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Early Joint Attention Behaviors in Infants at High Familial Risk for Autism Spectrum Disorder: association with cortical development

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Abstract

Joint attention is the ability to follow the gaze of others, which allows infants to share a common focus on individuals or objects. Impairments in initiating and responding to joint attention are some of the earliest indicators of Autism Spectrum Disorder (ASD). Subcortical brain areas are implicated in joint attention, but less is known about cortical regions and joint attention behaviours in infancy. In this longitudinal study, 101 high-risk infants (64% males) with an older biological sibling with ASD underwent MRI scanning at 4 or 6 months of age and were assessed for joint attention behaviours at 2 years of age. Brain volumes were automatically extracted. High-risk infants with ASD demonstrated atypical initiating and responding joint attention behaviours compared to those who did not. When examining cortical regions in relation to initiating and responding to joint attention behaviours, significant associations were found between the left posterior cingulate gyrus and impaired initiating joint attention in infants who developed ASD. Additionally, the right cuneus was associated with impaired initiating joint attention in this group. Better characterization of the neural mechanisms underlying initiating joint attention can help identify biomarkers to assess the efficacy of therapies to promote improved social and behavioural outcomes.

Highlights

• Joint Attention (JA) impairments are some of the earliest indicators of ASD diagnosis.

• Subcortical areas play a role in JA behaviours, with less focus on cortical regions in infancy.

• High-risk infants were assessed using MRI at 4 or 6 months and JA assessments at 2 years.

• Significant differences in JA behaviours between ASD and non-ASD groups were evident.

• Posterior cingulate cortex and cuneus volumes were associated with JA behaviours.

Introduction

Autism Spectrum Disorder (ASD) is a heritable neurodevelopmental disorder that affects two major domains in individuals: social communication and interactions and restricted and repetitive behaviours and interests (RRBI), as well as sensory processing difficulties (APA, 2022). Behavioural symptoms such as a lack of interest in social situations and interactions are usually present in the first year of life and become even more evident during the second year of life (APA, 2022). Worldwide, ASD is estimated to affect close to 1% of the population, with some variability between countries (APA, 2022). The prevalence rate, however, is higher (19%) if the infant has an older biological sibling with an ASD diagnosis (Ozonoff et al. 2011). In Canada, ASD is estimated to affect 2% of children and youth (Public Health Agency of Canada, 2022). The median age of diagnosis in Canada is 3.7 years, and 53.7% of children have been diagnosed before age five (Public Health Agency of Canada, 2022).

There is robust evidence that behavioural signs of ASD can emerge during the first two years of life, and that early access to intervention is associated with gains in social and behavioural functioning (Di Giorgio et al., 2016; Ip et al., 2019; Landa, 2018; Osterling et al., 2002; Ozonoff et al., 2011; Zwaigenbaum, 2010). Among the earliest of these signs are difficulties with Joint Attention (JA) (Bottema-Beutel, 2016; Bruinsma et al., 2004; Charman, 2003; Ibanez et al., 2013; Werner & Dawson, 2005). JA refers to the coordination of attention between the infant, a social partner and a third referent, such as an object, person or event, and it depends on the capacity to engage in eye contact and to track where another person is looking (Bruinsma et al., 2004; Dawson et al., 2004; Tomasello et al., 2005). These skills begin to appear at approximately 2 to 4 months of age and are refined over the first two years (Gredebäck et al., 2010; Mundy, 2018; Mundy & Jarrold, 2010). Episodes of shared attention in early childhood are thought to provide the experience that drives cortical specialization for face processing and language, thereby scaffolding the neural systems that later support social cognition (Landa, 2018; Mundy, 2018).

JA encompasses a set of behaviours that share the goal of attending to something together with another person (Bottema-Beutel, 2016; Bruinsma et al., 2004). Two components are commonly distinguished. Responding to joint attention (RJA) refers to gaze following, in which the infant shifts attention to the location or object indicated by a partner's gaze or gesture. Initiating joint attention (IJA) refers to the infant's spontaneous use of eye contact or gestures to direct a partner's attention toward an object or event of interest (Bottema-Beutel, 2016). Both components are inherently triadic, involving the infant, the partner and a shared referent. Infants who are later diagnosed with ASD frequently show reduced gaze following and limited pointing or showing (Mundy, 2018), and difficulties with IJA appear to be more common than difficulties with RJA in this population (Gangi et al., 2014; Ibanez et al., 2013; Mundy, 2018). A child may therefore follow another person's gaze yet rarely initiate episodes of shared interest.

Currently, no single biomarker alone can identify infants at risk of developing ASD later in life. However, age-specific differences in neuroanatomy between those with and without ASD indicate a need to investigate brain development at early ages. Previous studies found that volumetric and cortical thickness alterations were associated with social and language development in ASD (Doyle-Thomas et al., 2013; Duerden et al., 2012; Libero et al., 2014; Stigler et al., 2011; Van Rooij et al., 2018).

Functional neuroimaging studies indicate that both cortical and subcortical regions support JA. RJA has been linked to activity in the superior temporal, intraparietal, temporal polar, orbitofrontal and insular cortices, whereas IJA has been linked to the frontal pole, dorsal frontal cortex, superior temporal and intraparietal cortices, posterior cingulate and sensorimotor cortices (Mundy, 2018). The networks supporting the two forms of JA may partly overlap, particularly in frontal and temporal regions (Billeci et al., 2017). Subcortically, the amygdala, striatum and hippocampus have been implicated in JA more broadly (Gordon et al., 2013; Mundy, 2018). Few studies have related subcortical volumes to JA in ASD. Mosconi et al. (2009) reported that larger amygdala volumes were associated with poorer JA at 2 and 4 years of age. In our prior work with infants at familial risk for ASD, thalamic and hippocampal volumes at 4 to 6 months of age predicted later ASD diagnosis among infants who did not initiate JA, consistent

with the involvement of these structures in social attention and motivation (Montenegro et al., 2022). Whether comparable associations exist between cortical volumes and IJA or RJA in infancy remains unclear.

In the current study, infants who were at high risk for ASD, defined as having an older biological sibling with a confirmed ASD diagnosis, were followed with MRI and developmental assessments. Infants underwent MRI scanning acquired early in life, between 4 and 6 months of age. Assessments of ASD symptomatology, including IJA and RJA behaviours, occurred at 2 years of age. Infants were also assessed by a specialist to determine if they met the diagnostic criteria for ASD. Understanding the neuroanatomical and functional correlates of IJA and RJA in high-risk infants could aid in advancing early identification and intervention strategies for ASD. While atypical JA behaviors are recognized indicators of ASD, examining the underlying brain mechanisms can offer further insights into the developmental pathways, which may contribute to social communication difficulties. In turn, our first aim was to examine the prevalence of delays in IJA and RJA early in life in relation to an ASD diagnosis. Our second aim was to examine the relationship between neuroanatomical features, focusing on cortical brain volumes, and IJA and RJA in high-risk infants, with consideration of their ASD diagnosis, adjusting for age, and biological sex.

Methods

2.1 Participants

This study was a secondary analysis of imaging and behavioural data from 131 infants enrolled in a longitudinal study and made available through the National Database for Autism Research, part of the National Institute of Mental Health Data Archive (NDA) (Payakachat et al., 2016). Infants were recruited at multiple sites in the United States and Canada participating in the Autism Centers of Excellence (ACE) Program and the Infant Brain Imaging Study (IBIS) Network, and data from both programs were pooled for the present analysis. Every infant had an older biological sibling diagnosed with ASD. A sample drawn from the same NDA collections was described in our previous report (Montenegro et al., 2022); the present study differs in its focus on cortical volumes and on JA behaviours observed at 2 years of age.

MRI was performed at 4 or 6 months of age, and behavioural assessments were administered at several later time points. The present analysis used the Autism Diagnostic Observation Schedule (ADOS) administered during the second year of life. Because data collection spanned several years, children were assessed with either the ADOS-Generic (ADOS-G; Lord et al., 2000) or the ADOS, Second Edition (ADOS-2; Lord et al., 2012).

All infants with an MRI scan at 4 or 6 months of age were initially considered (n = 131); when scans were available at both ages, the earlier scan was used. Thirty infants without behavioural data were excluded, yielding a final sample of 101 infants (64% male). Child race and ethnicity were reported by parents or caregivers: 73.3% of infants were White, 13.9% were of more than one race, 1% were Black and 1% were

Asian; 83.2% were non-Hispanic, 5% were Hispanic, 10.9% were of unknown ethnicity and no response was recorded for 1%. Children were 23 to 31 months of age (mean 24.7 months) at the time of the ADOS. ASD diagnostic status was determined by an experienced licensed clinician, informed by the ADOS and the Mullen Scales of Early Learning (Mullen, 1995). Overall, 20.8% of infants received an ASD diagnosis, 85.7% of whom were male. Sample characteristics are presented in Table 1.

Table 1
Sample Description

Measure	
N	101
Biological Sex, %	
Male	64%
Female	36%
ASD Diagnosis, %	20.8%
Male	85.7%
Female	14.3%
MRI scan Age, months, Mean [Range]	5.7 [4–6]
Race, %	
White	73.3%
More than one race	13.9%
Black	1%
Asian	1%
Ethnicity, %	
Non-Hispanic	83.2%
Hispanic	5%
Unknown	10.9%
Did not answer	1%
ADOS Age, months, Mean [Range]	24.7 [23–31]
ADOS IJA Score	0.4 [0–2]
ADOS RJA Score	0.25 [0–3]
Mullen Age, months, Mean [Range]	24.3 [12–31]
Visual Reception Raw Domain Score	26.8 [12–34]
Fine Motor Domain Raw Score	24.4 [16–31]
Receptive Language Domain Raw Score	23.6 [12–33]
Expressive Language Domain Raw Score	21.2 [12–34]

Measure	
Vineland Age, months, Mean [Range]	24.4 [12–33]
Communication Domain Raw Score	30.6 [17–40]
Daily Living Domain Raw Score	45.2 [34–59]
Socialization Domain Raw Score	44.64 [25–58]
Motor Skills Domain Raw Score	30.4 [24–42]

2.2 Behavioural measures

The ADOS is a standardized, semi-structured observational assessment of social interaction, communication, play and restricted and repetitive behaviours that is used, together with other clinical information, to inform ASD diagnosis from 12 months of age through adulthood (Lord et al., 2000; Lord et al., 2012). The ADOS-G was published in 2000 and the ADOS-2 in 2012; the ADOS-2 added a Toddler Module to the four original modules. Module selection depends on the child's age and expressive language, with Module 1 intended for children using no speech to simple phrases and Module 2 for children using phrase speech who are not yet verbally fluent (Lord et al., 2012). Administration takes approximately 30 to 60 minutes. In the present sample, 54 children completed ADOS-G Module 1, 1 completed ADOS-G Module 2, 44 completed ADOS-2 Module 1 and 2 completed ADOS-2 Module 2.

Items are coded on the basis of the child's behaviour across the administered activities, generally on a scale from 0 (no abnormality of the type specified) to 3 (abnormality to a degree that may interfere with functioning); codes of 7 (abnormality in the general area but not of the type specified), 8 (not applicable) and 9 (unknown or missing) are also available (Lord et al., 2000; Lord et al., 2012). The RJA item is scored from 0 to 3 and the IJA item from 0 to 2. Item coding is equivalent across the ADOS-G and ADOS-2, allowing data from the two editions to be combined (Lord et al., 2012).

JA is coded both from a structured task designed to elicit it and from spontaneous behaviour throughout the session, and the JA task is the same across Modules 1 and 2 of both editions (Lord et al., 2012). For RJA, the examiner calls the child's name, says 'look' and shifts gaze toward a target; if the child does not orient, the bid is repeated with a more pronounced gaze shift and then a point. IJA is coded whenever the child spontaneously directs the examiner's or caregiver's attention to an object using a three-point gaze shift (e.g., person–object–person or object–person–object), a criterion that distinguishes sharing interest from requesting the object (Lord et al., 2012).

2.3 Typical and Atypical JA

Using the corresponding ADOS scores, infants were classified as presenting typical IJA, atypical IJA, typical RJA, and atypical RJA. Scores of 0 indicated that the behaviour was typical, while scores of 1, 2, or 3 indicated that some abnormality in the behaviour was present, meaning that the behaviour was

considered atypical. Scores 7, 8, and 9 were excluded from the analysis as they did not specify the presence or absence of the behaviour.

2.4 MRI acquisition

MRI acquisition and processing followed the procedures described in our previous study (Montenegro et al., 2022). Briefly, T1-weighted images (160 sagittal slices; TR/TE = 2400/3.16 ms; voxel size 1×1×1 mm^3) were acquired on a Siemens 3T scanner (Erlangen, Germany), and images obtained at 4 or 6 months of age were used for segmentation.

2.5 MR image processing

After visual inspection for motion and other artifacts, images were processed with the Infant FreeSurfer recon-all pipeline using age-specific 4- or 6-month atlases (de Macedo Rodrigues et al., 2015; Fischl, 2012; Zöllei et al., 2020). Segmentations were reviewed in FreeView, and errors in subcortical grey matter were corrected manually by a trained rater in ITK-SNAP (Montenegro et al., 2022). Cortical grey matter volumes were derived from the Desikan–Killiany parcellation ('aparc'; Desikan et al., 2006), and global and subcortical volumes from the 'brainvol' and 'aseg' outputs (Fischl, 2002). The cortical regions examined in each hemisphere were the caudal anterior cingulate, caudal middle frontal, cuneus, entorhinal, frontal pole, fusiform, inferior parietal, inferior temporal, insula, isthmus cingulate, lateral occipital, lateral orbitofrontal, lingual, medial orbitofrontal, middle temporal, parahippocampal, paracentral, pars opercularis, pars orbitalis, pars triangularis, pericalcarine, postcentral, posterior cingulate, precentral, precuneus, rostral anterior cingulate, rostral middle frontal, superior frontal, superior parietal, superior temporal, supramarginal, temporal pole and transverse temporal regions. In total, 70 cortical and 12 subcortical volumes were extracted per participant, along with 204 regional measures of volume, surface area and cortical thickness.

2.6 Statistical analysis

Analyses were conducted in SPSS (v.27). The study had two aims: (1) to determine whether atypical RJA and IJA at 2 years of age were associated with an ASD diagnosis in infants at familial risk for ASD; and (2) to determine whether cortical grey matter volumes in infancy (Section 2.5) were associated with RJA and IJA, and whether these associations differed by diagnostic group.

For the first aim, separate chi-square tests compared the proportions of infants with atypical IJA and atypical RJA between diagnostic groups (ASD vs. no ASD), and odds ratios were calculated to estimate the relative likelihood of an ASD diagnosis given atypical JA. As two hypotheses were tested, a Bonferroni-corrected alpha of $p < 0.025$ (0.05/2) was applied.

For the second aim, generalized linear models with an identity link were fitted with IJA or RJA (ADOS) as the dependent variable and diagnostic group and the left- or right-hemisphere cortical volumes as independent variables, adjusting for age and biological sex. Separate models were fitted for each hemisphere and each JA type; accordingly, a Bonferroni-corrected alpha of $p < 0.0125$ (0.05/4) was

applied. Where a significant main effect of a region was observed, a follow-up model including the diagnostic group × region interaction was fitted.

Results

3.1 Initiating and responding to Joint Attention

From the IJA and RJA items from the ADOS, infants received a score of 0, 1, 2 and 3. Scores of 0 indicated typical behaviour, and scores of 1, 2, or 3 indicated atypical behaviour. For the RJA item, 86 infants (85.1%) received a score of 0, indicating typical RJA behaviour, while 8 (7.9%) received a score of 1, 4 (4%) received a score of 2, and 3 (3%) infants received a score of 3, indicating atypical RJA behaviour. For IJA, 68 infants (67.3%) had scores of 0, indicating typical IJA behaviour, while 26 infants (25.7%) had scores of 1 and 7 (6.9%) had scores of 2, indicating some abnormality in IJA behaviour. For the IJA item, no infant received a score of 3, as 2 is the highest score given for this particular item. Scores of 0 were classified as typical, while scores of 1, 2, or 3 were classified as atypical. Scores of IJA and RJA were binarized as typical and atypical for the subsequent analysis.

High-risk infants who developed ASD demonstrated greater atypical IJA (33%, $n = 33$, $X^2 = 20.3$, $p < 0.001$) and RJA (15%, $n = 15$, $X^2 = 24.2$, $p < 0.001$) behaviours compared to high-risk children who did not receive a diagnosis (Fig. 1). Subsequent odds ratio analyses indicated that atypical IJA in high-risk infants was associated with a 10.5 (3.36–32.8) times greater likelihood of having an ASD diagnosis, and atypical RJA was associated with 15.2 (4.3–53.6) times greater odds of having an ASD diagnosis.

3.2 Total Brain Volumes

As part of an exploratory analysis, total cerebral volumes (TCV) were compared between diagnostic groups. Results from a two-sample t-test revealed no differences in TCV between those with an ASD diagnosis and those without. The mean value for those who did not develop ASD (M = 634839.3, n = 81) was lower than the mean score for those who did (M = 654947.8, n = 20); however, this difference was not statistically significant (t(33)=-1.3002, p = 0.2024, 95% CI [-51550.72, 11333.72].

3.3 Neural correlates of responding to joint attention

We examined the neural correlates of RJA in relation to infant cortical volumes in the right hemisphere. A significant main effect of group ([HR-N] B=-.958, 95%CI -1.26 - -0.657, p < 0.001), and the right pars triangularis (B= -0.0003, 95%CI -0.001 - -0.00007 p = 0.009) and the right supramarginal gyrus ([HR-N] B=-0.000, 95%CI -0.0003- -0.00007, p = 0.002) was found. The subsequent interaction analysis (diagnostic group x the right pars triangularis) revealed only a significant effect for children who did not receive an ASD diagnosis (B= -0.0003 95%CI -0.0006 - -0.0002, p < 0.001). No association between diagnostic group and the right supramarginal gyrus were evident in a subsequent interaction analysis (p > 0.0125).

When examining RJA behaviours and the association with left hemisphere volumes significant main effects of group ([HR-N] B=-.441, 95%CI -0.763 - -0.119, p = 0.007) and left pars orbitalis volumes (B= -0.0003, 95%CI -0.0003 - -0.00007 p = 0.006) were evident. The interaction analysis revealed that only children who did not receive an ASD diagnosis did the pars orbitalis show a negative association with RJA behaviours (B= -0.0003, 95%CI -0.0005 - -0.0001, p = 0.006).

3.3 Neural correlates of initiating joint attention

When performing an initial generalized linear model with the left hemisphere volumes, a significant main effect of group ([HR-N]B=-0.879, 95%CI -1.179- -0.578, p < 0.001) was evident, along with significant effects of the left posterior cingulate gyrus (B = 0.001, 95%CI 0.0002–0.001, p < 0.001) and middle temporal gyrus (B=-0.001, 95%CI -0.0002- -0.00006, p < 0.001) with IJA behaviours.

A subsequent interaction analysis for the diagnostic group and left posterior cingulate gyrus revealed that only children with an ASD diagnosis showed a significant positive relationship with volumes and impaired IJA behaviours (B = 0.001, 95%CI 0.0005–0.001, p = 0.0001, Table 2, Fig. 2), an effect not seen in the children who did not receive a diagnosis (B = 0.001, 95%CI 0.0001–0.001, p > 0.0125, Fig. 2). The middle temporal gyrus in the left hemisphere also demonstrating an association with IJA behaviours were only altered in children who did not receive an ASD diagnosis in a subsequent interaction analysis (B=-0.0002, 95%CI -0.0003- -0.00009, p < 0.001). When examining the data using the right hemisphere volumes in relation to IJA behaviours, there were significant main effects of group ([HR-N]B=-0.629, 95%CI -0.262- -0.042, p < 0.001) and right cuneus (B=-0.0002, 95%CI -0.0004 – -0.00009, *p* < 0.001), and the right superior parietal lobule (B = 0.0001, 95%CI 0.000009–0.0002, *p* = 0.005) volumes, adjusting for age and sex.

A subsequent interaction analysis (right cuneus x diagnostic group) was performed, and infants with an ASD diagnosis who had difficulties with IJA had larger right cuneus volumes (B = 0.0002, 95%CI 0.0001–0.0003, p < 0.001), compared to children who did not receive an ASD diagnosis (B = 0.0001, 95%CI 0.0001–0.0003, p > 0.0125). The interaction between right superior parietal volumes and ASD diagnosis revealed a significant effect for children who did not receive a diagnosis (B=-0.0001, 95%CI -0.0002 - -0.00004, p = 0.002) but not in children who received a diagnosis (B=-0.00007, 95%CI -0.0001 - -0.00001, p = 0.1).

Table 2
Results of a generalized linear model demonstrating the interaction of posterior cingulate volumes with ASD diagnosis in relation to challenges with initiating joint attention

Variables	**95% Confidence Interval**			
	Beta value	**Lower**	**Upper**	**p value**
Biological sex (females)	-0.231	-0.447000	-0.015000	0.036
Age	0.026	-0.225000	0.278000	0.838
TD * posterior cingulate gyrus	0.001	0.000000	0.001000	0.014
ASD * posterior cingulate gyrus	**0.001**	**0.000000**	**0.002000**	**0.0002**
Caudal anterior cingulate gyrus	0.000000	-0.001000	0.000000	0.327
Caudal middle frontal gyrus	-0.000019	0.000000	0.000000	0.842
Cuneus	0.00	-0.000060	0.000000	0.215
Inferior parietal gyrus	-0.000023	0.000000	0.000000	0.713
Inferior temporal gyrus	-0.000040	0.000000	0.000048	0.377
Isthmus cingulate gyrus	0.000079	0.000000	0.000000	0.583
Lateral occipital gyrus	-0.000024	-0.000077	0.000030	0.384
Lateral orbitofrontal gyrus	0.000000	-0.000009	0.000000	0.072
Lingual gyrus	0.000026	-0.000074	0.000000	0.606
Medial orbitofrontal gyrus	-0.000008	0.000000	0.000000	0.896
Middle temporal gyrus	**0.00**	**0.000000**	**-0.000065**	**0.0009**
Parahippocampal gyrus	-0.000032	0.000000	0.000000	0.766
Paracentral gyrus	0.00	-0.001000	0.000029	0.074
Pars opercularis gyrus	0.000003	0.000000	0.000000	0.972
Pars orbitalis gyrus	0.00	0.000000	0.000062	0.214
Pars triangularis gyrus	0.00	0.000000	0.000007	0.062
Pericalcarine gyrus	0.000004	0.000000	0.000000	0.977
Postcentral gyrus	0.000011	0.000000	0.000000	0.877
Precentral gyrus	0.000018	0.000000	0.000000	0.834
Precuneus gyrus	0.00006	-0.000069	0.000000	0.362

Variables	95% Confidence Interval			
	Beta value	Lower	Upper	p value
Rostral anterior cingulate gyrus	0.00	-0.001000	0.000000	0.223
Rostral middle frontal gyrus	-0.000007	0.000000	0.000091	0.886
Superior frontal gyrus	0.000050	-0.000023	0.000000	0.176
Superior parietal gyrus	-0.000020	0.000000	0.000062	0.582
Superior temporal gyrus	-0.000080	0.000000	-0.000004	0.04
Supramarginal gyrus	-0.000012	0.000000	0.000084	0.801
Frontal pole	0.00	0.000009	0.000000	0.039
Temporal pole	0.000045	-0.000078	0.000000	0.475
Transverse temporal gyrus	0.001000	0.000079	0.002000	0.032
Insula	-0.000032	0.000000	0.000000	0.733
Fusiform gyrus	0.00	0.000000	-0.000005	0.04

Discussion

In the current study, we examined JA behaviours and cortical brain volumes in young infants who had an increased familial risk of developing ASD. We examined the odds of responding to and initiating JA behaviours and ASD development, as well as a linear regression to examine the association of JA behaviours and cortical volumes in high risk infants with and without ASD. Infants who were diagnosed with ASD were significantly more likely to demonstrate atypical JA behaviours at 2 years of age for both responding to and initiating JA compared to those who did not develop ASD. High-risk infants who were diagnosed with ASD and did not demonstrate initiating Joint Attention (IJA) behaviours showed alterations in the left posterior cingulate and right cuneus volumes at 4–6 months of age compared to those who did not develop ASD. Findings regarding cortical brain volumes, specifically larger left posterior cingulate and right cuneus volumes in high-risk infants diagnosed with ASD who did not initiate JA, highlight the potential role of these brain structures in ASD development. Findings could inform future research into the neurobiological mechanisms underlying ASD and may contribute to the development of more targeted interventions.

Consistent with the present findings, previous studies have reported atypical JA in infants at elevated likelihood of ASD, with IJA typically more affected than RJA (Charman, 2003; Gangi et al., 2014; Ibanez et al., 2013). Compared with gaze following, IJA places greater demands on the infant, who must be motivated to spontaneously share an experience with another person, and it is therefore regarded as the more complex of the two skills (Mundy, 2018). Early JA experience is thought to support the emergence

of perspective taking and, more broadly, the social brain. Limited JA experience may therefore reduce opportunities to establish and strengthen the networks that underlie social cognition and may contribute to the emergence of ASD symptoms (Mundy, 2018). In our study, we found impaired JA behaviours for both RJA and IJA in high-risk infants who were diagnosed with ASD relative to those who did not. These findings confirm previous reports that impaired JA is an important ASD predictor. JA proficiency takes time to develop, and younger infants may show more marked differences in both RJA and IJA behaviours. Future studies with larger samples and wide age ranges would aid in clarifying typical and atypical IJA and RJA developmental trajectories.

Several cortical and subcortical brain areas are implicated in JA behaviours, and neural circuitries for IJA and RJA may overlap (Billeci et al., 2017). In this study, we found that the larger left posterior cingulate, as well as smaller right cuneus, were implicated in delayed IJA behaviours and were seen in high risk infants with an ASD diagnosis. The posterior cingulate is an important brain region that plays a role in regulating someone's attention (Leech & Sharp, 2014). This brain region is highly connected to other brain regions involved in attention more broadly, and it has been suggested that it has a role in narrowing the focus of attention (Leech & Sharp, 2014). The activation of the posterior cingulate has been associated with IJA behaviours in 12 month old toddlers, as well as adults (Eggebrecht et al., 2017; Schilbach et al., 2010). Eggebrecht et al (2017) found a stronger association between IJA and the activation posterior cingulate default mode network in 12-month-old toddlers compared to 24-month-olds, who showed more distributed activation in the brain. The authors suggest that as infants get older, they increase their capacity to diversify strategies to engage in IJA, such as verbal communication, while 12-month-olds infants rely more on gaze shifts and gestures. This suggests that activation of the posterior cingulate cortex may have a crucial role in IJA development, especially when infants are still developing these skills. In our study, infants with an ASD diagnosis who did not initiate JA had larger left posterior cingulate gyrus volumes.

In the study, we also found that infants who have delayed IJA behaviours had smaller right cuneus and were associated with an ASD diagnosis. The cuneus is an important brain region involved in spatial analysis and visual integration, as well as attention and reward processing (Cohen et al., 2011). Although this brain region has not been directly associated with JA behaviours in infants, the visual spatial aspect of JA is suggested to be key in differentiating it from face processing (Mundy, 2018). JA behaviours require the infant to be able to process spatial information such as their own position in space, the position of others and a third element, as well as the direction of the gaze (Mundy, 2018). Additionally, the cuneus has been associated with attention and reward processing, which are considered key to JA behaviours, especially IJA (Mundy, 2018). Motivation is considered a crucial aspect of IJA, as in this type of behaviour the infant is the one initiating the interaction (Mundy, 2018). It has been suggested that the ability to assign reward value to the attention gaze shifts is essential for developing JA (Mundy, 2018). This is consistent with the social motivation theory of JA and with previous findings, which found an association between JA behaviours and activation of other brain areas related to reward (Mundy, 2018; Schilbach et al., 2010).

These early brain alterations could be related to social attention impairments in children with ASD. JA behaviours are an important early predictor of ASD development and may be key to understanding the social and communication impairments characteristic of the disorder. Infants who present atypical JA might be at risk of missing opportunities to establish and reinforce the brain networks crucial for the development of social cognition. Better characterization of the underlying neural mechanisms in JA can help identify biomarkers to assess the efficacy of JA interventions to promote improved social outcomes in high-risk infants.

Our study has several strengths in that it included a sample comprised exclusively of infants with a familial risk of developing ASD who were followed longitudinally with imaging and behavioural assessments. While the study population is rare, further investigation of heterogenous samples is needed to support our findings in typically developing infants who are at minimal risk for an ASD diagnosis. Findings from this study are limited to a population with an increased familial risk for developing ASD. This population, even if not diagnosed with ASD, can still present characteristics of a broad autism phenotype (BAP). Another key limitation of the study was that the JA assessment was included in one of the diagnostic assessments (ADOS), which was used to assess outcomes. However, the children's diagnosis was not only based on the ADOS assessment tool but was also based on other tools, parent report questionnaires, as well as clinical judgement.

Conclusions

In a heterogeneous cohort of infants who were at high risk for the development of ASD, we examined behavioural measures of IJA and RJA. We found that infants who developed ASD were more likely to demonstrate atypical IJA and RJA behaviours at 2 years of age compared to those who did not. However, in the atypical IJA group there were neuroanatomical changes that were seen in those infants with an ASD diagnosis. Alterations in the posterior cingulate and cuneus were associated with atypical IJA in infants with an ASD diagnosis. The findings suggest that these brain regions, which are involved in social cognitive processes, may show early developmental alterations that are associated with joint attention behaviours in high-risk infants. While the study does not establish a direct predictive relationship between brain region size and ASD diagnosis, it highlights the importance of understanding how neuroanatomical features relate to early signs of social cognitive difficulties. Further, a better understanding and improved characterization of the early behavioural signs of JA, as well as the underlying neural mechanisms, could aid in identifying biomarkers for future interventions to promote optimal social and behavioural outcomes in at-risk infants.

Abbreviations

ACE: Autism Centers of Excellence; ADOS: Autism Diagnostic Observation Schedule; ADOS-G: Autism Diagnostic Observation Schedule – Generic; ADOS-2: Autism Diagnostic Observation Schedule, Second Edition; ASD: autism spectrum disorder; BAP: broad autism phenotype; CI: confidence interval; DSM: Diagnostic and Statistical Manual of Mental Disorders; HR-ASD: high-risk infants who developed ASD;

HR-N: high-risk infants who did not develop ASD; IBIS: Infant Brain Imaging Study; IJA: initiating joint attention; JA: joint attention; MRI: magnetic resonance imaging; NDA: National Institute of Mental Health Data Archive; RJA: responding to joint attention; RRBI: restricted and repetitive behaviours and interests; TCV: total cerebral volume; TE: echo time; TR: repetition time.

Declarations

Ethics approval and consent to participate

This study is a secondary analysis of de-identified data obtained from the NIMH Data Archive (NDA; collection IDs 19 and 2027). The original ACE and IBIS studies were approved by the institutional review boards of each participating site, and written informed consent was obtained from the parents or legal guardians of all participating infants, all of whom were under 16 years of age, prior to enrolment. Access to the data was granted under an approved NDA Data Use Certification. The present secondary analysis was [approved by / reviewed and determined exempt from further review by] the [full name of Western University Research Ethics Board] (reference number [XXXX]).

Consent for publication

Not applicable.

Availability of data and materials

The data analysed in this study are available from the NIMH Data Archive (https://nda.nih.gov; collection IDs 19 and 2027) to qualified researchers with an approved NDA Data Use Certification. Derived data supporting the findings of this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JTPM conceptualized the study, processed the imaging data, conducted the statistical analyses and drafted the manuscript. ESN contributed to the statistical analyses and interpretation of the data and critically revised the manuscript. EGD conceptualized and supervised the study, acquired funding,

contributed to the interpretation of the data and critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

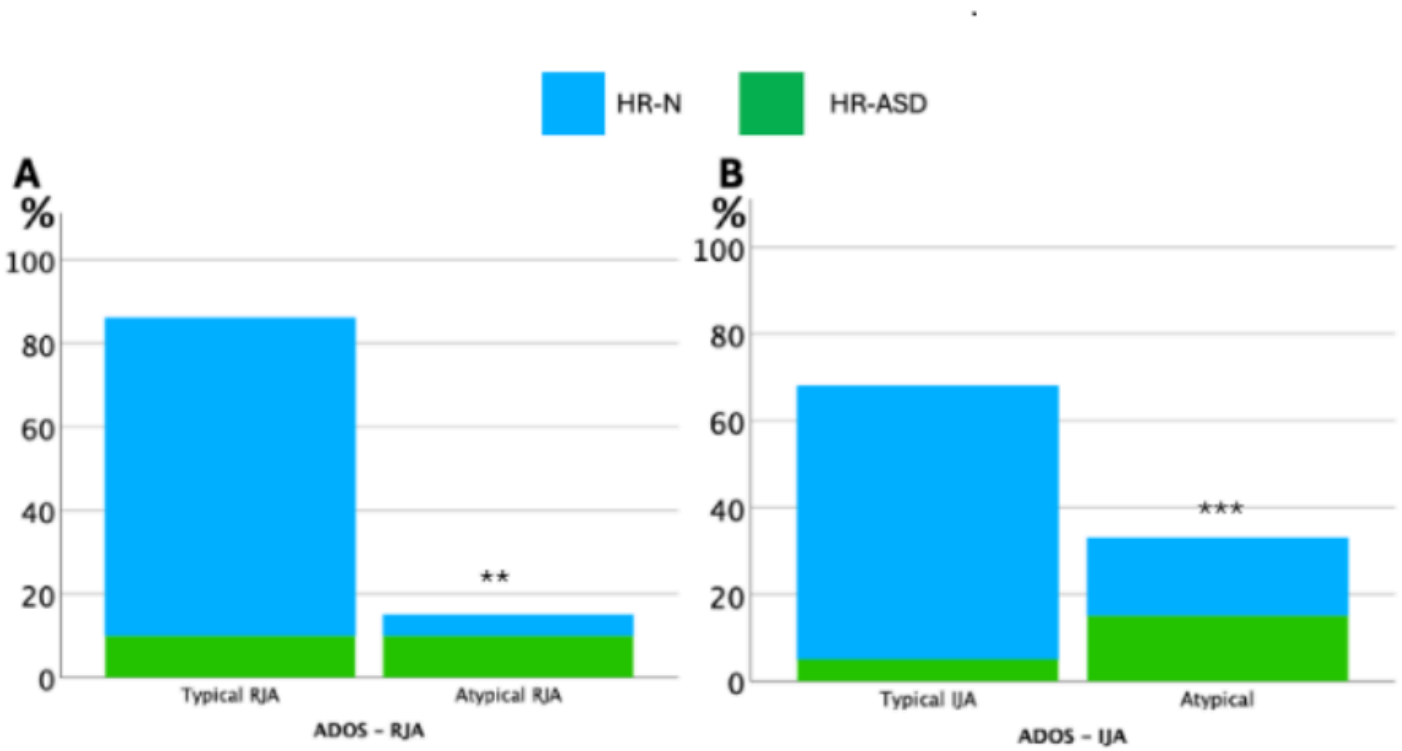


Figure 1

High-risk infants who developed ASD (HR-ASD) were significantly more likely to demonstrate atypical Responding to Joint Attention (RJA) and Initiating Joint Attention (IJA) behaviours (based on the Autism Diagnosis Observation Schedule, ADOS) compared to those who did not develop ASD (HR-N). *** $p<0.001$

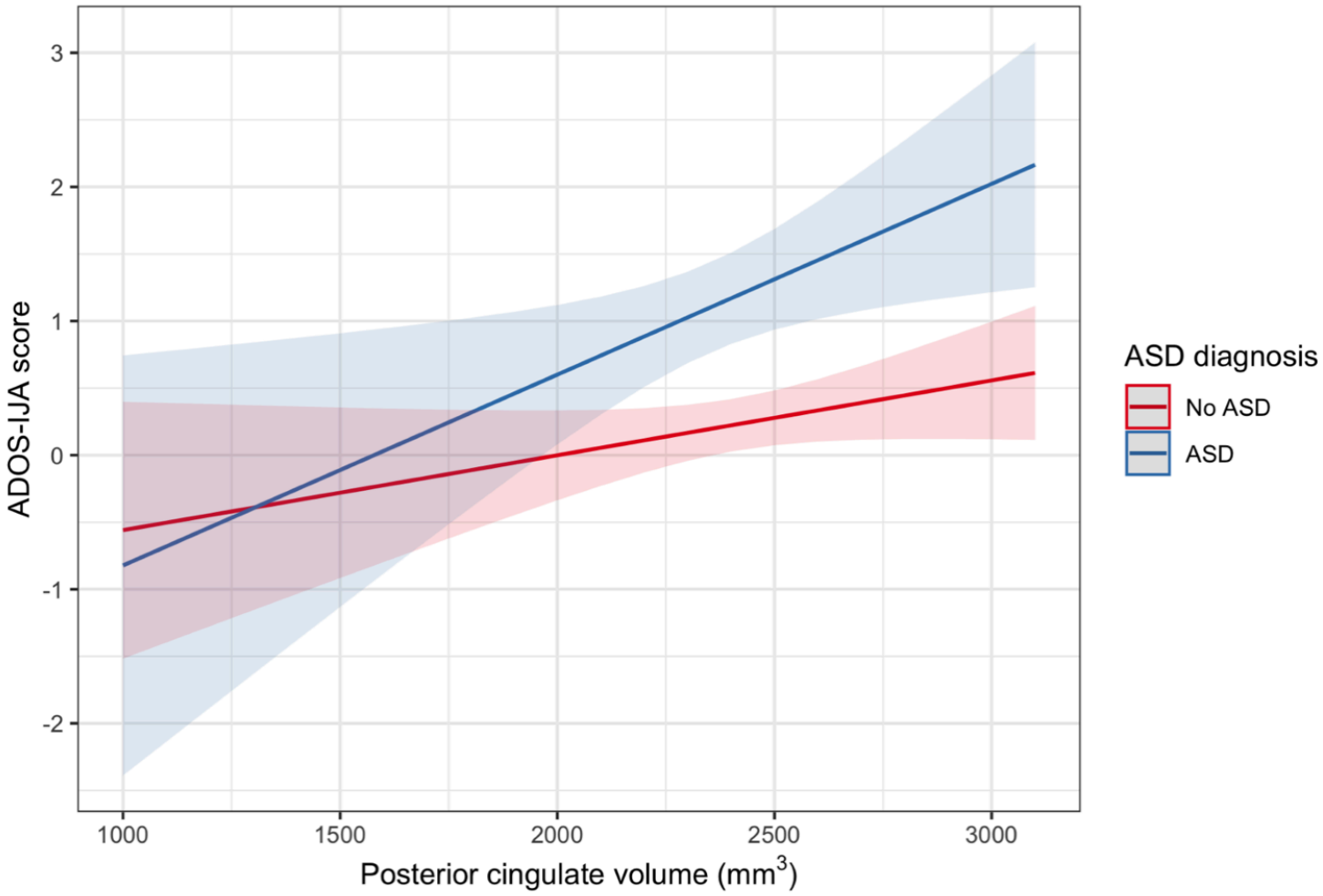


Figure 2

High-risk infants who developed ASD (blue line) who had challenges with Initiating Joint Attention (IJA) had larger Posterior Cingulate in the left hemisphere compared to those who did not develop ASD (red line). *** p<0.001