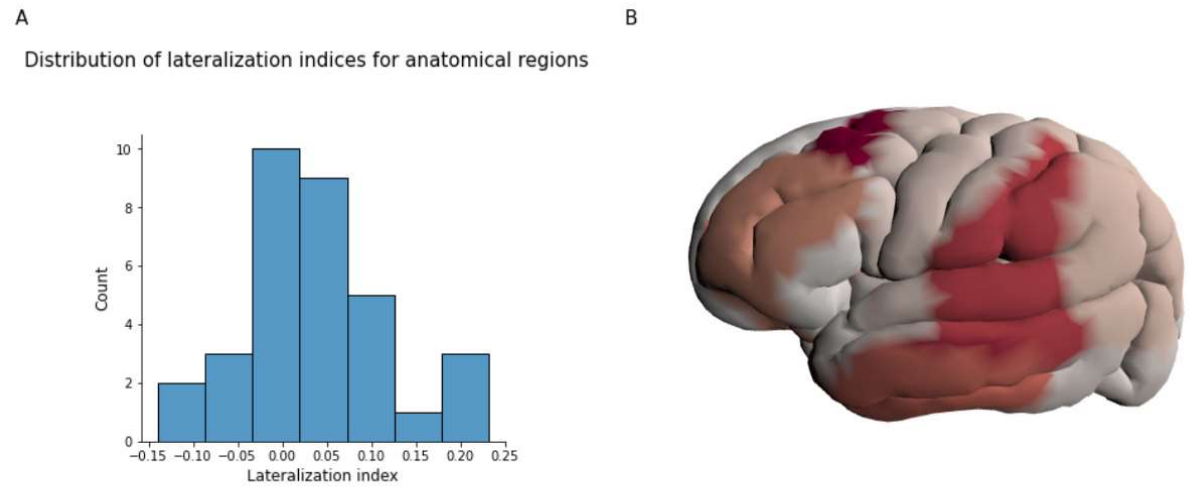

Figure 3. A) Distribution of mean lateralization indices at 6 months for control infants. Y axis represents the total number of brain regions. Lateralization values were calculated only for the gamma frequency band. B) Spatial source estimations of lateralization values at 6 months for one subject. Lateralization values are color-coded linearly according to the percentile. Low

lateralization values are shown in gray while higher lateralization values are shown in dark red (100^{th} percentile).

Table 4 Top lateralized regions
Mean lateralization values and standard z scores and directionality for the highly lateralized sources. Regions with a lateralization value ± 2 SD away from the mean at each timepoint are shown. These values represent mean lateralization within the gamma frequency band for the control group only.

Top lateralized sources at 6 months			
Region	Lateralization index	z-score	Hemisphere bias
Posterior middle frontal gyrus	0.23	2.28	left
Superior temporal gyrus	0.22	2.17	left
Para hippocampal gyrus	-0.14	-2.12	right
Top lateralized sources at 12 months			
Region	Lateralization index	Z-score	Hemisphere bias
Medial orbitofrontal Gyrus	0.29	-2.7	right
Inferior frontal gyrus (Pars orbitalis)	0.23	2.0	left

Abnormal lateralization in the Auditory Cortex (STG)

A mixed-effects multi-factorial linear regression model with site and sex as covariates revealed no differences between the outcome groups at 6 months ($p>0.05$), corroborating the results obtained from the repeated measures ANOVA. There were also no significant effects or interactions between testing site ($p>0.05$) and lateralization as shown in Figure 1. C. Nevertheless, there was a significant effect of outcome group on lateralization found in the STG

(p <0.05). No differences in groups were significant in the other brain regions (p>0.05) as shown in Figure 4.A.

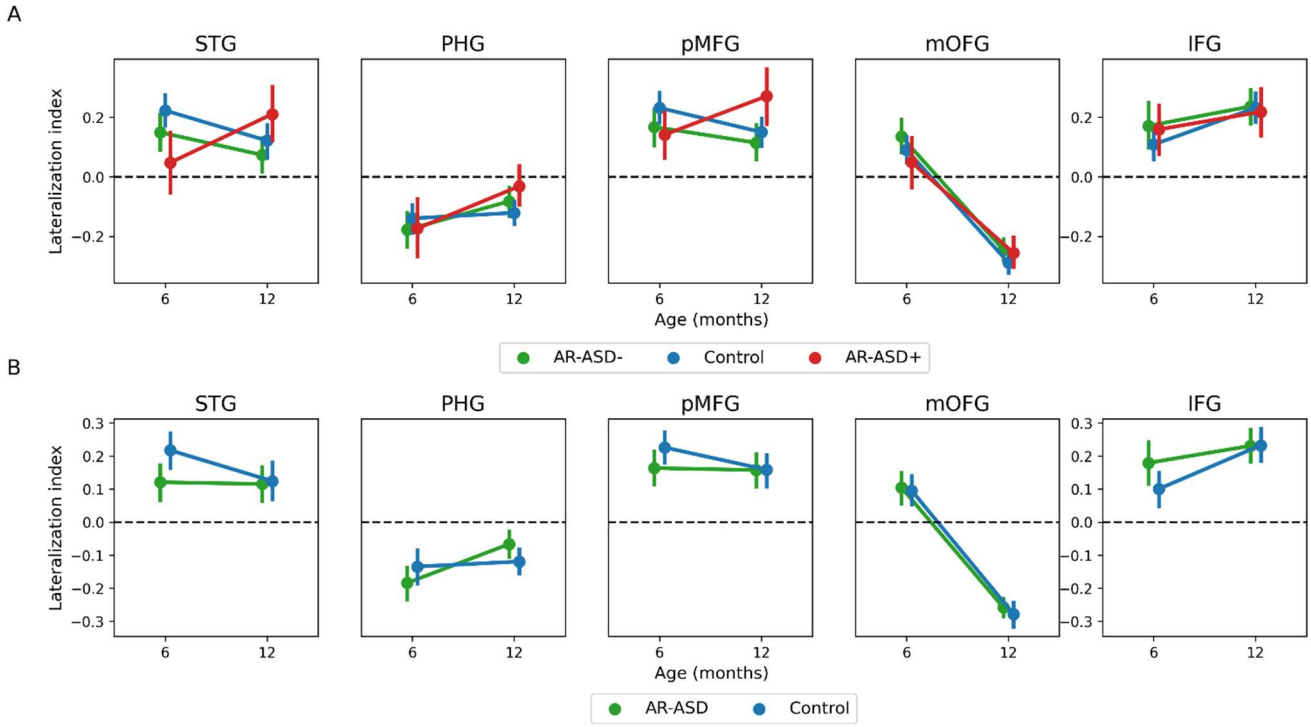

Figure 4. Mean lateralization indices as a function of age (6 months to 12 months). Analyses are presented for each of the resting-state brain regions: STG, PHG, pMFG, mOFG and IFG (Pars orbitalis). A) Contrasts between outcome groups: AR-ASD- (green), Control (blue) and AR-ASD+ (red). B) Contrasts between risk groups: AR-ASD (green), Control (blue). Negative values represent right hemisphere dominance while positive values represent left-hemisphere dominance.

Follow-up post-hoc tests revealed that at 6 months, there was a significant difference between the STG lateralization scores of the Control and the AR-ASD+ groups (p=0.028). On average, controls had more leftward lateralization compared to the AR-ASD+ group (Figure 4.A). There were also no significant effects for sex and testing site (p's >0.05). When grouped by risk status, we found no significant differences in lateralization in any of the regions (Figure 4. B). However, these analyses should be taken with caution given the opposing slopes shown by both the AR-ASD+ and AR-ASD- (Figure 4.A).

Developmental trajectories of lateralization

We further examined developmental changes in neurotypical controls. Analyses revealed a significant effect of time for three anatomical regions including the STG ($p<0.05$), the mOFG ($p<0.001$) and the IFG ($p<0.01$). In the mOFG, there was a shift from no lateralization at 6 months to rightward lateralization at 12 months but no significant differences between diagnostic groups. In the IFG, there was a significant increase toward more leftward lateralization from 6 months to 12 months. Finally, our model revealed significant differences in the developmental trajectories of the STG ($p<0.05$) between the control and AR-ASD+ groups. Infants in the control group had a significant -0.033 unit decrease from leftward lateralization to less lateralization. Contrastingly, the infants in the AR-ASD+ showed an increase in lateralization of +0.038 units between 6 and 12 months as shown in Figure 4.A. Moreover, post hoc analyses revealed that neither the AR-ASD+ nor the AR-ASD- group had a significant change in the lateralization of the STG. Hence, our results showed that, unlike the control group which saw a significant decrease in lateralization during the first year of life, autistic infants showed an increase in lateralization. Developmental trajectories in other regions were not significant ($p's<0.05$).

Discussion

This study aimed to assess if infants at risk for autism displayed atypical lateralization patterns during the first year of life. Using data from a longitudinal infant cohort, we analyzed resting-state brain oscillations and revealed four important findings. First, we found that autistic infants showed atypical lateralization patterns at 12 months of age when compared to the at-risk and control groups. Second, we found that these group differences were only statistically

significant in the gamma frequency range but not in the theta, alpha, or beta range. Third, using source estimation we found five highly lateralized brain regions in typically developing infants. These include the pMFG, PHG, and STG at 6 months and the mOFG and IFG at 12 months of age. Of these lateralized regions, only the STG displayed significant differences between the autistic and control groups. Lastly, contrary to our hypothesis, we found no significant effects of autism risk on brain lateralization.

Increased left gamma band lateralization in ASD

We first hypothesized that differences in lateralization would emerge at 6 months of age. However, our analysis revealed that autistic infants had more left hemisphere gamma activation at 12 months compared to the AR-ASD- and control groups. These findings are consistent with previous studies on face processing detailing abnormal gamma lateralization in children at risk for autism (Keehn et al., 2015). Gamma band power has been associated with emotion recognition, face classification, perception, selective attention, memory, motivation, and behavioral control (Cartocci et al., 2021; Herrmann et al., 2004; Sirota et al., 2008; Yang et al., 2020). In a recent review, (Bosman et al., 2014) argued that gamma band activity does not possess a single universal function in the brain but rather acts as a global coordination system that spans multiple cognitive processes. This is because gamma band activity is linked to gamma-aminobutyric acid (GABA) neurons, which are thought to drive inhibitory pathways (Bosman et al., 2014; Buzsáki & Wang, 2012; Tozzi, 2015). Therefore, the increase in left gamma lateralization displayed by the autism group could signal a disruption of the developmental processes that regulate inhibition in the brain.

In this regard, our findings seem to support the excitation-inhibition imbalance theory of autism (Sohal & Rubenstein, 2019; Zikopoulos & Barbas, 2013) which states that many of the phenotypes seen in autism result from increased inhibition in the brain's signaling pathways. In terms of directionality, we found that the AR-ASD+ group showed left hemisphere dominance while the control and AR-ASD- groups displayed no asymmetries. Gamma band activity in the left hemisphere has been associated with language processing and sound discrimination (Cantiani et al., 2019; Śmigasiewicz et al., 2017); however some studies suggest that in infancy both hemispheres tend to be equally active (Anaya et al., 2021; Emerson et al., 2016). This idea is evidenced by perinatal stroke studies, where damage to either the right or left hemisphere can lead to language deficits (Russell-Giller et al., 2021; Trauner et al., 2013). Therefore, a lack of bilateral activation in the AR-ASD+ group could point to early patterns of atypical development.

In neurotypical controls, simultaneous bilateral activation during infancy is hypothesized to index the early development of interhemispheric cross-communication as each hemisphere becomes more specialized at carrying out specific roles (Cartocci et al., 2021). In our study, this trend towards symmetry was present in the AR-ASD- and control groups but not in the AR-ASD+ group, suggesting that having a family history of autism is not enough to drive abnormal lateralization. Furthermore, our findings seem to suggest that differences in lateralization arise significantly earlier than previously thought. Atypical gamma band power has been reported in autistic children aged 7-12 years old (C.-G. Wang et al., 2022) however, our findings indicate that deviations from typical lateralization develop around the first year of life. One potential cause for these early patterns could be linked to gene influences. Structural and functional lateralization of the brain is thought to begin during fetal development as a result of gene-driven changes. This is especially relevant in the case of ASD given that a significant overlap exists

between genes associated with autism and genes thought to be necessary for hemisphere lateralization (Postema et al., 2019). However, more research is needed to understand what specific genes and interactions lead to differences in developmental trajectories. As previously discussed, having a sibling with a positive autism diagnosis does not seem to be enough to cause changes in lateralization, which means that other factors such as environmental influences and epigenetic effects could be at play.

Effects of familial risk, sex, and testing site

A secondary goal of this study was to examine some of the factors that contribute to atypical lateralization. Overall, neither the repeated measures ANOVA nor the linear mixed effects model revealed significant interactions between familial risk and lateralization. Furthermore, we had hypothesized that infants in the AR-ASD- group would show an intermediate phenotype, displaying more lateralization than controls but less than the AR-ASD+ group (AR-ASD+ > AR-ASD- > Control). However, the opposite was true, we found that whenever AR-ASD+ infants had elevated lateralization values for one hemisphere, AR-ASD- tended to have lower values than all groups (AR-ASD+ > Control > AR-ASD-). This phenomenon referred to as the compensatory mechanism hypothesis by Kaiser et al. (2010), suggests that unaffected children possess compensatory brain mechanisms and/or protective factors that over engage brain processes to compensate for risk factors. This compensatory mechanism could also explain why we observed no effects of familial risk in our statistical models. However, it should be noted that in our risk analyses, we pooled the AR-ASD- and AR-ASD+ groups together into a single at-risk group. By averaging groups, we lose specificity and obtain an average value that is the mean of both outcomes which in turn more closely resembles the control group. Therefore, these results should be interpreted with caution. This issue has been

discussed in detail in other studies (Rozga et al., 2011) and solutions have been proposed to further understand these interactions.

In terms of sex effects, we found no evidence for significant effects on lateralization. Despite research suggesting that males have more brain asymmetry than females (Kovalev et al., 2003), both male and female participants exhibited similar trajectories in lateralization. Finally, given that data collection occurred at two clinical sites with different environments (London and Seattle), we tested for differences in testing location. Our model revealed no significant interactions between the testing site and the diagnostic group. Strikingly, AR-ASD+ infants had nearly identical lateralization patterns at 12 months in both the London and Seattle sites, further strengthening the validity of our results. Considering the common discrepancies in infant EEG studies, replicating results across independent sites is promising.

Lateralization differences in the STG (Auditory cortex)

New advances in source estimation techniques allow researchers to identify brain areas that generate observed EEG signals. To our knowledge, this is the first time source estimation has been used to explore brain lateralization in infants, offering new avenues to document hemisphere asymmetries in both clinical and non-clinical populations. Using age-appropriate templates, we found five highly lateralized regions during the first year of life, including the pMFG, PHG, mOFG, IFG, and STG. Only the latter revealed differences between the AR-ASD+ group and typically developing controls. Our results indicated that typically developing infants had leftward lateralization of the auditory cortex at 6 months and then a lack of lateralization at 12 months, while infants in the AR-ASD+ group showed the opposite trajectory.

The STG, which comprises a large part of the auditory cortex, is associated with phoneme discrimination and auditory attention (Luo & Poeppel, 2007), a precursor for language learning. Research has shown that the auditory cortex is highly lateralized in adults, and language deficits have been theorized to be caused by a failure of the left auditory cortex to specialize for language (Eyler et al., 2012), offering new avenues to study language delays in autism. Recent studies have shown that even systems known to lateralize in adults show symmetry during development (Emerson et al., 2016). A longitudinal study using functional connectivity found that lateralization of the auditory cortex follows a u-curve. Infant brains start highly lateralized during fetal development, then they shift towards symmetry after birth, peaking at around 11.5 months and finally they go back to being lateralized until they reach adult levels (Emerson et al., 2016). This shift towards symmetry during the first year is thought to index a rapid development of structural connectivity between homologous brain regions. Despite having fewer time points, our typically developing group followed this u-curve of early lateralization followed by a shift toward no lateralization. In contrast, AR-ASD+ infants displayed a lateralization value near zero at 6 months and then an increase toward left hemisphere dominance at 12 months. This initial lack of asymmetry in the auditory cortex could be due to an increase in right hemisphere activity as well as a failure to create effective bilateral connections by 12 months.

Research using fMRI data during sleep has shown that toddlers diagnosed with autism have greater right hemisphere activation when compared to controls (Courchesne, 2002). Gamma band activity in the right hemisphere is associated with sensory integration of auditory and linguistic input. Therefore, an increase in right hemisphere activation could signal deficiencies in sensory integration and language processing. Similarly, Rolison et al. (2021) found that children with ASD had stronger intrahemispheric connectivity and less interhemispheric connectivity in

the right auditory cortex. Together, these findings point to the fact that in autism, atypical lateralization patterns may be driven by the right auditory cortex developing fewer synaptic connections with other core brain networks. One possible cause for these changes could be due to synaptic pruning. There is strong evidence of synaptic dysfunction in ASD resulting in aggressive over-pruning of axons (Hansel, 2019; Thomas et al., 2016). This is supported by the fact that the onset of pruning occurs later in development for babies with autism (Thomas et al., 2016) which is consistent with our finding that brain lateralization differences emerge at 12 months of age. These synaptopathies can lead to the overactivation of one hemisphere and atypical lateralization patterns, which in turn can lead to a wide array of symptoms. More research is needed to assess how lateralization can directly affect cognitive processes and to what extent it can exacerbate autism symptoms.

Limitations and Future directions

We should begin by highlighting the limitations of conducting imaging research on infants. Most EEG acquisition techniques have been designed to study adults, and thus collecting data from infants poses many issues. These include high inter-individual heterogeneity in infant populations, shifts in established EEG rhythms, failure to locate optimal reference electrodes, poor fit of EEG caps due to varying head sizes, data attrition, differences in arousal states and more (Noreika et al., 2020). Moreover, our study is limited by the use of cross-sectional data to investigate brain development. Stroganova et al. (2007) argued that contradictions among EEG studies on autism could be due to averaging across groups without considering critical periods during development. In our study, we were limited by the number of recordings we had for each age group. Having more data points will improve the accuracy of the results by allowing us to

fully see how lateralization patterns change over time. We should also highlight that for statistical reasons, we grouped 7-month-old participants from the London site with 6-month-old participants in Seattle. This procedure was also done at the second time point (14-month-old London data was averaged with 12-month-old Seattle data). Given that the brain undergoes major changes in infancy, grouping these datasets can lead to age-specific confounds.

Furthermore, we should highlight the challenges of conducting research on neurodevelopmental disorders. Autism is a heterogeneous disorder with various symptoms and causes, making it challenging to study group effects (Lombardo et al., 2019). Averaging data across groups or conditions is informative, but this approach often fails to capture the complexity of individual trajectories. For these reasons, we recommend that future studies attempt to include a more heterogeneous sample, one that encompasses a wide range of symptoms and diverse groups. Recently, new approaches have been developed to account for these issues with a new generation of statistical models (Gartstein et al., 2020; Matusik et al., 2021). Future research should take advantage of approaches such as dimensional models of ASD or stratified models where researchers include a wide array of subtype labels as opposed to a single autism label (Lombardo et al., 2019).

Finally, one of the common features of ASD is language delay (for the IBIS Network et al., 2018; Lindell & Hudry, 2013). It is estimated that nearly 50% of children with ASD suffer from language impairments, yet the underlying biological mechanisms behind these deficits are not fully understood (Mody & Belliveau, 2013). Given that language processing is one of the most consistently lateralized processes in the brain, future studies should investigate how lateralization in infancy can be used to predict language outcomes in ASD. Our team is currently working on analyzing the relationship between early lateralization in language regions and the

development of language skills during toddlerhood. This will not only advance our knowledge of autism, but it will also offer new avenues to create better diagnostic tools and advise earlier interventions.

Conclusion

Establishing the development of brain lateralization is an important first step toward improving our understanding of the etiology of ASD. Overall, our study showed that atypical gamma band lateralization is present in infants diagnosed with ASD. We also observed significant differences in the lateralization in various brain regions, including the auditory cortex, thought to be important for language learning. The interplay between lateralization and developmental trajectories is complex but measuring developmental changes in infants can provide insights into factors that contribute to ASD and its symptoms. More research is needed to understand how lateralization develops past infancy and how these differences can affect behavior, as this can help better inform clinical assessments and move towards more personalized treatments.

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