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Restricted and repetitive behavior and brain functional connectivity in infants at risk for developing autism spectrum disorder

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Abstract

Background—Restricted and repetitive behaviors (RRBs), detectable by 12 months (mo) in many infants later diagnosed with autism spectrum disorder (ASD), may represent some of the earliest behavioral markers of ASD. However, brain function underlying the emergence of these key behaviors remains unknown.

Methods—Behavioral and resting-state functional connectivity (fc) magnetic resonance imaging data were collected from 167 children at high and low familial risk for ASD at 12 and 24mo (n=38 at both time points). Twenty infants met criteria for ASD at 24 mo. We divided RRBs intofour subcategories (restricted, stereotyped, ritualistic/sameness, self-injurious) and used a data-driven approach to identify functional brain networks associated with the development of each RRB subcategory.

Results—Higher scores for ritualistic/sameness behavior were associated with less positive fc between visual and control networks at 12 and 24 mo. Ritualistic/sameness and stereotyped behaviors were associated with less positive fc between visual and default mode networks at 12 mo. At 24 mo, stereotyped and restricted behaviors were associated with more positive fc between default mode and control networks. Additionally, at 24 mo, stereotyped behavior was associated with more positive fc between dorsal attention and subcortical networks, while restricted behavior was associated with more positive fc between default mode and dorsal attention networks. No significant network-level associations were observed for self-injurious behavior.

Conclusion—These observations mark the earliest known description of functional brain systems underlying RRBs, reinforce the construct validity of RRB subcategories in infants, and implicate specific neural substrates for future interventions targeting RRBs.

Keywords

Autism spectrum disorder; brain development; restricted and repetitive behavior; functional connectivity; functional magnetic resonance imaging; infant

Introduction

In the first two years of typical childhood development, restricted and repetitive behaviors (RRBs) contribute to a cascade of progressive events that engender flexible and complex patterns of goal-directed behavior. However, recent evidence suggests that elevated levels of RRBs comprise some of the earliest emerging behavioral manifestations of autism spectrum disorder (ASD) and are observed as early as 12 months of age in infants later diagnosed with ASD (1–4). Along with deficits in social communication and interaction, RRBs comprise the defining core features of ASD (5), a common neurodevelopmental disorder that is among the most highly heritable of psychiatric conditions (6). The elevated levels of RRBs characteristic of ASD are impairing; the intensity and inflexibility associated with these repetitive actions and limited interests constrains opportunities to access environmental input important for learning and social development (7). Additionally, RRBs in both children and adults have been linked to alterations likely to broadly affect task performance, including abnormal sensory processing and deficits in cognitive control and executive functioning (8–14). Neural correlates of ASD include atypical local and network-level brain structure and resting-state functional networks from early development through adulthood (14–30). Elucidating the relationships between RRBs and the maturation of the brain's functional networks during typical and atypical early development may enhance early risk assessment, inform developmental models of ASD pathogenesis, and provide a neurophysiological foundation for novel interventions focused on RRBs.

The RRB domain encompasses a heterogeneous set of behaviors—intense preoccupations, stereotyped movements, and resistance to change (5)—that may be better conceptualized as distinct subcategories (7, 31, 32). Factor analytic studies in both young children and adults support the existence of considerable structure within the RRB domain, where a five-factor model both provides superior precision in RRB behavioral profiling (33, 34) and highlights developmental trajectories of unique RRB subcategories evident as early as 12 months (4, 31). However, characterizing the specific neural contributions to the emergence of these behaviors has proven challenging (35–38), due in part to the significant methodological challenges of imaging brain function in infants and toddlers. Most studies using either task-based functional MRI (fMRI) or resting-state functional connectivity MRI (fcMRI) have focused largely on adulthood, rather than the first years of life when such behaviors begin to emerge.

Here, we aimed to characterize the relationship between subcategories of RRBs and functional connectivity (fc) within and between putative brain networks over a pivotal time

in development for both ASD-specific behavioral features (3, 4) and functional network organization (39–42). To quantify RRBs across four subcategories in a sample of 12-month old infants and 24-month old toddlers at high and low familial risk for ASD, we used the Repetitive Behavior Scale-Revised (RBS-R) (32). In the same infants, brain functional network architecture was measured using resting-state fcMRI. We took a data-driven approach to assessing brain-behavior relationships because, as both RRBs and brain function exhibit significant maturation throughout early childhood, findings from older individuals may not extend to infants and toddlers. Functional connections most associated with RBS-R subcategory factor scores were identified using generalized linear modeling. We then used enrichment analyses, adapted from large-scale genome-wide association studies, to identify network pairs exhibiting a significantly increased density of these strong brain-behavior relationships (43, 44). This established statistical method facilitated a brain-wide approach while constraining the burden of multiple comparisons. We hypothesized that: (1) the functional connections most strongly associated with RRBs would involve the default mode network, the frontoparietal control network, the salience network, and striatal regions of the subcortical network (38, 45) – networks previously implicated with RRBs in studies on older participants, and (2) RBS-R subcategories previously combined into an alternate behavioral category (33, 34) would be associated with overlapping patterns of functional network pairs.

Materials and Methods

Participants

Participants were recruited as part of an ongoing, multisite, Autism Centers of Excellence Network study — the Infant Brain Imaging Study (IBIS), which has collected a large infant sibling sample with prospective brain-behavioral data across a crucial time window during which ASD develops. Individuals were assessed and scanned at each of four clinical sites: University of North Carolina, University of Washington, The Children's Hospital of Philadelphia, and Washington University in St. Louis. The research protocol was approved by the institutional review boards at all clinical sites, and parents provided written informed consent after receiving a detailed description of the study.

Infants were classified as high-risk (HR) if they had at least one sibling with a diagnosis of ASD, or low-risk (LR) if they had at least one typically developing older sibling and nofirst or second degree relatives with ASD or an intellectual disability. Participants were subsequently assigned diagnostic outcome labels: HR-ASD-positive, HR-ASD-negative, or LR-ASD-negative, depending on clinical best estimate, applying the DSM-IV-TR (5) checklist to all available data at 24 months. LR-ASD-positive subjects were omitted from the analyses (Table 1). Because HR children show elevated occurrence rates of RRBs relative to LR controls (4), this sample provided a sufficient range of RBS-R scores to adequately detect relationships between behavioral scores and dimensional metrics of brain function. All included participants contributed both behavioral and fcMRI data at visits corresponding to 12 and/or 24 months of age (range: 11.1–15.0 months and 22.4–27.0 months, respectively). All datasets were subject to stringent fcMRI quality control criteria and IBIS behavioral and structural MRI inclusion criteria (21) (see the Supplement for details). Age groups did not significantly differ by proportion of children later diagnosed with ASD

(Fisher's exact test, p=0.36), HR participants (p=1.0), girls (p=0.47), or cognitive development (Mullen composite standard score, Welch's t-test, p=0.24).

Behavioral assessment

RRBs were assessed using the RBS-R (32), a parent/caregiver rated questionnaire consisting of 43 items that has been validated for use among toddlers and preschool age children (4, 33, 34). Responses focused on the counts of items-endorsed rather than on severity scores, as the latter may be more susceptible to rater bias (4). The 43 items have been conceptually grouped into six subscales: stereotyped behavior, self-injurious behavior, compulsive behavior, ritualistic behavior, sameness behavior, and restricted behavior (32). In line with previous factor analytic studies (33, 34), ritualistic and sameness subtests were combined into a single factor. The compulsive factor was excluded as this subscale was not developmentally appropriate for the subjects included in the current study (4). The present study focused on the remaining four factors: restricted, stereotyped, ritualistic/sameness, and self-injurious behaviors (Figure 1A–D; Supplemental Table S1). There was no effect of site on RRB scores, and age-in-months was not correlated with RRB score (Supplement; Supplemental Table S2).

Imaging acquisition

Anatomical and functional brain imaging was carried out at all clinical sites using identical, cross-site calibrated 3-T Siemens TIM trio scanners (Siemens Medical Solutions, Malvern, PA), each equipped with standard 12-channel head coils. All infants were scanned during natural sleep (43). Each of two to three acquisitions was comprised of 130 temporally contiguous frames spanning 5.4 minutes. See the Supplement for details.

fMRI preprocessing and fidelity optimization

Data were preprocessed to reduce artifacts (*i.e.* BOLD signal changes not resulting from neural activity) and spatially registered to a 3 mm isotropic space using previously outlined procedures (41, 46). Small degrees of head motion-induced artifact can significantly alter correlations in resting-state data and confound interpretations of functional connectivity, particularly in studies of development where age is a factor of interest (47–49). To optimize data fidelity and minimize artifact, stringent thresholds in motion censoring "scrubbing" based on frame-to-frame displacement (FD; calculated as the sum of the absolute values of the six different realignment estimates—X, Y, Z, pitch, yaw, roll—at every time point (50)), number of contiguous frames, and total frame number were maintained. Frames with calculated FD ≥ 0.2 mm were marked for censoring. See the Supplement for further details. Exactly 150 frames, corresponding to 6.25 minutes, of high-quality, low-motion MRI data were used from each participant within each age group.

fcMRI preprocessing

Following previously described procedures (50), data were voxel-wise demeaned and detrended within runs, while censored frames were ignored. Nuisance waveforms (including the global signal) were regressed voxelwise from the data, ignoring censored frames (Supplement). In frames marked for censoring, data were replaced by interpolated values

computed by least-squares spectral analysis (50, 51). Interpolated data were only included for bandpass filtering and did not factor into correlation values. Finally, the data were spatially smoothed using a Gaussian kernel (6 mm FWHM isotropic).

Definition of ROIs and functional connectivity computation

The derivation of 230 regions of interest for studies on this population was previously described (41, 43) (Supplemental Figure S1). ROI-specific timecourses were calculated by averaging the timecourses of all voxels contained within 10 mm diameter spheres. Functional connectivity (fc) values were calculated as the pairwise zero-lag Pearson correlation between each of the 26,335 pairs of ROI timecourses, and then Fisher-z transformed.

Derivation of putative functional networks in infants and toddlers

We utilized a previously described cross-age functional brain network model composed of these 230 ROIs from a longitudinal cohort of N=48 children with clean fcMRI data at both 12-and 24-months (43) (see the Supplement for details). This model of the combined infant-toddler functional brain networks included 13 putative networks with naming informed by published adult networks (47): visual (Vis), temporal default mode network (tDMN), posterior cingulate DMN (pcDMN), anterior DMN (aDMN), somato-motor network (SMN), somato-motor network 2 (SMN2), dorsal attention network (DAN), posterior frontal parietal control network (pFPC), anterior FPC (aFPC), subcortex (SubCtx), cingulo-opercular (CO), posterior CO (pCO), and salience (Sal) (Figure 1; Supplemental Figure S1) (43, 52). To generate complementary analyses using adult functional networks, we adapted a functional brain network structure derived from a published independent fcMRI dataset of typical adults (53).

Statistical Analysis

Differences in RRB subcategory scores across age were calculated across the larger IBIS sample of participants who contributed behavioral data (N = 467 at 12 months, N = 379 at 24 months, where n = 327 had data at both time points) with the Wilcoxon signed-rank test (alpha level of 0.0125 reflecting Bonferroni correction for the four behaviors tested). Using the matched fcMRI-RBS-R data, generalized linear modeling was used to examine the predictive relationship between brain fc and RRB subcategory scores separately for each of the 26,335 ROI pairs, at each time point, yielding two 26,335-element matrices of regression coefficients for each RRB subcategory (e.g. Figure 2A). Specifically, we fit a fixed-effect negative binomial regression with the relevant RBS-R subcategory factor as outcome and the ROI-ROI fc values as predictors. The negative binomial distribution provided optimal modeling for the RBS-R inventories that contained heavily zero-weighted integer count data (Figure 1 A–D; (14)), based on goodness-of-fit statistics that indicated superiority to a Poisson distribution model. Enrichment analyses were used to determine whether strong (defined as $p \leq 0.05$, uncorrected; e.g., Figure 2B) brain-behavior relationship values (i.e., regression coefficients between RBS and fc for each ROI-pair) were significantly clustered within specific network pairs (43) (see the Supplement for details). A McNemar test was performed to determine whether patterns of brain-behavior relationships significantly differed between the 12- and 24- month groups. Stringent, brain-wide empirical significance

levels—reflecting the 1.25% false positive rate—were determined using randomization (43). An alpha of 0.0125 was used to account for the four behavioral factors analyzed. The randomization procedure preserved the correlation and missing-data patterns in the data (e.g., infants assessed at 12 months only) and produced two separate brain-wide null distributions for statistical evaluation of the data—one for each time point (Supplement). Primary results include network pairs either significantly enriched at both time points, or significantly enriched at one age and significantly different in their set of brain-behavior relationships between age groups (e.g. Figure 2D). In contrast, network pairs that exhibit significant enrichment at one time point –but do not differ statistically from null results at the other time –are presented as discovery findings that may provide potential targets for future hypothesis-driven studies.

Results

Behavioral characterization

We analyzed behavioral and neuroimaging data collected from infants at 12 (n=118) and/or 24 months of age (n=87; n=38 children provided data at both ages) (Table 1). Restricted interests, stereotyped mannerisms, and self-injurious behavior scores did not show significant differences across age (restricted p=0.77; stereotyped p=0.72; self-injurious=0.61), whereas ritualistic/sameness behavior showed a significant age-related increase ($p=1.8\times10^{-4}$; consistent with previous findings (4)).

Restricted behavior associations with functional connectivity

The primary findings in relation to restricted behavior include only two of the possible 91 total network pairs: the tDMN-DAN and tDMN-pFPC at 24 mo (Figure 2). Each network pair exhibited significant clustering of positive brain-behavior relationships (Figure 2D), meaning that more positive fc values between these brain regions were associated with higher restricted behavior scores. Though the associations between fcMRI and restricted scores were positive within these two network pairs, the range of the fcMRI values, themselves, within the tDMN-DAN and tDMN-pFPC were remarkably distinct (Supplemental Figure S2). Specifically, in 77% of the tDMN-DAN ROI pairs, predominantly negative fc values were exhibited. The observation of a positive relationship between fc and restricted behavior in the context of predominantly negative fc for ROI pairs indicates that strongly negative tDMN-DAN fc is associated with fewer restricted behaviors. In contrast, 70% of tDMN-pFPC connections contributing to enrichment showed predominantly positive fc values. In addition to these primary findings, two discovery-level findings were also observed at 12 mo: negative fc-restricted relationships in Vis-tDMN and positive fc-restricted relationships in Vis-SMN2.

Stereotyped behavior associations with functional connectivity

Primary findings include three network pairs: Vis-tDMN at 12 months, as well as DAN-SubCtx and tDMN-pFPC at 24 months (Figure 3). At 12 months, Vis-tDMN connections showed significant clustering of strong negative brain-behavior relationships (Figure 3D), with 77% exhibiting predominantly negative fc (Supplemental Figure S3). In contrast, at 24 months, greater stereotyped scores were associated with more positive fc between tDMN-

pFPC and DAN-SubCtx (Figure 3). Of tDMN-pFPC connections contributing enrichment, 83% showed primarily positive fc, while 89% of implicated DAN-SubCtx ROI pairs showed primarily negative fc values (Supplemental Figure S3). Of the subcortical ROIs contributing to enrichment, four ROIs, all located in the putamen/lentiform nucleus, were implicated markedly more frequently than the others (MNI coordinates: −31.4, −11.5, −0.3; 30.5, −13.9, 1.7; 23.3, 10.2, 1.5; 28.5, 0.8, 4.0). Discovery findings include three network pairs at 12 months (Figure 3C), including enrichment of positive fc-stereotyped relationships within the visual network (Vis-Vis) and negative fc-stereotyped relationships within the Vis-pFPC and pcDMN-pFPC (Figure 3B).

Ritualistic/sameness behavior associations with functional connectivity

Primary findings include higher ritualistic/sameness scores associated with less positive fc between Vis-tDMN at 12 months (with 82% of connections showing primarily negative fc) (Figure 4; Supplemental Figure S4), as well as less positive fc between Vis-pFPC at both 12 and 24 months (with primarily negative fc in 85% of connections at 12 months and 90% of connections at 24 months). Of the implicated Vis-pFPC connections, 16% (9/55) of connections at 12 months and 23% (9/39) of connections at 24 months were implicated at both time points. Discovery findings included four additional network pairs: enrichment of positive fc-ritualistic relationships within Vis-Vis and Vis-pcDMN at 12 months, enrichment of negative fc-ritualistic relationships within tDMN-pcDMN at 12 months, and enrichment of positive fc-ritualistic relationships between the tDMN-pFPC at 24 months (Figure 4).

Self-injurious behavior associations with functional connectivity

No primary level findings were observed in the fc-self-injurious relationships at either age (Supplemental Figure S5). A discovery level finding was observed at 24 months within Vis-DAN.

Convergence across RRB subcategories

As detailed above, Vis-tDMN was associated with both stereotyped and ritualistic/sameness behaviors at 12 months, and at 24 months tDMN-pFPC was associated with both stereotyped and restricted behaviors (Figure 5 for summary of results). In each case, convergence at the network level was also represented at the level of individual ROI connections (Figure 6). Present in the convergent findings at both ages are tDMN ROIs predominantly distributed around the lateral right temporal lobe and the right temporal-parietal junction.

Discussion

Though exhibitions of RRBs reflect crucial stages of early typical development, accumulating evidence suggests that early elevation of these behaviors may provide a potent early risk marker for later diagnosis of ASD. Our primary findings (summarized in Figure 5) reveal that: (1) neural signatures of RRB subcategories are distinct between 12 and 24 months of age, with the single exception of negative Vis-pFPC fc associations with ritualistic/sameness behavior (Figure 4); (2) at 12 months of age, fc between Vis-tDMN is significantly associated with both ritualistic/sameness and stereotyped behaviors (Figures 3,4,6); (3) at 24 months of age, tDMN-pFPC fc is significantly associated with both

stereotyped and restricted behaviors (Figures 2,3,6); (4) at 24 months of age, fc between tDMN-DAN is significantly associated with restricted behavior (Figure 2); and (5) at 24 months of age, fc between DAN-SubCtx is significantly associated with stereotyped behavior (Figure 3).

First, our results show that higher scores for restricted behavior—defined by a limited range of focus, interest, or activity—are associated with reduced anti-phase correlations (less negative fc) between the tDMN and the DAN, as well as more positive fc between tDMN-pFPC. Interactions between regions within the DAN, the default mode network (DMN), and the frontoparietal control (FPC) network, have been shown to shift connectivity and network affiliation in a dynamic, flexible, and adaptive manner to support specific task demands (45, 54–61). Increased exhibition of RRBs has been shown to be associated with task-evoked and resting-state fc patterns of networks including the DMN and central executive networks (corresponding to our FPC (45)). An anti-correlated relationship between the DAN and DMN is well documented in both task and resting-state fMRI studies in adults (62–64), with weaker anti-correlations predicting greater impairment in attention and inhibitory control (65), and providing a possible mechanism for limited cognitive flexibility. Further, resting-state anti-correlated patterns between DAN and DMN have been observed to emerge over the first year of life and become increasingly anti-correlated by 24 months (66). Our results add empirical support to the hypothesis that inverse functional relationships between DAN and DMN regions reflect healthy typical development, and that abnormal network dynamics between the tDMN, DAN, and pFPC may underlie rigid and repetitive behaviors and interests (45, 55, 66–69).

The stereotyped behavior factor, which includes apparently purposeless movements repeated in a similar manner, was associated with more positive fc between tDMN-pFPC and DAN-SubCtx at 24 months, as well as decreasing fc between Vis-tDMN at 12 months. The convergent findings between restricted and stereotyped behaviors (tDMN-pFPC) are consistent with factor analytic studies that grouped items from these two behaviors into a single factor (33, 34). Additionally, we observed that DAN connectivity with subcortical regions, primarily the putamen/lentiform nucleus and cerebellum, was uniquely associated with stereotyped behavior. These findings provide further empirical support for significant involvement of cortico-striatal-thalamo-cortical circuitry in stereotypies (70–72). Further, atypical recruitment and regulation of visual cortical regions and atypical visual attention have been linked with RRB symptomology (73–75) and abnormalities in the control of visual attention have been shown to persist throughout infancy in children who are later diagnosed with ASD (23, 76–78).

The ritualistic/sameness behavior factor, which contains items related to visual preference (e.g., likes same movie/scene played continuously), was associated with less positive fc between Vis-tDMN (79, 80) at 12 months, as well as between Vis-pFPC at both 12 and 24 months. Studies in older children have shown similar associations between greater ASD symptomology and reduced resting-state fc between the visual network and other large-scale functional networks including motor and salience networks (74, 81). Given previous studies that have linked RRBs to atypical sensory response patterns including hyper responsivity to sensory stimuli and sensory seeking behavior (9–11, 14), our findings support the hypothesis

that early disordered fc involving the visual network may engender later disruptions in higher order behaviors (82, 83).

The convergence at 12 months between stereotyped and ritualistic/sameness behaviors (Vis-tDMN) was unexpected, as different RBS-R factor schemes categorize these two behaviors as lower vs higher order, respectively (34, 84, 85). Although these behaviors show distinct developmental trajectories and outward manifestations, these are the two RBS-R factors that show the most robust associations with atypical sensory features (10, 11). The highly overlapping involvement of Vis-tDMN suggests that the two behavioral subcategories may share a common etiology.

Our convergent findings across RRB subcategories highlight connectivity between temporal regions of the infant DMN with Vis and pFPC networks. Of the 22 tDMN ROIs, 17 were located along either side of the superior temporal sulcus (STS; as were a number of implicated pFPC ROIs). Both Vis-tDMN and tDMN-pFPC included a subgroup of tDMN ROIs located in the right posterior STS (pSTS) and nearby temporal parietal junction region. The right pSTS has been implicated in social functions affected in ASD, including processing biological motion and eye gaze (86), as well as basic perceptual functions (e.g., audiovisual integration) (87–91) and the control of visual attention (92). Decreased activation of the STS during visuomotor learning in individuals with ASD has been linked to more severe RRBs (93). Thus, the observed RRB-fc relationships involving the STS, particularly right STS, by 12 months of age, support common neurophysiological bases for the development of atypical social and RRB behaviors and the presentation of ASD as a clinical syndrome. This overlap in neural substrates is also consistent with prior behavioral studies showing that both social and RRB features load onto a primary factor underlying the continuum of autistic traits (94).

Several limitations and future directions merit discussion. First, because we included participants with longitudinal and cross-sectional data in order to maximize sample size at each time point, cross-age comparisons involve some non-overlapping participants. Future studies utilizing exclusively longitudinal data to elucidate within-subject trajectories will be required to better understand how these networks instantiate behavior across development. Second, differences may exist between high- and low-risk groups both within and across age groups in brain-behavior relationships, and the network architecture underlying RRB subcategories may differ in children who develop ASD. However, our study was not designed or powered to address these questions; rather, this sample provided the range of behavior required to adequately elucidate the observed brain-RRB relationships. These behaviors are continuously distributed, and by capitalizing on the variance afforded by this mixed group we maximized our chances of identifying important relationships for this initial study of fcMRI correlates of RRBs in the first two years of life. This work sets the stage for future studies comparing brain-behavior relationships in larger age-specific, risk, and outcome sub-groups. Third, though our set of subcortical and cerebellar ROIs was not comprehensive, the functionally-defined ROIs in the current study are well vetted (41), and recent related work demonstrated the utility and validity of enrichment analyses using these ROIs as a novel method for analyzing brain-behavior relationships (43, 52). Fourth, our fcMRI processing included global signal regression (GSR), an established approach to

removing motion-induced artifacts from fcMRI data (50, 95). Recent studies have established that GSR in combination with volume censoring is superior to other denoising procedures for the removal of motion artifact (96), though a limitation of this approach is that current methods cannot rule out the concomitant removal of genuine neural signal. Given that motion-related artifacts present a major confound in fc analyses (47, 49, 95, 97), our approach conservatively accounted for motion-related artifacts to minimize the risk of spurious interpretations of fc-behavior relationships. Finally, differences between the infant/toddler and adult networks may be attributed to age-related development, but may also reflect methodological differences due to possible changes in functional network organization during sleep (98–100).

The implicated network pairs for RRB subcategories were different from those implicated for initiation of joint attention (43) and alsofor walking and gross motor behaviors (52). These non-overlapping findings support the specificity of the brain-behavior relationships revealed with our fcMRI enrichment approach. Future studies that systematically analyze the overlap between networks enriched for specific RRB subcategories and other early emerging behavioral features associated with ASD, particularly atypical sensory response patterns and motor development, could provide further insight into the complex relationship between dimensional aspects of behavior and underlying neurobiology in typical and atypical development. Comparing the trajectories of these early developmental brain-behavior relationships across different outcome groups would offer the potential for future identification of predictive biomarkers to aid in distinguishing typical and atypical early development. Furthermore, given the paucity of intervention practices targeted toward RRBs in ASD (101), changes in associated brain fc may be useful in tracking the efficacy of novel interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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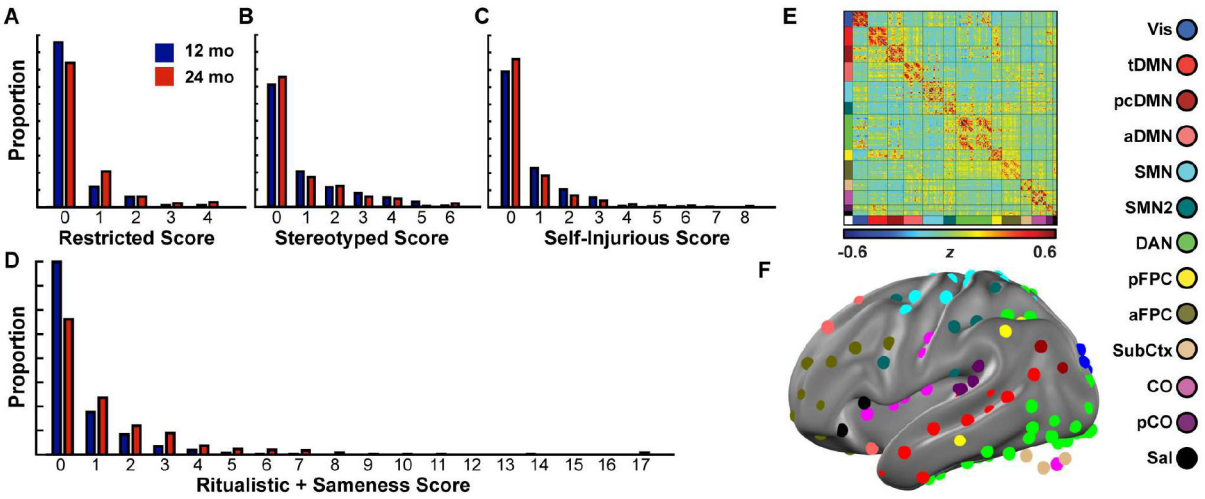

Figure 1. Restricted and repetitive behaviors and functional connectivity in infants

The number of items endorsed for each RBS-R factor at both 12 months old (mo; blue) and 24 mo (red): (A) the restricted behavior factor includes four items pertaining to limited range of focus, interest, or activity (e.g., preoccupation with part of object); (B) the stereotyped behavior factor includes six items relating to repeated, purposeless movements (e.g., arm flapping); (C) the self-injurious factor includes eight items relating to repeated actions that can cause injury to the body (e.g., hair pulling); (D) the ritualistic/sameness factor includes seventeen items relating to performing activities of daily living in a similar manner or resistance to change (e.g., arranging/ordering). Also see Supplemental Table S1. (E) An Infomap-sorted mean fcMRI matrix derived from the correlation structure between 230 functionally-defined regions of interest (ROIs). See Supplemental Figure S1. (F) Left lateral view of the ROIs on the brain surface, colored according to network assignment (see Materials and Methods for details and definition of network abbreviations). For clarity, ROIs in the cerebellum are displayed without the cerebellar structure.

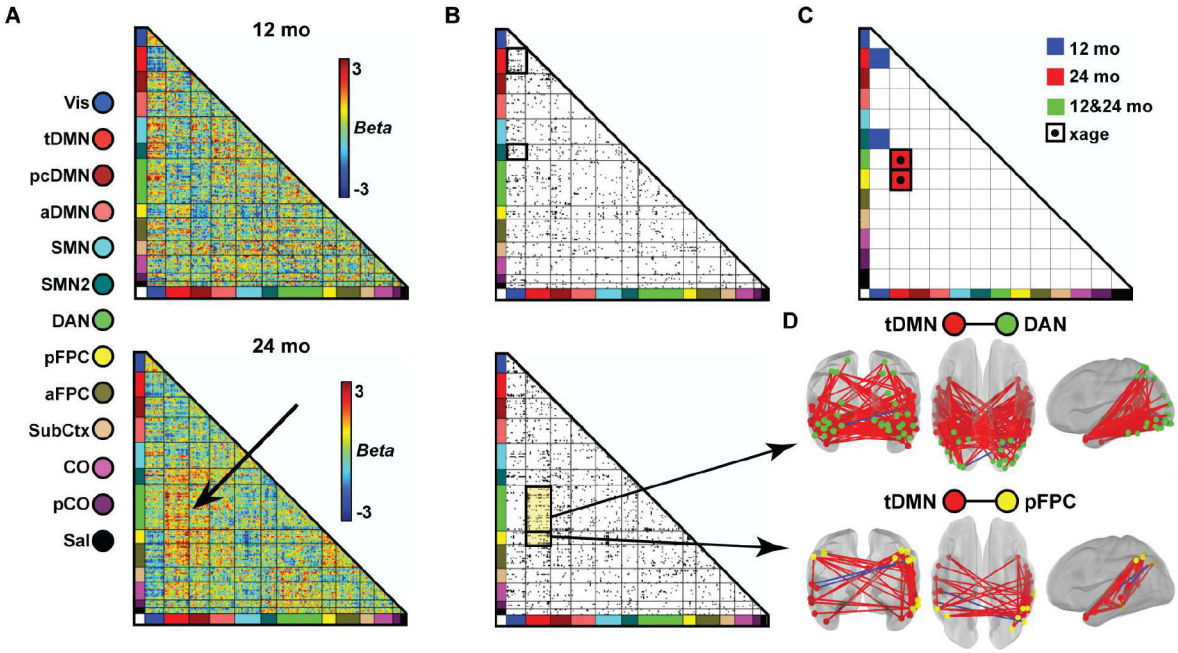

Figure 2. Connections showing a strong relationship to restricted behavior are concentrated in temporal default mode—dorsal attention and temporal default mode—posterior frontoparietal control network pairs at 24 months.

(A) Strong positive and negative brain-behavior relationships cluster by sign, within a subset of network blocks (note the visually striking red clustering at 24 mo but not at 12 mo indicated by the arrow). (B) Functional connections showing a strong relationship to restricted behavior are defined as those with $p \leq 0.05$. Quantifying the level of clustering with enrichment analyses (see Materials and Methods and Supplemental Figure S2) reveals that strong brain-behavior relationships are constrained to a minority of network pairs that differ across age (enriched network pairs outlined in black). (C) Only two functional network pairs significantly enriched at either age (■ 12 mo; ■ 24 mo) also exhibit significant differences across age groups (• ; tested via McNemar χ^2): tDMN-DAN and tDMN-pFPC, (see Supplemental Table S3). (D) For each primary result, ROI pairs contributing to enrichment are visualized on a surface representation of the cortex. Ball color denotes functional network membership and line color joining ROI pairs denotes the sign of brain-behavior relationship (red-positive; blue-negative). The signs of brain-behavior relationships are largely consistent within network pairs. See Supplemental Figure S2 for more detailed analysis of the fc underlying these brain-behavior relationships.

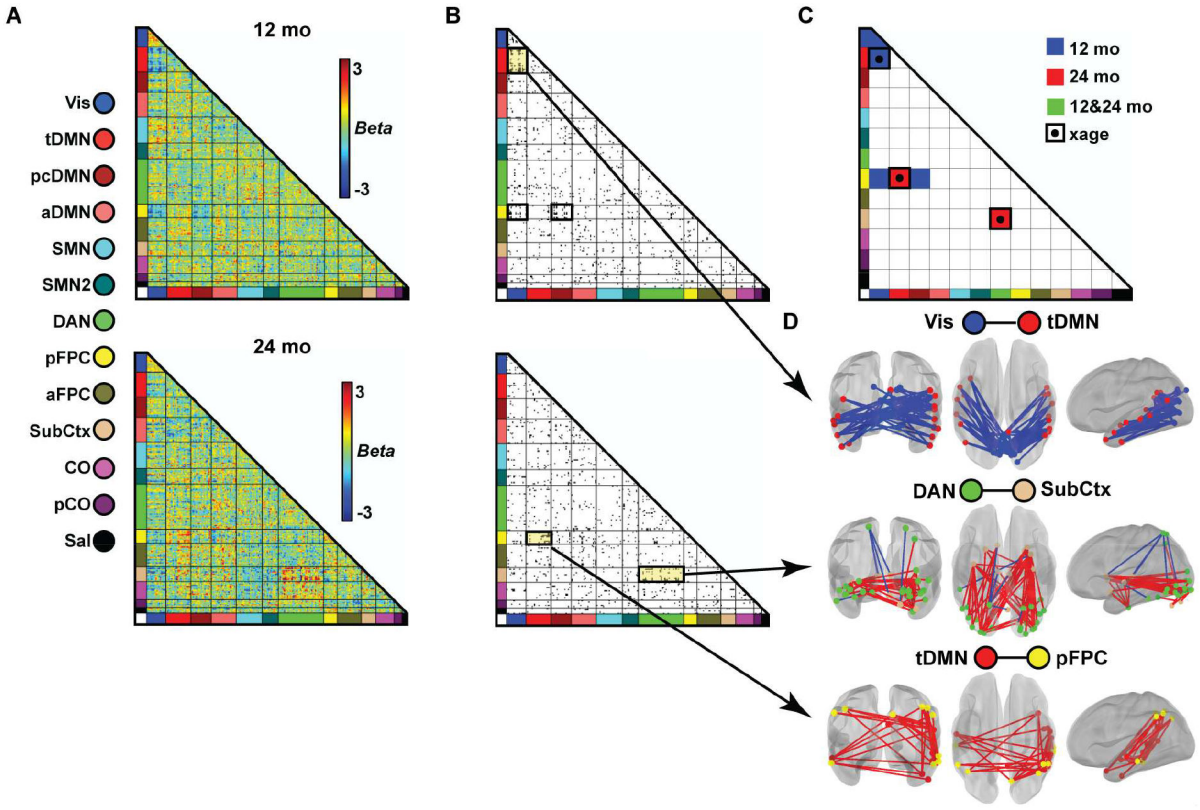

Figure 3. Strong fc-stereotyped relationships cluster within temporal default mode—visual network connections at 12 months and dorsal attention—subcortex and temporal default mode—posterior frontoparietal control network connections at 24 months.

Analyses are as outlined in Figure 2. (A) Negative binomial regression based relationships between fc and stereotyped behavior scores. (B) Significant clustering of strong brain-behavior associations ($p \leq 0.05$) is restricted to a subset of network pairs (outlined in black). (C) Primary findings include tDMN-Vis enrichment at 12 mo (but not 24 mo) and DAN-SubCtx and tDMN-pFPC enrichment at 24 mo (but not 12 mo;). See Supplemental Figure S3 for enrichment and McNemar (age group comparison) analyses. See Supplemental Table S3 for statistics. (D) At 12 mo, the Vis-tDMN network pair showed primarily negative fc-stereotyped relationships while at 24 mo both network pairs showed primarily positive fc-stereotyped relationships. See Supplemental Figure S3 for more detailed analysis of the fc underlying these brain-behavior relationships.

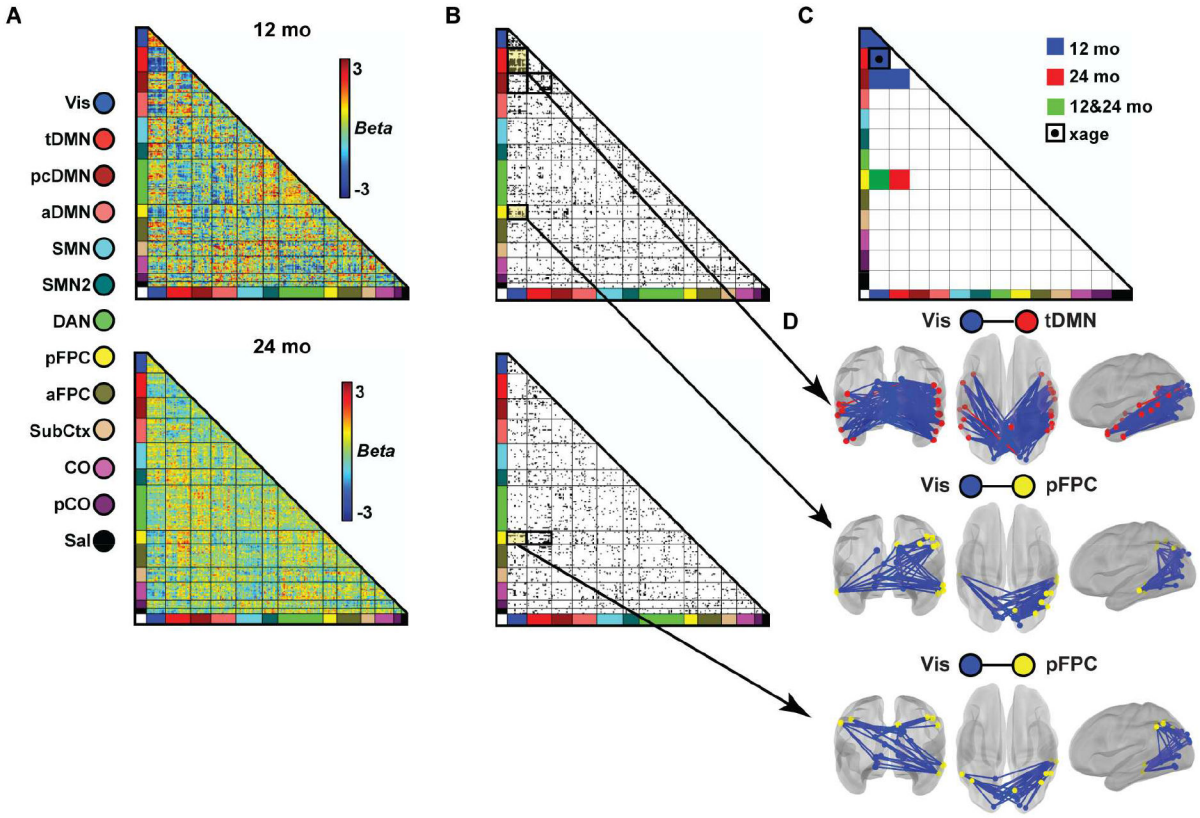

Figure 4. Strong fc-ritualistic/sameness relationships cluster within visual-temporal default mode network connections at 12 months and visual—posterior frontoparietal control network connections at 12 and 24 months. Analyses follow those outlined in Figure 2.

(A)Note the particularly visually striking cluster of negative fc-ritualistic/sameness behavior relationships in the Vis-tDMN network pair at 12 mo. (B) Significant clustering of strong brain-behavior associations ($p \leq 0.05$) is restricted to a subset of network pairs. (C) Primary findings included tDMN-Vis enrichment at 12 mo (but not 24 mo; indicated with dot in a blue box) and Vis-pFPC pair enrichment at both 12 mo and 24 mo (indicated with a green box). See Supplemental Figure S4 for McNemar (age group differences) analysis and Supplemental Table S3 for statistics. (D) Both Vis-tDMN (at 12 mo) and Vis-pFPC (at 12 mo and 24 mo) showed primarily negative fc-stereotyped relationships: higher ritualistic and sameness scores are associated with less positive fc between Vis and both tDMN and pFPC. See Supplemental Figure S4 for more detailed analysis of the fc underlying these brain-behavior relationships.

RRB / fc	Enriched Network Pair	Sign fc-RRB	Ritual/ Sameness	Stereotyped	Restricted
	Vis – pFPC	↓	12 24		
	Vis – tDMN	↓	12	12	
	DAN – SubCtx	↑		24	
	tDMN – pFPC	↑		24	24
	tDMN – DAN	↑			24

Figure 5. Global patterns of RRB-fc relationships across age and behavior.

The first column depicts the nature of the brain-behavior relationship, that is, whether the relationship is positive or negative and whether it spans primarily positive or negative fc values. The second column contains the network pair in question. The third column emphasizes whether greater behavior scores were associated with increasing or decreasing fc between the network pair. The last three columns catalogue implicated behavior and time point combinations for the given network pairs. See Supplemental Figure S5 for more detailed analysis of the self-injurious RBS-R subcategory. See Supplemental Figure S6 for the global RRB-fc relationships as derived using adult-based functional networks.

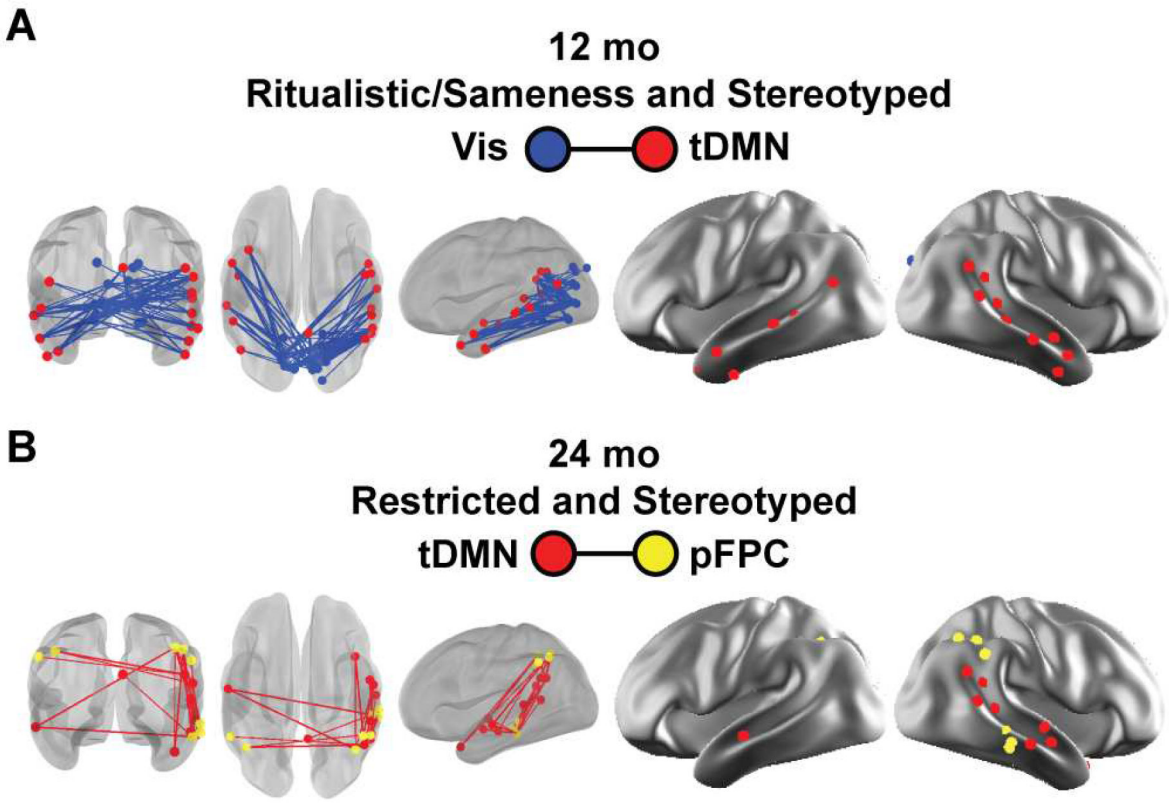

Figure 6. ROIs contributing to enrichment across behavior factors.

Analyses revealed two network pairs, one at 12 mo and one at 24 mo, implicated with multiple behaviors. (A) Functional connections between Vis and tDMN that showed a strong relationship to both stereotyped and ritualistic/sameness behavior at 12 mo. (B) Functional connections between the pFPC-tDMN that showed a strong relationship to both restricted and stereotyped behavior at 24 mo are visualized on the brain. As above, the color of the ROI denotes the functional network, and the color of the connecting bar denotes the sign of the brain-behavior relationship.

Table 1.

Demographics

	12-month age group	24-month age group	Number participants with data available at both time points (n)
Sample size with			
RBS-R	467	379	327
Low motion fcMRI	135	107	48
Both[a]	118	87	38
Outcome group[a]			
LR−	31	20	12
HR−	76	56	24
HR+	11	11	2
Number of Males[a]	74	50	22
Age in months[a]	12.5 (0.5)	24.6 (0.6)	-
Mean Mullen Early Learning Composite score (SD)[a]	98.0(18.2)	99.8(20.8)	-
Mean RBS-R score (SD)[a]			-
Restricted	0.3 (0.8)	0.4 (0.9)	-
Stereotyped	0.6(1.2)	0.7 (1.3)	-
Ritualistic + Sameness	0.6 (1.6)	1.4 (1.9)	-
Self-Injurious	0.4 (0.8)	0.5 (1.1)	-

[a]Numbers reflect the group of participants providing both RBS-R and low motion fcMRI data

RBS-R: Repetitive Behavior Scale-Revised

fcMRI: functional connectivity: Magnetic Resonance Imaging

LR−: Low-risk, negative ASD diagnosis

HR−: High-risk, negative ASD diagnosis

HR+: High-risk, positive ASD diagnosis

SD: Standard deviation