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Journal

Cerebral Cortex, 34(2)

Authors

Chen, Bosi
Olson, Lindsay
Rios, Adriana
et al.

Publication Date

2024-01-31

DOI

10.1093/cercor/bhae005

Peer reviewed

OXFORD

Cerebral Cortex, 2024, **34**, 112–120
https://doi.org/10.1093/cercor/bhae005
Advance access publication date 27 January 2024
Original Article

Reduced covariation between brain morphometry and local spontaneous activity in young children with ASD

Bosi Chen [1,*], Lindsay Olson[2], Adriana Rios[3], Madison Salmina[3], Annika Linke[3,4], Inna Fishman[3,4]

[1]Department of Child and Adolescent Psychiatry, New York University School of Medicine, New York, NY 10016, United States
[2]Department of Psychiatry, University of California San Francisco, San Francisco, CA 94107, United States
[3]Department of Psychology, Brain Development Imaging Laboratories, San Diego State University, San Diego, CA 92120, United States
[4]SDSU Center for Autism and Developmental Disorders, San Diego State University, San Diego, CA 92120, United States

*Corresponding author: Bosi Chen, Department of Child and Adolescent Psychiatry, New York University School of Medicine, One Park Avenue, 7th Floor, New York, NY 10016, United States. Email: Bosi.chen@nyulangone.org

While disruptions in brain maturation in the first years of life in ASD are well documented, little is known about how the brain structure and function are related in young children with ASD compared to typically developing peers. We applied a multivariate pattern analysis to examine the covariation patterns between brain morphometry and local brain spontaneous activity in 38 toddlers and preschoolers with ASD and 31 typically developing children using T1-weighted structural MRI and resting-state fMRI data acquired during natural sleep. The results revealed significantly reduced brain structure–function correlations in ASD. The resultant brain structure and function composite indices were associated with age among typically developing children, but not among those with ASD, suggesting mistiming of typical brain maturational trajectories early in life in autism. Additionally, the brain function composite indices were associated with the overall developmental and adaptive behavior skills in the ASD group, highlighting the neurodevelopmental significance of early local brain activity in autism.

Key words: ASD; brain structure; brain function; early childhood; multimodal neuroimaging.

Introduction

While the current consensus is that ASD originates prenatally, affecting early fetal neurodevelopment (Courchesne et al. 2020), the clinical diagnosis of ASD cannot be made before behavioral symptoms fully manifest (with the median age at diagnosis in the United States currently being 49 months; Maenner et al. 2023), substantially limiting our ability for early identification. The implications of delayed detection and identification are significant, given the profound impact of early interventions on the developing brain, especially in the first years of life, during the critical window of rapid brain maturation and peak experience-dependent neuroplasticity (Tau and Peterson 2010).

Although cumulative neuroimaging evidence has shown alterations in both structural (i.e. neuroanatomy) and functional developments of the brain in ASD, these studies are largely based on older children and adolescents, with only a few consistent findings emerging from neuroimaging studies in infants and toddlers at risk for, or with early diagnosis of autism. Multiple studies have reported early brain overgrowth, including enlarged brain volumes and head circumferences, accelerated surface area (SA) expansion, and increased structural connectivity across white matter (WM) tracts in the first years of life in young children with ASD, at a group level, when compared to typically developing (TD) age peers (Courchesne et al. 2001; Hazlett et al. 2005, 2011; Wolff et al. 2012; Xiao et al. 2014; Solso et al. 2016). In addition to enlarged brain volumes, young children with ASD and enlarged head circumference are also reported to have elevated extra-axial cerebrospinal fluid volumes (Shen et al. 2013, 2017, 2018). Besides these early structural brain findings in ASD detected with anatomical and diffusion MRI, a small but growing number of studies have examined the functional brain organization and connectivity in infants and toddlers with (or at risk for) ASD using fMRI acquired during natural sleep. Earlier studies have primarily focused on brain function in putative language regions and reported reduced fMRI activation in response to speech sounds, absent or reversed hemispheric lateralization for speech processing, and diminished interhemispheric connectivity between language regions in young children with ASD (Dinstein et al. 2011; Eyler et al. 2012; Lombardo et al. 2015). More recent studies have investigated the whole-brain intrinsic functional connectivity (iFC) and functional networks in infants with high familial risk for ASD (due to having an older sibling with autism) who were followed prospectively (Eggebrecht et al. 2017; Emerson et al. 2017; Marrus et al. 2018; McKinnon et al. 2019). While these prospective studies provided unique opportunities to study neurodevelopment before the behavioral symptoms of ASD emerge, this sampling design is inherently biased, given the exclusive focus on children from families with a significant familial risk (while most individuals with ASD do not have older siblings with the disorder; Szatmari et al. 2016). More recent studies examining the resting-state functional connectivity in toddlers diagnosed with ASD (age = 1.5–3.5 years) found disruptions in multisensory circuitry, including atypically increased iFC between visual and sensorimotor networks (Chen B et al. 2021) and between thalamus and sensory cortices (Linke et al. 2023), which was associated with greater autism symptoms and poorer clinical outcomes, such as sleep disturbances.

Received: October 24, 2023. **Revised:** December 21, 2023. **Accepted:** January 2, 2024

Critically, a vast majority of neuroimaging studies in ASD, including those in toddler and preschool years reviewed above, have examined the brain structural and functional indices separately using MRI data from a single modality (e.g. fMRI or anatomical MRI), with patterns of covariation between the brain structural and functional development being largely overlooked. With regard to neuroanatomy or morphometric brain development, both cortical thickness (CT) and SA contribute to the cortical volume growth, albeit each following distinct, nonoverlapping maturational trajectories (Brown et al. 2012; Wierenga et al. 2014) rooted in distinct neurobiological processes, including distinctive genetic underpinnings (Panizzon et al. 2009; Strike et al. 2019). The normative developmental trajectories of CT and SA have been extensively studied, with cortical thinning and SA expansion shown across most of the brain during toddler and preschool years (Remer et al. 2017; Bethlehem et al. 2022; Frangou et al. 2022). As noted above, the limited evidence available on the brain volumetric and morphometric developments in early childhood in ASD suggests that these trajectories may be accelerated (i.e. have an earlier peak) in young children with ASD (Courchesne et al. 2001; Hazlett et al. 2005, 2011; Schumann et al. 2010; Xiao et al. 2014). The first years of life are also a period of rapid development of brain functional organization and activity, which can be estimated with the BOLD signal using fMRI. Although resting-state fMRI data have been primarily used—whether in general population, in ASD, or in other clinical populations—to examine the large-scale functional connectivity patterns based on the strength of the correlations between the BOLD signal fluctuations in spatially distant brain regions (Biswal et al. 1995; Fox and Raichle 2007), resting-state fMRI data can also be used to quantify local spontaneous brain activity within a given brain region. For example, regional spontaneous brain activity can be characterized with a fractional amplitude of low-frequency fluctuation (fALFF) metric, which measures the relative contribution of low-frequency BOLD signal fluctuations to the entire frequency range, which is detectable by BOLD-optimized MRI sequences (Zou et al. 2008; Zuo et al. 2010). Only a handful of studies have investigated the local spontaneous activity in ASD, with evidence of disrupted local activity observed in school-aged children, adolescents, and adults, albeit with mixed and region- and age-specific pattern of results (Di Martino et al. 2014; Itahashi et al. 2015; Guo et al. 2017; Karavallil Achuthan et al. 2023). However, no published study to date has investigated the local spontaneous activity in the first years of life in ASD, limiting our knowledge of the maturational aspects and early developmental trajectories of the local spontaneous brain activity in ASD.

Motivated by the dearth of research leveraging multimodal MRI data in early childhood in ASD and aiming to improve our understanding of the multivariate relationships between brain structure and function in early neurodevelopment in ASD, this study set out to examine the covariation patterns between brain morphometry and local spontaneous activity in young children with ASD as compared to TD age-matched peers by using both structural MRI and resting-state fMRI data acquired during natural sleep. We utilized canonical correlation analysis (CCA), a statistical method allowing the investigation of joint multivariate relationships, to identify a set of brain morphometric and local spontaneous activity measures that are maximally correlated (indicating comaturation) in typical development and to compare this brain structure–function covariation pattern to that observed in the ASD cohort. We hypothesized that young children with ASD would exhibit reduced brain structure–function correlations when compared to TD children.

Materials and methods

Participants

This study includes data from participants enrolled in the San Diego State University (SDSU) Toddler MRI Project, a longitudinal study of early brain markers of ASD (see Supplemental Materials for the project's inclusion and exclusion criteria). The research protocol was approved by the institutional review boards of SDSU, 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. The current study includes cross-sectional data (from one of the longitudinal study visits completed between 2016 and early 2020) from 38 young children with ASD and 31 TD children, age = 1.5–5.5 years, for whom both high-quality T1 (anatomical) and 2 runs of resting-state fMRI data acquired during natural sleep were available. Participants with ASD and TD children were matched at the group level on age (see Table 1 for demographic and developmental characteristics of the sample).

Diagnostic and developmental assessment

Diagnoses of ASD or clinical best estimate (Ozonoff et al. 2015) in children younger than 3 years of age were established upon enrollment using standardized measures in combination with expert clinical judgment in accordance with the current recommendations by the American Academy of Pediatrics and Society for Developmental and Behavioral Pediatrics (Weitzman and Wegner 2015; Lipkin and Macias 2020). Because diagnostic evaluation has been repeated at follow-up visits in the context of the larger longitudinal Project, only data from children with confirmed diagnosis, based on the DSM-5 (American Psychiatric Association 2013) diagnostic criteria, were included in the current study. ASD diagnoses were supported by the Autism Diagnostic Observation Schedule-Second Edition (Lord et al. 2012) administered by research-reliable clinicians, the Social Communication Questionnaire (Rutter et al. 2003), or the Autism Diagnostic Interview-Revised (Lord et al. 1994) administered to caregivers of children older than 36 months, and expert clinical judgment. Developmental skills were assessed in all (TD and ASD) participants with the Mullen Scales of Early Learning (MSEL; Mullen 1995), a clinician-administered standardized assessment of cognitive, language, and motor developments. Total developmental quotient (DQ) was calculated as an average of 4 DQs (for each MSEL subscale: Receptive Language, Expressive Language, Fine Motor, and Visual Reception) derived by dividing the subscale age-equivalence score by the child's chronological age and multiplying by 100 (Messinger et al. 2013). The DQ metric was utilized to avoid the relatively common floor effect of the MSEL Early Learning Composite Standard Score, which was observed in 7 out of 38 children in the ASD cohort (consistent with other reports in cohorts of young children with ASD (Lord et al. 2006; Munson et al. 2008). The Vineland Adaptive Behavior Scales, Second Edition, Survey Interview (Vineland-II; Sparrow et al. 2005), a semi-structured interview, was administered to caregivers to assess the child's adaptive development skills demonstrated at home and other settings, with the Adaptive Behavior Composite (ABC) score used in the analysis. For inclusion and retention in the TD group, children had below-clinical cutoff scores on the ASD screener, the SCQ (all TD scores $\leq$10; see Table 1), and demonstrated developmental skills falling no more than 1.5 SD below the normative mean for their age on measures of early learning and development (the MSEL subscales).

Table 1. Participant characteristics.

	ASD ($n = 38$)	TD ($n = 31$)	ASD versus TD	
	Mean ± SD (Min–Max)	Mean ± SD (Min–Max)	t/X^2	*P*-value
Age at scan (months)	44.6 ± 14.8 (18–69)	44.2 ± 13.7 (18–65)	$t(67) = 0.14$	0.89
Gender (M/F)	30/8	16/15	$\chi^2(1) = 5.74$	0.02
Ethnicity (Hispanic/non-Hispanic)[a]	16/18	9/22	$\chi^2(1) = 2.23$	0.14
Race (White/more than one/Black/Asian)[a]	21/8/0/2	22/5/3/0	—	—
Gestational age (weeks)[b]	38.6 ± 2.3 (31–43)	39.6 ± 1.1 (37–42)	$t(59) = -2.00$	0.05
Birth weight (grams)[c]	3230.0 ± 571.8 (2041–4394)	3511.2 ± 366.7 (2863–4082)	$t(59) = -2.26$	0.03
Delivery method (vaginal/C-section)[c]	24/11	21/9	$\chi^2(1) = 0.02$	0.90
Maternal education level (%)[d]				
High school or some college credit, but < 1 year	34%	6%	—	—
Associate degree/vocational school	11%	6%	—	—
Bachelor's degree	11%	35%	—	—
Master's degree	24%	42%	—	—
Professional degree (MD, PhD, JD)	11%	10%	—	—
MSEL total DQ[e]	74.8 ± 23.0 (14–107)	103.5 ± 13.2 (71–134)	$t(66) = -6.15$	<0.001
Vineland-II adaptive behavior composite	75.9 ± 10.5 (55–100)	106.1 ± 12.7 (80–127)	$t(66) = -10.75$	<0.001
SCQ total score[f]	16.3 ± 7.9 (3–35)	4.0 ± 2.9 (0–10)	$t(58) = 7.79$	<0.001
ADOS-2 calibrated severity score	6.3 ± 2.1 (2–10)	—	—	—
RMSD (mm)	0.13 ± 0.04 (0.05–0.21)	0.10 ± 0.03 (0.05–0.18)	$t(67) = 3.28$	0.002
Total brain volume (cm^3)	1,095.4 ± 98.5 (787.9–1,298.9)	1,067.2 ± 105.2 (813.9–1,293.5)	$t(67) = 1.15$	0.26
Gray/white CNR	2.1 ± 0.2 (1.7–2.5)	2.0 ± 0.2 (1.3–2.3)	$t(67) = 1.86$	0.07

Note: M = male; F = female; MSEL = Mullen Scales of Early Learning; Vineland-II = Vineland Adaptive Behavior Scales, 2nd Edition; SCQ = Social Communication Questionnaire; ADOS-2 = Autism Diagnostic Observation Schedule, Second Edition; RMSD = root mean square displacement; CNR = contrast to noise ratio; TD = typically developing; DQ = developmental quotient. [a]Ethnicity data are missing for 4 ASD participants, and race data are missing for 5 ASD and 1 TD participants; [b]Gestational age data are missing for 4 ASD and 1 TD participants. [c]Birth weight data are missing for 2 ASD children, and delivery mode is missing for 3 ASD and 1 TD children. [d]Maternal education data are missing for 3 ASD participants. [e]MSEL total DQ data is missing for 1 ASD participant. [f]SCQ data are missing for 6 ASD and 3 TD participants.

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 by using a Nova Medical 32-channel head coil. First, a multiband echo planar imaging (EPI) sequence allowing the simultaneous acquisition of multiple slices was used to acquire 2 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 next with a fast 3D spoiled gradient recalled 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 3 navigator scans and real-time prospective motion correction (White et al. 2010), and images were bias-corrected using the GE PURE option. On the night of the scan, noise protection was achieved with MRI compatible headphones (MR Confon) and earplugs. Scanning commenced after approximately 30–50 min of sleep. For details on the habituation protocol in preparation for MRI data acquisition during sleep, see Supplemental Materials.

MRI data preprocessing, brain structural and functional variables, and analytic strategy

For details on MRI data preprocessing, see Supplemental Materials. Two brain morphometric measures, SA and CT, were extracted for each participant from 34 regions of interest (ROIs) per hemisphere from the Desikan-Killiany atlas implemented in FreeSurfer (Desikan et al. 2006). Local spontaneous activity was indexed with the fALFF measure extracted from the fMRI data in each voxel and was averaged within the same ROIs. FALFF was calculated as the power of BOLD signal within the low-frequency range (0.01–0.1 Hz) divided by the total power of the entire frequency spectrum by using the implementation included with the CONN toolbox. The SA, CT, and fALFF variables of interest were submitted to linear regressions to exclude potential confounds; namely, CNR and total brain volume were regressed out of the 2 morphometric measures (SA and CT), and head motion indexed by mean RMSD across 2 fMRI runs was regressed out of the local spontaneous activity measure (fALFF).

In order to investigate the covariation patterns between brain structure (SA and CT) and function (local spontaneous activity: fALFF), sparse canonical correlation analysis (SCCA) was implemented using the "PMA" package in R (Witten et al. 2009). CCA is a multivariate statistical technique that identifies the linear combinations of 2 sets of variables—such as brain morphometry and local spontaneous activity measures—with maximal correlation between them (Hardoon et al. 2004). CCA is particularly suited to identifying the source of common statistical variation among data from multiple modalities (such as brain anatomical and functional variables) without assuming any directionality (Zhuang et al. 2020). To avoid model overfitting and enhance interpretability of the structure–function covariation, SCCA, a variant of CCA, was used because it identifies the parsimonious sources of variation by setting a maximum number of variables with minimal contribution to interpretable linear combinations to exactly 0 (thereby inducing sparsity on canonical coefficients). A pair of canonical variates (CVs)—a structural and a functional

CV—capturing the highest brain structure–function correlation among TD children was extracted from SCCA. In order to examine whether young children with ASD show a comparable structure–function covariation pattern to that observed in neurotypical development, the corresponding canonical vectors derived from the TD data were applied to the ASD data. Significance of the difference in canonical correlations (or correlations between CVs generated with the SCCA) between the TD and ASD groups was determined with permutation testing. Specifically, bootstrapping was carried out by randomly splitting the whole (combined ASD and TD) sample in half, with 1,000 iterations, and calculating the difference in canonical correlations by applying the canonical vectors derived from half of the sample to the other half. The group difference in canonical correlation was determined to be statistically significant at $P < 0.05$ on the bootstrapping distribution.

Associations between age and the CVs capturing maximally correlated brain morphometry and local activity variables were examined with linear regressions conducted separately in the TD and ASD groups. Finally, associations between CVs and overall developmental and adaptive behavior skills were examined with linear regression models, with structural CV or functional CV as predictors and MSEL Total DQ or Vineland-II ABC as outcome variables, controlling for age and sex (with separate regression models in the ASD and TD groups).

Results

The results of the SCCA performed on the TD data revealed a significant, positive canonical correlation between the brain morphometry and local spontaneous activity ($r = 0.81$, $P < 0.001$; see Fig. 1A). Structural and functional CVs contributing to this canonical correlation are presented in Fig. 2, which depicts canonical coefficients illustrative of the relationship between the initial variables (i.e. SA, CT, and fALFF) and the CVs for each ROI in the left (top panel) and right (bottom panel) hemispheres. As can be seen in Fig. 2, this pair of CVs was characterized by a generally reduced SA and greater CT being associated with lower fALFF, with only 1 exception of higher fALFF in the right cuneus cortex. Specifically, the structural CV implicated lower SA in bilateral orbitofrontal, anterior cingulate, and inferior frontal cortices and greater CT in bilateral caudal middle frontal, lateral orbitofrontal, and inferior frontal cortices and cuneus, precuneus, pericalcarine, and supramarginal cortices (see Fig. 2 legend for a detailed list of ROIs). Together, lower SA and higher CT in these regions covaried with lower fALFF in left inferior frontal, caudal and rostral middle frontal, superior frontal, and supramarginal cortices and right orbitofrontal cortex, and higher fALFF in cuneus.

After applying the canonical vectors derived from the TD data to the ASD group, the structure–function canonical correlation found in the ASD group was reduced ($r = 0.25$, $P = 0.136$; see Fig. 1B). To determine whether this difference between the canonical correlations observed in the TD and ASD groups was significant, permutation testing with 1,000 iterations was conducted to estimate the bootstrapping distribution by randomly splitting the dataset in half and calculating the difference in structure–function canonical correlations by applying the canonical vectors derived from half of the sample to the other half. Permutation testing (see Fig. 1C) determined that the structure–function correlation in the ASD group was significantly reduced ($P < 0.05$).

By testing for links between the CVs of brain morphometry and local activity and child's age, linear regressions revealed that both structural and functional CVs were significantly, negatively correlated with age in the TD ($r = -0.72$ and -0.75, respectively), but not in the ASD group ($r = -0.26$ and -0.25, respectively; see Fig. 3), with significant diagnostic group by age interactions for both structural CV ($P = 0.01$) and functional CV ($P = 0.005$).

Finally, linear regression models testing for relationships between CVs and overall developmental and adaptive behavior skills among children with ASD revealed significant associations between functional CV and overall developmental skills (Mullen Total DQ; partial $r = -0.43$, $P = 0.009$) and adaptive functioning (Vineland-II ABC; partial $r = -0.37$, $P = 0.026$) after controlling for age (see Fig. 3B). No significant associations with behavioral indices were found for the structural CV, and there were no relationships between the structural or functional CVs and developmental or adaptive skills in TD children (the latter likely due to the smaller range of behavioral scores in the TD group, as expected in typical development).

Discussion

We used both structural MRI and fMRI data acquired during the same scanning session to examine the covariation patterns between brain morphometry and local spontaneous activity in young children with ASD compared to age-matched TD children. A multivariate statistical approach—CCA—was implemented to identify a pair of CVs or linear combinations of brain morphometric (SA and CT) and local spontaneous activity measures (fALFF) that maximally covary in typical development, indicating comaturation. The CCA revealed a general covariation pattern of lower SA and higher CT associated with overall lower fALFF in TD children. This pattern of structure–function covariation (between brain structural metrics and local brain activity) was found to be significantly reduced in children with ASD, as determined with permutation testing. We also set out to examine whether the CVs capturing maximally correlated brain morphometry and local activity variables are associated with age as well as the overall developmental and adaptive behavior skills in children with ASD and in TD peers. Age-related analyses revealed that, while the CVs of brain structure and function were significantly associated with age, cross-sectionally, in TD children, these age relationships were not observed in the ASD group. Furthermore, among young children with ASD, the functional CV capturing local spontaneous activity across the brain (which covaries with brain structural metrics) was significantly associated with indices of general development and adaptive behavior skills.

Weaker brain structure–function coupling early in life in autism

Most notably, these results provide initial evidence of reduced brain structure–function correlation in young children with ASD relative to TD children, suggesting that the covariation or close dependence between brain morphometry and local spontaneous activity in ASD deviates from typical neurodevelopment during early childhood. Although the covariation between brain structure and function has not been previously studied in young children, with or without autism, a recent study (Qi et al. 2020) reported results of a fusion analysis between fALFF and gray matter (GM) volume in school-age children and adults with ASD. Utilizing the ABIDE datasets (Di Martino et al. 2014, 2017), the authors reported findings linking autism symptoms with patterns of covariance between greater fALFF in broadly distributed cortical regions (e.g. dorsolateral prefrontal, inferior frontal, and superior/middle temporal gyrus) but reduced fALFF in subcortical

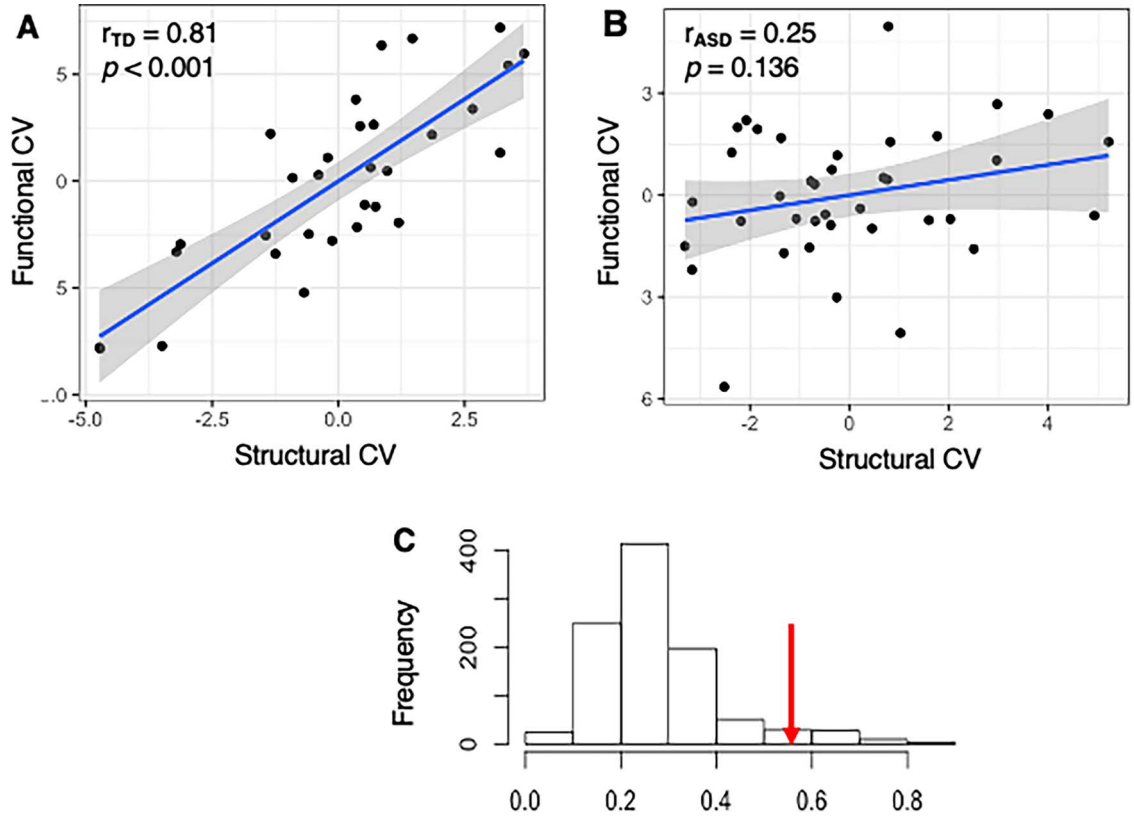

Fig. 1. Scatterplots representing canonical correlations between structural and functional CVs in the A) TD and B) ASD groups. C) Bootstrapping distribution of the difference in canonical correlations after randomly splitting the whole sample in half and applying the canonical vectors derived from one half of the sample to the other half (1,000 iterations); arrow indicates the difference in canonical correlations depicted in panels A and B ($r_{TD} - r_{ASD} = 0.57$).

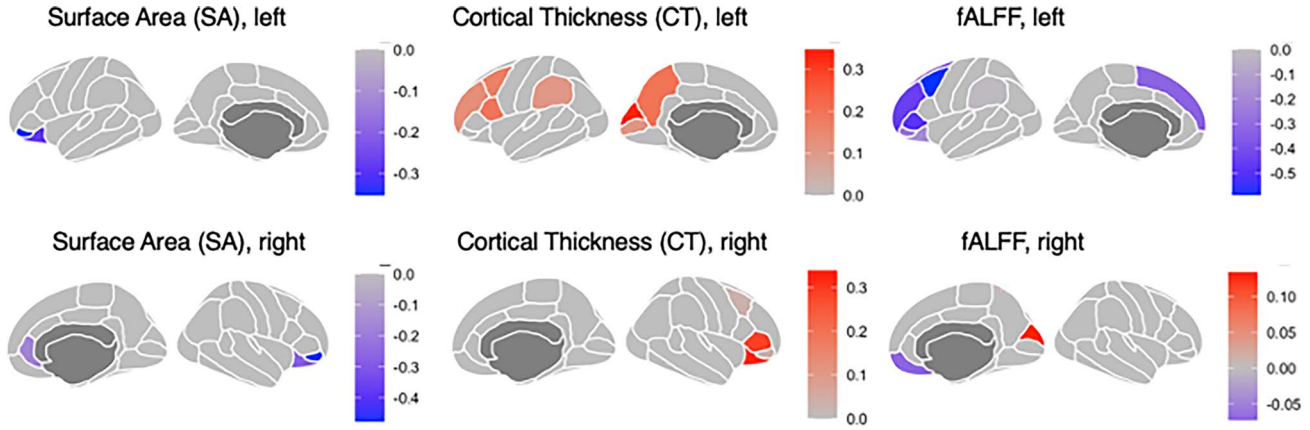

Fig. 2. Canonical vectors of SA, CT, and fALFF from bilateral ROIs with maximized structure–function correlation in TD children, derived from SCCA. Top and bottom panels depict ROIs from left and right hemisphere, respectively. ROIs contributing to each structural and functional canonical vectors are: for SA, L pars orbitalis, L lateral orbitofrontal, R pars orbitalis, R lateral orbitofrontal, and R rostral anterior cingulate; for CT, L cuneus, L precuneus, L pars opercularis, L caudal middle frontal, L rostral middle frontal, L pericalcarine, L supramarginal, R lateral orbitofrontal, R pars triangularis, R caudal middle frontal, and R pars orbitalis; for fALFF, L caudal middle frontal, L pars triangularis, L rostral middle frontal, L superior frontal, L pars orbitalis, L lateral orbitofrontal, L supramarginal, R cuneus, and R medial orbitofrontal. L = left; R = right.

regions (e.g. thalamus and caudate) and greater GM volumes in partially overlapping cortical areas such as dorsolateral prefrontal and superior/middle temporal gyrus. Also using the ABIDE dataset from school-age children, Chen and colleagues identified atypical concordance patterns between the function (measured with ALFF) in GM and WM regions, with higher GM/WM functional covariance observed in children with ASD and linked with autism symptoms (Chen H et al. 2021). While these results are not directly comparable to the present findings due to considerable methodological differences and disparate age range, they highlight the need for multimodal neuroimaging studies utilizing multivariate statistical methods, which allow modeling complex neurodevelopmental processes jointly and examining how they codevelop across time and individuals in ASD. Our study also contributes to the broader literature on the development of structure–function coupling in human brain networks and how it relates to cognitive

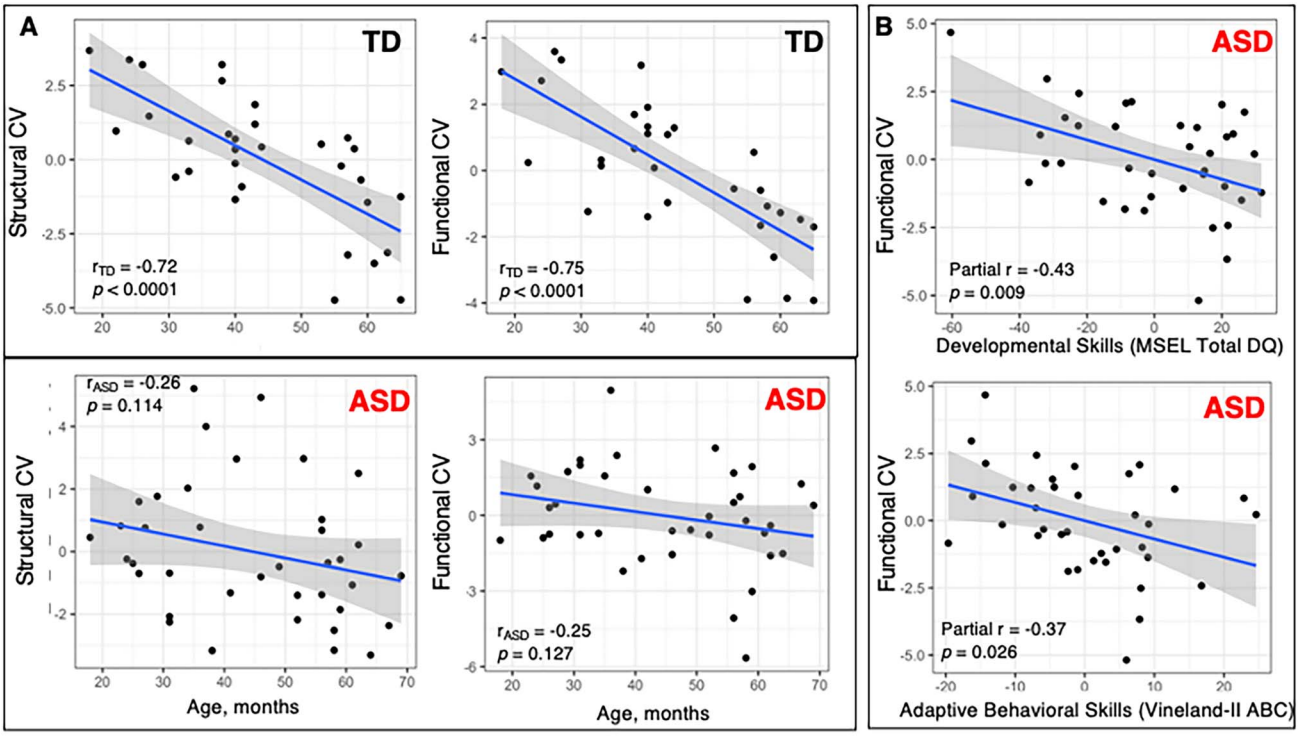

Fig. 3. A) Correlations between structural and functional CVs and age, plotted separately in the TD (top) and ASD (bottom) groups. B) Partial correlations* between functional CV and MSEL Total DQ (top) and Vineland-II ABC (bottom) in children with ASD (* = controlling for age; values on the X- and Y-axes represent residuals).

development and psychopathology (Baum et al. 2020). Overall, our finding of the weaker brain structure–function coupling in children with ASD suggests that the fundamental aspects of brain development may be uncoupled early in life in autism, likely contributing to the disrupted circuit formation, with distributed effects on brain function and connectivity across the entire lifespan.

Atypical age-related effects: evidence of mistimed brain development trajectories in autism

The importance of studying developmental trajectories jointly across different brain maturation indices, especially during early childhood, is further supported by the differential age-related effects (albeit observed cross-sectionally) in both brain morphometry and local spontaneous activity detected in our study. Namely, we found that the structural and functional CVs (underlying the brain structure–function coupling) were significantly associated with age in typical development, but such a relationship was absent among children with ASD. This suggests that maturational trajectories of covariation between the brain structure and function may be mistimed in early childhood in ASD. This observation is in line with other findings of atypical age-related effects observed in unimodal studies examining the maturation of functional network connectivity and cortical myelination across early childhood in ASD (Chen B et al. 2021; Chen et al. 2022). These findings extend the notion of atypical neurodevelopment and mistimed brain maturational trajectories in autism to early childhood. Given the profound brain maturational changes, peak neuroplasticity, and remarkable advances in cognitive, behavioral, and socio-emotional developments characterizing the first years of life (Tau and Peterson 2010; Bornstein 2014), it is critical to examine brain maturation and its timing in autism during this developmental period rather than making inferences from neuroimaging studies in older children and adolescents (cf. Uddin et al. 2013; He et al. 2020). It is possible that the variable (distinct from neurotypical) brain maturational trajectories, including atypical brain structure–function coupling, in young children with autism contribute to variable treatment response among children with autism (Vivanti et al. 2014) despite the robust evidence of the efficacy of early interventions (Landa 2018). Critically, the links between CV capturing the brain's local spontaneous activity and overall developmental and adaptive behavior skills detected in the ASD group suggest that brain function, specifically local spontaneous activity, may be a meaningful neurobiological feature that is related to developmental and behavioral outcomes in ASD.

Potential limitations

While this study is the first known investigation of the multivariate relationship between brain morphometry and local spontaneous activity in the first years of life in ASD, interpretation of its results is somewhat limited by the moderate sample size due to known challenges of acquiring high-quality multimodal MRI data in young children and in particular in children with neurodevelopmental disorders (Nordahl et al. 2016; Turesky et al. 2021; Hendrix and Thomason 2022). As such, we applied a parsimonious multivariate model (SCCA) to extract composite indices that capture maximally correlated brain morphometry and local activity variables. This data-driven approach allowed for the examination of the overall structure–function covarying patterns with simultaneous data reduction, which is most appropriate for high-dimensional data with a moderate sample size. However, CCA also comes with some limitations; for instance, the relationship between the 2 modalities (sets of variables) is assumed to be linear and the directionality of the linear relationship (or

canonical correlations) identified with CCA is indeterminate (Zhuang et al. 2020). Additionally, this approach is not suitable for identifying region-specific abnormalities in ASD. Future larger-scale and longitudinal studies are needed to examine the age-related trajectories of the brain structure–function covariation patterns longitudinally. Although we cannot rule out the impact of the imbalanced gender distribution in the ASD and TD groups on the observed effects, the evidence of sex effects on early brain overgrowth in ASD is mixed and inconclusive (Campbell et al. 2014; Molani-Gol et al. 2023). Finally, as with any correlational approach, the identified function–structure covarying patterns do not infer causation. Hence, we cannot discern if the reduced brain structure–function correlation in ASD originates from atypical brain morphometry, local spontaneous activity, or other neurodevelopmental processes not directly examined in this study. However, the observed links with developmental and adaptive behavior skills suggest that brain function (local spontaneous activity) may be particularly clinically relevant at this age.

Conclusion

To our knowledge, this study is the first to characterize the brain structure–function covariation, using multimodal MRI measures acquired during the same scanning session and a multivariate pattern analysis, in the first years of life in ASD. The overall brain structure–function correlation was significantly reduced in young children with ASD compared to TD children, and the neurotypical age-related relationship in the structural and functional indices capturing maximally correlated brain morphometry and local activity measures was absent in the ASD group, suggesting mistimed developmental trajectory of the brain structure–function coupling. Furthermore, the identified association between the index of the local spontaneous activity and the overall developmental and adaptive behavior skills in the ASD cohort highlights the importance of local brain activity in early developmental outcomes.

Acknowledgments

This research was supported by the National Institutes of Health (R01 MH107802 to IF). The first author (BC) was supported by the Autism Speaks Royal Arch Mason Predoctoral Fellowship and the Society of Clinical Child and Adolescent Psychology/American Psychological Association (APA) Division 53 Donald Routh Dissertation Grant Award. 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 Mikaela Kinnear, PhD, and Lisa Mash, PhD, of SDSU, and Tiffany Wang, MS, of UCSD, 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.

Author contributions

Bosi Chen (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Lindsay Olson (Data curation, Investigation, Writing—review & editing), Adriana Rios (Data curation, Project administration, Writing—review & editing), Madison Salmina (Data curation, Project administration, Writing—review & editing), Annika Linke (Conceptualization, Data curation, Investigation, Methodology, Writing—review & editing), and Inna Fishman (Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing—review & editing)

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

Conflict of interest statement: None declared.

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