Published in final edited form as:

J Child Psychol Psychiatry. 2021 February ; 62(2): 160–170. doi:10.1111/jcpp.13268.

Greater functional connectivity between sensory networks is related to symptom severity in toddlers with autism spectrum disorder

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Abstract

Background: Symptoms of autism spectrum disorder (ASD) emerge in the first years of life. Yet, little is known about the organization and development of functional brain networks in ASD proximally to the symptom onset. Further, the relationship between brain network connectivity and emerging ASD symptoms and overall functioning in early childhood is not well understood.

Methods: Resting-state fMRI data were acquired during natural sleep from 24 young children with ASD and 23 typically developing (TD) children, aged 17–45 months. Intrinsic functional connectivity (iFC) within and between resting-state functional networks was derived with independent component analysis (ICA).

Results: Increased iFC between visual and sensorimotor networks was found in young children with ASD compared to TD participants. Within the ASD group, the degree of overconnectivity between visual and sensorimotor networks was associated with greater autism symptoms. Age-related weakening of the visual-auditory between-network connectivity was observed in the ASD but not the TD group.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Supplementary methods: MRI data analysis and ICA.

Table S1. Descriptive information for the retained independent components and clusters (ROIs).

Figure S1. Connectivity matrices for within- and between-domain iFC (averaged *z*-values within and between functional domains) for ASD and TD groups.

Figure S2. Heat map and scatterplots of partial correlations between developmental indices and between-domain connectivity values in the ASD group.

Figure S3. Heat map of partial correlations between developmental indices and between-domain connectivity values in the typically developing (TD) group.

Figure S4. Age-related iFC trajectories (partial correlation plots, controlling for head motion) for Visual-Auditory between-domain iFC, plotted for the ASD and TD groups.

Conflict of interest statement: No conflicts declared.

Conclusions: Taken together, these results provide evidence for disrupted functional network maturation and differentiation, particularly involving visual and sensorimotor networks, during the first years of life in ASD. The observed pattern of greater visual-sensorimotor between-network connectivity associated with poorer clinical outcomes suggests that disruptions in multisensory brain circuitry may play a critical role for early development of behavioral skills and autism symptomatology in young children with ASD.

Keywords

Brain networks; functional connectivity; early childhood; autism spectrum disorders; neuroimaging

Introduction

Autism spectrum disorders (ASDs) comprise a group of neurodevelopmental disorders clinically characterized by social communication deficits and restricted and repetitive behaviors (American Psychiatric Association, 2013). These impairments affect the individual's ability to function socially, at school, at work, or in other areas of life, often throughout the life span. Symptoms of ASD emerge in the first years of life and can be reliably identified during the second year of life (Chlebowski, Robins, Barton, & Fein, 2013; Pierce et al., 2019). Yet, most children with ASD are not diagnosed until approximately 4 years of age (Baio et al., 2018) creating a missed opportunity for early implementation of interventions shown to be most effective in the first years of life, at the time when the brain undergoes profound maturational changes providing a fertile ground for maximal learning and improvements. In typical neurodevelopment, the early years are marked by major morphological changes in cortical lamination (Petanjek, Judas, Kostovic, & Uylings, 2008), neuronal differentiation and axon myelination (Huttenlocher, 1984; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008), synaptogenesis and synapse elimination (Huttenlocher & Dabholkar, 1997), and intragyrar connectivity (Mrzljak, Uylings, Van Eden, & Judas, 1990). These progressive and regressive processes contribute to the increasing cortical differentiation and specialization of neural pathways, through continuous activity-dependent interactions between brain regions (Fair et al., 2009; Johnson, 2000, 2003), characterizing a typical maturational course for brain circuits.

The extent to which in ASD these neurodevelopmental processes take an aberrant path in the early years, proximally to the symptom onset, remains largely unknown. Despite the sizeable (albeit often inconsistent) evidence of atypical brain structure, function, and connectivity in older children, adolescents and, to a lesser degree, adults with ASD (Ecker, Bookheimer, & Murphy, 2015; Hull et al., 2016), the current understanding of brain network organization and connectivity in the first years of life in autism is limited by the scarcity of brain imaging studies in young children (before 4–5 years of age) due to the challenges of acquiring usable imaging data at that age. Within this more limited MRI literature on infants and toddlers with ASD, a relatively well-established finding is atypically increased brain growth in the first years of life (Courchesne et al., 2001; Hazlett et al., 2005; Hazlett et al., 2011; although see Nordahl et al., 2011). This early brain overgrowth appears to affect both white and gray matter volumes (Hazlett et al., 2005), is driven by surface area rather than

cortical thickness expansion, and, based on longitudinal evidence, reflects accelerated growth rate between ages one and two years (Hazlett et al., 2011). Additionally, a number of cross-sectional and longitudinal diffusion-weighted imaging (DWI) studies have reported increased fractional anisotropy (FA) across multiple white matter tracts (e.g., corpus callosum, cingulum, arcuate fasciculus) in infants and toddlers who either have been or are later diagnosed with ASD (Conti et al., 2017; Solso et al., 2016; Wolff et al., 2012; Xiao et al., 2014). Notably, these findings of increased structural connectivity indices (i.e., increased FA) in the first years of life in autism are in contrast with generally reduced connectivity (i.e., lower FA) reported in older children and adults with ASD (Travers et al., 2012), suggesting an accelerated white matter growth in the first years of life, consistent with the aforementioned atypical volumetric growth trajectories.

Besides these findings of early structural brain abnormalities in ASD detected with anatomical and diffusion MRI, a growing number of studies using functional MRI (fMRI) acquired during natural sleep (Dean et al., 2014; Nordahl et al., 2016) have contributed unique information on the functional architecture of neural networks in infants and toddlers with ASD. Studies using fMRI activation to speech stimuli delivered during natural sleep have largely focused on brain function in putative language regions and found reduced neural activity in response to speech sounds, absent or reversed hemispheric lateralization typically associated with language processing, and diminished interhemispheric synchronization of language region activation patterns in young children (1–4 years) with ASD (Dinstein et al., 2011; Eyler, Pierce, & Courchesne, 2012; Lombardo et al., 2015; Redcay & Courchesne, 2008). Additionally, a handful of studies have examined intrinsic functional connectivity (iFC) in infants and toddlers who have been, or are later diagnosed with ASD. While Shen and colleagues (Shen et al., 2016) reported weaker cortical and subcortical amygdala connectivity in preschoolers with ASD (mean age 3.5 years) compared to typically developing controls, all the other studies to date have utilized data acquired in infants with high familial risk for ASD, due to having an older sibling with autism (i.e., the Infant Brain Imaging Study [IBIS]). The evidence beginning to emerge from this cohort of at-risk infants followed prospectively suggests that (a) whole-brain iFC patterns at 6 months appear to predict clinical best-estimate diagnosis of autism at two years (Emerson et al., 2017) and (b) distinct functional brain networks identified in both low- and high-risk infants at 12 months are associated with the emergence of gross motor (walking; Marrus et al., 2018) and fundamental social skills (initiation of joint attention; Eggebrecht et al., 2017), as well as with restricted and repetitive behaviors (McKinnon et al., 2019), both at 12 and 24 months. Notably, while these prospective studies provided important insights into the development of functional brain networks underlying specific behavioral outcomes (i.e., walking and joint attention), three (Eggebrecht et al., 2017; Emerson et al., 2017; Marrus et al., 2018) out of the four studies focused on outcomes shared by all high- and low-risk children.

In the face of this evidence, still little is known about the organization and development of functional brain networks in ASD proximally to the onset of core symptomatology. The human brain is intrinsically organized into large-scale, coherent functional networks, which reflect strong coupling of the ongoing brain activity fluctuations in different brain regions, robustly detected under different mental states, including wakefulness, sleep, and anesthesia

(Power, Fair, Schlaggar, & Petersen, 2010; Raichle, 2010). Functional brain networks, including primary sensory and, more variably, higher-order supramodal networks, such as default mode and frontoparietal networks, have been reliably identified early in life in typical development (Fransson et al., 2007; Gao, Alcauter, Elton, et al., 2015; Gao, Alcauter, Smith, Gilmore, & Lin, 2015), with some observed even prenatally with fetal imaging methods (Thomason et al., 2013). While the primary sensory networks undergo subtle refinement and strengthening over the first two years of life, and substantially resemble adult topology by age two (Gao, Alcauter, Elton, et al., 2015; Lin et al., 2008), higher-order functional networks are far from the adult-like organization in the first postnatal years, and undergo prolonged development over the first decades of life (Dosenbach et al., 2010; Fair et al., 2008; Gao, Alcauter, Elton, et al., 2015), in parallel with the order in which behavioral and cognitive skills emerge (Johnson, 2001). These trajectories of functional network integration and differentiation have not been mapped in ASD, and it remains unknown how or when the network maturation in the first years of life in ASD deviates from typical development, and whether it is related to ASD symptomatology and overall functioning.

In the current study, we examined the large-scale functional networks in toddlers and preschoolers with ASD, compared to typically developing (TD) controls, between the ages of 1.5 and 3.5 years, using resting-state fMRI acquired during natural nocturnal sleep. We utilized independent component analysis (ICA), a data-driven approach, to derive resting-state functional networks (RFNs), and compared the iFC within and between RFNs in the ASD and TD cohorts. We hypothesized that, when compared to matched TD controls, young children with ASD would exhibit atypical iFC patterns involving primary sensorimotor networks and that the atypical connectivity would be associated with more severe autism symptoms and impaired developmental outcomes.

Methods

Participants

Participants were enrolled in the San Diego State University (SDSU) Toddler MRI Project, an ongoing longitudinal study of early brain markers of ASD. Children between the ages of 16 and 48 months with a diagnosis of ASD or behavioral concerns consistent with ASD symptoms were referred to the Toddler MRI Project from specialty autism clinics, state-funded early education and developmental evaluation programs, local pediatricians, service providers, and community clinics. Typically developing (TD) children were recruited from the community. Participants in either group were screened and excluded for any comorbid neurological disorders (e.g., cerebral palsy), history of perinatal CNS infection or gross CNS injury, nonfebrile seizures, and contraindications for MRI. Participants with known syndromic forms of ASD (e.g., fragile X or Rett syndrome), as ascertained from parent report, were also excluded. To limit known risk factors for developmental delays among children enrolled in the TD group, TD participants were also screened and excluded for prematurity (<36 weeks of gestation), family history (in first-degree relatives) of ASD, intellectual disability, or other heritable psychiatric or neurological disorders. The research protocol was approved by the institutional review boards of SDSU and University of California San Diego (UCSD), and the County of San Diego Health and Human Services

Agency. Written informed consent was obtained from the caregivers. This report includes cross-sectional data only from 24 children with ASD and 23 TD participants, matched at the group level on age and gender distribution (see Table 1).

Diagnostic and developmental assessment

Upon enrollment, diagnoses of ASD (or clinical best estimate (Ozonoff et al., 2015) in children younger than age 3 years) were established in all participants in the ASD group in a specialty clinic (SDSU Center for Autism and Developmental Disorders) based on the DSM-5 (American Psychiatric Association, 2013) criteria, supported by the Autism Diagnostic Observation Schedule-Second Edition (ADOS-2; Lord et al., 2012) administered by research-reliable clinicians, the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994), in children older than 36 months), and expert clinical judgment (by two senior authors). Developmental skills were assessed in all TD and ASD participants with the Mullen Scales of Early Learning (MSEL; Mullen, 1995), a clinician-administered assessment of cognitive, language, and motor development. Parents also completed the Social Communication Questionnaire (SCQ, Current form; Lord & Rutter, 2003), a screener for autism spectrum disorders, with no TD participants exceeding the cutoff score of 15 (all TD scores = 10; see Table 1).

MRI data acquisition

MRI data were collected during natural nocturnal sleep on a GE Discovery MR750 3T MRI scanner at the UCSD Center for Functional Magnetic Resonance Imaging, using a Nova Medical 32-channel head coil. A multiband multi-echo planar imaging (EPI) sequence allowing simultaneous acquisition of multiple slices was used to acquire two fMRI runs (400 volumes per each 6-min run) with high spatial resolution and fast acquisition (TR = 800 ms, TE = 35 ms, flip angle = 52°, 72 slices, multiband acceleration factor = 8, 2 mm isotropic voxel size, matrix = 104 × 104, FOV = 20.8 cm). Two separate 20 s spin-echo EPI sequences with opposing phase encoding directions were also acquired using the same matrix size, FOV, and prescription to correct for susceptibility-induced distortions. High-resolution anatomical images were acquired with a fast 3D spoiled gradient recalled (FSPGR) T1-weighted sequence (0.8 mm isotropic voxel size, NEX = 1, TE/TI = min full/1,060 ms, flip angle = 8°, FOV = 25.6 cm, matrix = 320 × 320, receiver bandwidth 31.25 Hz). Motion during anatomical scans was corrected in real-time using three navigator scans and real-time prospective motion correction (PROMO; White et al., 2010), and images were bias-corrected using the GE PURE option.

In preparation for the scan night, and to optimize MRI data acquisition, a comprehensive habituation protocol was implemented. An individualized scan night sleep strategy (e.g., time of arrival, approximating home-like sleeping arrangements, including access to a double MRI bed for co-sleeping families, rocking chair, modular playpen mounted on the MRI bed, and lighting in the MRI suite) was developed for each child, based on the typical bedtime routines and habits assessed in advance with an in-house Sleep Habits Questionnaire. To habituate the child to the scanning environment, the parents were instructed to practice nightly inserting soft foam child-size earplugs after the child had fallen asleep, and to play an mp3 file containing the MRI sounds of the scan sequences employed

in the study at progressively louder volumes for a week. On the night of the scan, noise protection was achieved with MRI compatible sound-reducing headphones and earplugs. In an attempt to standardize sleep stage during scans, scanning always commenced after approximately 15–30 min of sleep.

Data analysis

MRI data preprocessing.—MRI data were preprocessed with FMRIB's Software Libraries (FSL v5.0.10; Smith et al., 2004), MATLAB 2015b (Mathworks Inc., Natick, MA) using SPM12 (Wellcome Trust Centre for Neuroimaging, University College London, UK), and the CONN toolbox v17f (Whitfield-Gabrieli & Nieto-Castanon, 2012; <http://www.nitrc.org/projects/conn>). Preprocessing steps included correction for susceptibility-induced distortions using the two spin-echo EPI acquisitions with opposite phase encoding directions and FSL's TOPUP tools; motion correction using rigid-body realignment as implemented in SPM12; spatial smoothing using a 6 mm Gaussian kernel at full-width half maximum; outlier detection using the Artifact Detection Toolbox as installed with CONN v17f (ART; https://www.nitrc.org/projects/artifact_detect) to identify outlier volumes with frame-wise displacement (FD) >0.5 mm and/or changes in signal intensity >3 standard deviations; nuisance regression including censoring of outliers detected by the ART toolbox, regression of the 6 motion parameters and their derivatives, and the first five PCA components derived from the CSF and white matter compartments using aCompCor (Behzadi, Restom, Liau, & Liu, 2007); and band-pass temporal filtering (0.008–0.08 Hz).

The structural images were coregistered to the mean functional image, segmented and normalized to the Montreal Neurological Institute (MNI) atlas space using nonlinear registration, and the default tissue probability maps included with SPM12 (see Appendix S1 for details). The white matter (WM) and CSF probability maps obtained from segmentation of the structural image for each subject were thresholded at 0.95 and eroded by 1 voxel. These thresholded and eroded masks were applied to functional images to extract WM and CSF time courses, which were submitted to a principal component analysis with aCompCor (Behzadi et al., 2007) for subsequent nuisance regression. Functional images were directly normalized to MNI space with the same nonlinear registration as used for the structural images.

In order to ensure that the findings were not affected by group differences in motion, ASD and TD groups were matched, at the group level, on mean head motion indexed by root mean square of displacement (RMSD) across two fMRI runs, calculated from rigid-body realignment of the raw data prior to TOPUP correction, on the percentage of censored volume across two fMRI runs, and on the mean temporal signal-to-noise ratio (tSNR) across two fMRI runs (Table 1). Mean RMSD was also included as a covariate for all imaging analyses.

Independent component analysis.—Preprocessed fMRI data (concatenated across two runs) from all ASD and TD participants combined were entered into group independent component analysis (ICA) using CONN's ICA implementation (Calhoun, Adali, Pearlson, & Pekar, 2001) to generate maximally independent intrinsic functional networks. Each subject

contributed 800 volumes (across two runs) to the group ICA for a total of 37,600 3D volumes. Twenty independent components (ICs) were extracted, and each component's spatial distribution and time course were visually inspected by two raters. ICs identified as noise (Beckmann, 2012; i.e., motion, cerebral spinal fluid pulsations, signal from large blood vessels) were excluded from further analyses. The remaining ICs were compared to the 20 components generated by Smith et al. (2009) and the 8 components generated from the Human Connectome Project Consortium's 500 Subjects Release (https://db.humanconnectome.org/data/projects/HCP_500), both based on adult data, as well as to published pediatric RFNs (Manning, Courchesne, & Fox, 2013; Thornburgh et al., 2017). This resulted in 10 ICs being classified as RFNs and retained for functional connectivity analyses (for details on the three-step IC identification and selection process, see Appendix S1).

Functional connectivity analyses.—The retained ICs were thresholded at $z > 3.0$ and extracted as group RFN maps. Within these thresholded RFN maps clusters exceeding 200 voxels (see Table S1 for detailed cluster description) were extracted as regions of interest (ROIs) and entered into ROI-to-ROI connectivity analysis. Specifically, for each participant, the average time series of all voxels within each ROI was computed and then correlated with the average time series computed for every other ROI. The resulting Pearson's correlation coefficients (190 ROI-to-ROI pairs: $(20 \times 19)/2$) were converted to normally distributed z -values (using Fisher's r -to- z transformation) and entered into two-sample t -tests (including RMSD as covariate) to examine between-group (ASD vs. TD) functional connectivity patterns. Two-sided cluster-level false discovery rate (FDR) correction implemented in the CONN toolbox was applied (corrected $p_{\text{FDR}} < .05$).

Correlations with developmental and diagnostic indices.—Pearson's partial correlation analyses were conducted to examine relationships between connectivity indices emerging from the above FC analysis and autism symptoms (ADOS-2), controlling for head motion and overall developmental level indexed by MSEL Early Learning Composite. Due to the limited range and ordinal scale of the ADOS-2 Calibrated Severity Scores (CSS), not suited for correlational analyses, ADOS-2 Total scores yielding a wider range and more continuous distribution were utilized in behavioral correlations, while controlling for ADOS-2 Module.

Results

Participant demographic, diagnostic, and behavioral characteristics are presented in Table 1. As expected, groups differed on indices of cognitive, language, and motor development measured with MSEL, with significantly lower scores observed in toddlers and preschoolers with ASD. No TD participants had a MSEL Early Learning Composite score < 80 , which is equivalent to no more than 1.3 SD below the normative mean.

Resting-state functional networks identified in the combined ASD-TD sample

The 10 ICs classified as nonartifact functional networks (RFNs) largely resembled the previously reported networks in adults and children, including the visual, sensorimotor,

auditory, multimodal sensory, and salience networks (see Figure 1 for spatial maps and Table S1 for detailed clusters description).

Group differences in functional connectivity

Connectivity matrices of mean ROI-to-ROI connectivity (z -values) within TD and ASD groups are shown in Figure 2A. Direct group comparisons revealed significantly greater connectivity (corrected $p_{\text{FDR}} < .05$) between ROIs in visual and sensorimotor networks in the ASD group compared to the TD group, after controlling for RMSD (see Figure 2B). Because the ASD group included two children born prematurely (see Table 1), these analyses were repeated after excluding these two participants, with the results remaining largely unchanged. In order to further examine iFC differences, detection of which may have been impeded by the large number of comparisons, a post hoc analysis grouping RFNs and corresponding ROIs into five overarching functional domains (visual, sensorimotor, auditory, multimodal sensory, and salience; see Figure S1) was conducted. Direct group comparisons of the within-domain network connectivity, calculated as the mean iFC within all-domain ROIs, and between-domain network connectivity, calculated for all between-domain pairs (10 between-domain comparisons: $(5 \times 4)/2$), revealed no significant group differences after FDR correction (at $p_{\text{FDR}} < .05$; see Figure S1), although greater connectivity between all-visual and salience networks in the ASD group was observed at an uncorrected $p = .057$ with medium effect size (Cohen's $d = .55$).

Between-network connectivity and its links with developmental and clinical indices

Given that both ROI-ROI analyses and comparisons at the level of functional domains pointed to group differences in between-network connectivity involving visual, sensorimotor, and salience networks (Figure 2 and Figure S1), partial correlational analyses were conducted to examine whether between-network iFC was associated with developmental outcomes within the ASD group. Because, as expected in young children with ASD, there was a significant, negative correlation between autism symptoms measured with the ADOS-2 Total score and the overall developmental level indexed with the MSEL Early Learning Composite (ELC) score ($r = -.53$, $p = .008$), partial correlation analyses between 10 between-domain network connectivity indices (mean z -scores for 10 between-domain comparisons: Vis-SM, Vis-Aud, Vis-MSen, Vis-SN, SM-Aud, SM-MSen, SM-SN, Aud-MSen, Aud-SN, and MSen-SN) and autism symptomatology were conducted while controlling for ELC (as well as for RMSD and ADOS-2 Module). Results revealed a significant positive correlation between autism symptoms (ADOS-2 Total scores) and iFC between visual and sensorimotor domains ($r = .60$, $p_{\text{FDR}} < .05$), controlling for RMSD, MSEL ELC, and ADOS-2 Module, such that greater visual-sensorimotor between-domain connectivity was associated with greater ASD symptoms (see Figure 3). Results of the supplementary correlational analyses between iFC and MSEL developmental indices are depicted in Figures S2 and S3.

Age-related effects on between-network iFC

Partial correlation analyses of between-domain network connectivity and age, in months, were performed to examine whether age moderated between-group iFC effects, controlling for head motion. In children with ASD, a negative correlation with age was observed for the

connectivity between visual and auditory networks after controlling for RMSD ($r = -.54$, $p = .01$), with visual-auditory between-domain iFC weakening with age (Figure S4). This relationship was not present in TD toddlers ($r = -.22$, $p = .33$), and there was no significant group by age interaction.

Discussion

We used resting-state fMRI data acquired during natural sleep to examine large-scale resting-state functional networks in toddlers and preschoolers with ASD compared to matched TD controls. A set of RFNs, identified through data-driven group ICA, largely corresponded with RFNs previously reported in studies of older children and adults (e.g., visual, auditory, sensorimotor, salience networks). Functional connectivity analyses of within- and between-network connectivity revealed increased between-network connections in the ASD group, specifically between regions in the visual and sensorimotor networks. Critically, among the children with ASD, greater connectivity between the visual and sensorimotor functional domains was associated with increased autism symptomatology, while controlling for the overall developmental level.

Overconnectivity between sensory circuits in the first years of life in ASD

The finding of overconnectivity observed between visual and sensorimotor networks in young children with ASD is remarkable in the context of sensory processing abnormalities and multisensory integration deficits frequently reported in ASD. Prevalence estimates of abnormal sensory processing in children with ASD range from 60 to 96% (Dawson & Watling, 2000; Dunn, Myles, & Orr, 2002; Klintwall et al., 2011; Lane, Dennis, & Geraghty, 2011), and sensory disturbances are now recognized as part of the core symptoms of ASD in the DSM-5. Besides hypo- and/or hypersensitivity to sensory stimuli within single modality (e.g., visual, auditory, tactile, olfactory), children with ASD often exhibit impairments in integrating sensory information across different modalities (Baum, Stevenson, & Wallace, 2015; Iarocci & McDonald, 2006; Stevenson, Siemann, Schneider, et al., 2014; Stevenson, Siemann, Woynaroski, et al., 2014). These sensory symptoms typically manifest early in development (Baranek et al., 2013; Estes et al., 2015; Germani et al., 2014), as early as infancy, as demonstrated with prospective studies of infant siblings with high familial risk for ASD (Ozonoff et al., 2010). The early emerging sensory abnormalities are likely to have cascading effects on higher-order cognitive, social, and communicative impairments in ASD (Thye, Bednarz, Herringshaw, Sartin, & Kana, 2018) because of the close interconnections between motor, cognitive, social, and language development at this age (Oudgenoeg-Paz, Leseman, & Volman, 2015; Oudgenoeg-Paz, Volman, & Leseman, 2012; Walle & Campos, 2014).

Functional connectivity involving primary sensorimotor networks has been implicated in the development of motor skills as well as core symptoms of ASD (e.g., social deficits and restricted and repetitive behaviors) in prospective studies of infant siblings. Specifically, functional connectivity within and between motor and DMN networks was correlated with walking onset and gross motor function (Marrus et al., 2018), while connectivity between visual and higher-order networks, including dorsal attention network and posterior DMN,

was associated with initiation of joint attention (Eggebrecht et al., 2017). Finally, functional connectivity between visual and DMN as well as frontoparietal control network appeared to be related to certain aspects of restricted and repetitive behaviors (McKinnon et al., 2019). Although highlighting the role of primary sensory networks in the emergence of key developmental skills, including those associated with core symptoms of ASD (e.g., joint attention, restricted and repetitive behaviors), these findings are not specific to children with ASD, having been observed across both high- and low-risk infants. In a cohort more similar to ours (i.e., preschoolers with ASD, albeit somewhat older, with mean age reported as 3.5 years), Shen et al. (2016) observed reduced connectivity between primary visual cortex and sensorimotor regions that was related to sensory hypersensitivity in preschoolers with ASD. While at first this appears inconsistent with our finding of atypically increased connectivity between visual and sensorimotor networks, the disparity can likely be attributed to methodological differences between the studies, with ours focusing on comparisons at broader, network- and functional-domain levels, versus more targeted, seed-based analyses spotlighting connectivity of primary visual cortex, the earliest cortical area to process incoming visual information (in contrast to all primary and visual association cortices, with manifestly different connectivity fingerprints). This distinction, nonetheless, further highlights the scarcity of published data in this age group and the need for additional studies on brain network development and organization at this critical stage in young children with ASD.

There is some evidence that functional connectivity involving visual, motor, and somatosensory networks is decreased (Nebel et al., 2016; Oldehinkel et al., 2019), rather than increased in older (school-age) children and young adults with ASD. In line with this evidence, we have detected an age-related effect showing that, among young children with ASD, connectivity between visual and auditory circuits is decreasing with age (albeit cross-sectionally) across the sampled age range. Because this age-related decrease in iFC was absent in the TD group, these results may indicate a distinct developmental trajectory of sensory network maturation and differentiation in ASD, with greater ‘cross talk’ between different sensory networks early in life, followed by a more protracted weakening of the between-network functional connectivity, as compared to neurotypical trajectories. While direct comparisons between brain morphometric and iFC indices are, at best, tenuous, this trajectory of early functional overconnectivity followed by later underconnectivity appears to echo the account of the accelerated early brain overgrowth observed in autism during infancy and toddler years, reflecting disrupted neurodevelopmental pathways manifest across different scales and measurements of brain structure and function.

Early between-network overconnectivity in ASD associated with poorer developmental outcomes and increased symptomatology

The relationship observed between visual-sensori-motor overconnectivity and greater autism symptoms suggests that brain connections between primary sensory and motor circuits may play an important role in the development of early behavioral skills and autism symptomatology in children with ASD. There is extensive evidence that multisensory processing is crucial for developing fundamental communication and social skills. For example, the ability to integrate auditory and visual information on multisensory perceptual

tasks has been linked to greater communication and social skills in children with ASD (Mongillo et al., 2008; Woynarowski et al., 2013). Thus, greater connectivity between visual and sensorimotor networks may indicate inadequate integration of visual and somatosensory input into the socio-affective circuits, as shown in older, school-age children with ASD (Green, Hernandez, Bookheimer, & Dapretto, 2016). Overall, the increased cross talk between visual and sensorimotor networks in the first years of life and its links to greater autism symptomatology may signify that dysfunctional connectivity within primary sensory circuits has broad effects and may be implicated in the emerging autism symptomatology.

Potential limitations

One limitation of the present study is its relatively small sample size (due to the challenges of acquiring usable imaging data in this age group) and the use of cross-sectional data to investigate age-related FC effects. In the future, the analyses presented here may be extended to longitudinal data to elucidate within-subject trajectories of functional network development and its relationship with symptoms and developmental skills. Another limitation of the study is the lack of appropriate measures of sensory processing abnormalities in ASD. Finally, because fMRI data were acquired during natural sleep and sleep stage was not monitored with EEG, potential differences in sleep stage between ASD and TD groups could not be ruled out. Although precise sleep staging would be desirable, it is not feasible in this age group without risk of severe data loss; indeed, no studies to date have reported sleep staging with EEG during sleep MRI scanning in young children.

Lastly, it is also worth noting that, outside of the observed differences pertaining to the increased connectivity between visual and sensorimotor circuits in children with ASD, the patterns of functional connectivity within and between other networks examined in this study were largely comparable in the two groups. While this could be interpreted as evidence of broadly 'typical' neurodevelopment of functional brain networks in young children with ASD, a more plausible explanation involves a number of other neurobiological mechanisms not captured by BOLD signal but likely at play, reflecting atypical brain maturation processes in autism. Finally, it is worth considering that the additional fundamental group differences in network connectivity may have been masked by differential maturational trajectories across the sampled age range characterizing typically developing children and those with ASD (as evidenced by at least one connectivity effect with divergent age-related trajectories in ASD and TD children; see Figure S4).

Conclusions

Taken together, our results are the first to characterize the large-scale resting-state functional networks in toddlers and preschoolers with ASD and to demonstrate increased connectivity between visual and sensorimotor networks in the first years of life in ASD. This greater between-network connectivity involving visual and sensorimotor networks was correlated with less favorable clinical outcomes (i.e., greater autism symptoms), highlighting the role of primary sensory circuits in the emergence of autism symptomatology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported by the National Institutes of Health (R01 MH107802 to I.F.). The funding sources had no role in study design, writing of the report, or the decision to submit the article for publication. The authors are grateful to Chris Fong, M.A., and Lisa Mash, M.S., of San Diego State University, and Tiffany Wang, M.S., of University of California, San Diego, for invaluable assistance with data collection. The authors' strongest gratitude goes to the children and families who so generously dedicated their time and effort to this research. The authors have declared that they have no competing or potential conflicts of interest.

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Key points

- Symptoms of ASD emerge in the first years of life.
- Little is known about the organization and development of functional brain networks in ASD proximally to the onset of core symptomatology.
- Greater between-network functional connectivity involving sensory circuits (namely, between visual and sensorimotor networks) was identified in toddlers and preschoolers with ASD, compared to typically developing peers.
- Increased visual-sensorimotor connectivity was associated with poorer clinical outcomes.
- These findings point to disrupted functional network maturation and differentiation involving visual and sensorimotor networks in the first years of life in ASD.
- Links with clinical outcomes suggest that disruption in multisensory brain circuitry may play a critical role for early development of behavioral skills and autism symptomatology in young children with ASD.

Figure 1.

Intrinsic functional connectivity networks in toddlers with and without ASD. Results of the 20-dimensional group ICA; images are z statistics thresholded at $z = 3.0$ ($p < .001$) grouped into functional-domain categories as depicted. IC labels: Vis1 = occipital pole visual, Vis2 = medial visual, Vis3 = lateral visual, Vis4 = higher-order visual, SM1 = primary motor, SM2 = lateral sensorimotor, SM3 = medial sensorimotor, Aud = auditory, MSen = multimodal sensory, SN = salience. Images are presented in the Montreal Neurological Institute (MNI) space, in neurological convention (with the left side of the brain represented on the left)

Figure 2.

Connectivity matrices between RFN cluster item courses. (A) Normalized pairwise ROI-ROI (RFN clusters) correlation coefficients (z-values) are presented separately for the ASD (upper triangle) and TD (lower triangle) groups. Both axes represent the 20 RFN clusters (see Table S1 for detailed cluster description). Pixel color of each cell represents the magnitude of correlation for each region of interest (ROI) pair, with warmer colors indicating greater correlation coefficient values. (B) Difference connectivity matrix for ASD versus TD (ASD > TD) comparison. * denotes ROI-ROI pairs with significantly stronger connections at FDR corrected $p < .05$, after controlling for mean RMSD

Figure 3.

Relationship between autism symptomatology and visual-sensorimotor connectivity in the ASD group. Partial correlation between connectivity (z -scores) between all-visual and sensorimotor networks and ADOS-2 Total scores ($p_{\text{FDR}} < .05$). Increasing ADOS-2 Total values indicate greater symptom count and, hence, greater impairment. The values on the X and Y axes reflect residuals of ADOS-2 and z -scores, respectively, after controlling for RMSD, MSEL ELC, and ADOS-2 Module

Table 1

Participant characteristics

	ASD (n = 24)		TD (n = 23)		ASD vs. TD		p Value
	Mean ± SD (Min-Max)		Mean ± SD (Min-Max)		t/χ ²		
Age (months)	30.0 ± 7.3 (18–45)		28.9 ± 8.5 (17–44)		t(45) = 0.45		.65
Gender (M/F) ^a	15/9		14/9		χ ² (2) = 0.01		.91
Ethnicity (Hispanic/Non-Hispanic) ^a	12/12		5/18		χ ² (2) = 4.06		.04
Race (White/Black/More than one/Asian/Unknown)	13/0/8/1/2		14/2/4/2/1		-		-
Gestational age (weeks) ^b	38.7 ± 2.4 (31–43)		39.5 ± 1.3 (37–42)		t(43) = -1.45		.16
Birth weight (g) ^c	3,429 ± 617 (2,098–4,600)		3,410 ± 342 (2,806–4,026)		t(42) = 0.12		.90
Mullen Scales of Early Learning (MSEL)							
Visual Reception, <i>T-Score</i>	41.3 ± 16.0 (20–69)		56.9 ± 11.8 (36–79)		t(45) = -3.78		<.001
Visual Reception, <i>Age Equivalent</i>	25.4 ± 11.1 (11–57)		31.6 ± 9.2 (16–50)		t(45) = -2.06		.05
Fine Motor, <i>T-Score</i>	35.0 ± 11.1 (20–54)		51.3 ± 13.0 (23–80)		t(45) = -4.63		<.001
Fine Motor, <i>Age Equivalent</i>	23.2 ± 7.0 (13–45)		28.7 ± 9.7 (16–47)		t(45) = -2.22		.03
Receptive Language, <i>T-Score</i>	32.4 ± 13.5 (20–61)		54.9 ± 9.3 (30–76)		t(45) = -6.63		<.001
Receptive Language, <i>Age Equivalent</i>	20.0 ± 10.9 (7–44)		30.8 ± 7.7 (15–47)		t(45) = -3.91		<.001
Expressive Language, <i>T-Score</i>	32.6 ± 12.1 (20–62)		49.3 ± 10.2 (28–68)		t(45) = -5.10		<.001
Expressive Language, <i>Age Equivalent</i>	18.9 ± 10.2 (4–47)		28.0 ± 9.7 (13–42)		t(45) = -3.14		.003
Early Learning Composite, <i>Standard Score</i>	74.5 ± 19.8 (49–111)		106.4 ± 16.3 (80–136)		t(45) = -6.02		<.001
Social Communication Questionnaire (SCQ)	17.5 ± 8.0 (3–35)		5.1 ± 2.6 (0–10)		t(41) = 6.77		<.001
ADOS-2							
Toddler Module, <i>Total</i> ^d	17.6 ± 5.2 (9–25)		-		-		-
Module 1, <i>Total</i> ^d	13.4 ± 4.9 (7–21)		-		-		-
Module 2, <i>Total</i> ^d	12.7 ± 4.2 (8–16)		-		-		-
Calibrated Severity Score (<i>across Modules</i>)	6.75 ± 2.0 (3–10)		-		-		-
fMRI motion and SNR indices ^e							
Mean RMSD ^e	0.12 ± 0.04 (0.05 – 0.21)		0.10 ± 0.03 (0.05 – 0.18)		t(45) = 1.46		.15

	ASD (n = 24)		TD (n = 23)		ASD vs. TD		p Value
	Mean ± SD (Min-Max)		Mean ± SD (Min-Max)		t/X ²		
% of Volumes Censored ^e	2.41 ± 2.72 (0–8.63)		1.41 ± 1.64 (0–5.50)		t(45) = 1.49		.15
Mean temporal SNR ^e	30.2 ± 4.4 (20.0–36.5)		30.8 ± 4.1 (18.2–37.8)		t(45) = –0.56		.58

ADOS-2, Autism Diagnostic Observation Schedule, 2nd Edition; F, female; M, male; RMSD, root mean squared displacement; SNR, signal-to-noise ratio.

^aValues denote counts and corresponding chi-square *p* values. Remaining comparisons reflect two-sample *t*-tests and corresponding *p* values.

^bGestational age data are missing for 1 ASD participant. Two ASD participants were born before 36 weeks of gestation (at 31 and 35 weeks).

^cBirth weight data are missing for 1 TD and 2 ASD participants.

^dBecause the choice of ADOS-2 Module depends on the child's age and language level, 14 ASD participants completed the ADOS-2 Toddler Module; 7 completed the ADOS-2 Module 1; 3 completed the ADOS-2 Module 2.

^eMean RMSD, # of volumes censored, and mean temporal SNR were calculated across two fMRI runs.