

Restricted and Repetitive Behavior and Brain Functional Connectivity in Infants at Risk for Developing Autism Spectrum Disorder

Claire J. McKinnon, Adam T. Eggebrecht, Alexandre Todorov, Jason J. Wolff, Jed T. Ellison, Chloe M. Adams, Abraham Z. Snyder, Annette M. Estes, Lonnie Zwaigenbaum, Kelly N. Botteron, Robert C. McKinstry, Natasha Marrus, Alan Evans, Heather C. Hazlett, Stephen R. Dager, Sarah J. Paterson, Juhi Pandey, Robert T. Schultz, Martin A. Styner, Guido Gerig, Bradley L. Schlaggar, Steven E. Petersen, Joseph Piven, and John R. Pruett Jr., for the IBIS Network

ABSTRACT

BACKGROUND: Restricted and repetitive behaviors (RRBs), detectable by 12 months in many infants in whom autism spectrum disorder (ASD) is later diagnosed, 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 24 months ($n = 38$ at both time points). Twenty infants met criteria for ASD at 24 months. We divided RRBs into four 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 months. Ritualistic/sameness and stereotyped behaviors were associated with less positive fc between visual and default mode networks at 12 months. At 24 months, stereotyped and restricted behaviors were associated with more positive fc between default mode and control networks. Additionally, at 24 months, stereotyped behavior was associated with more positive fc between dorsal attention and subcortical networks, whereas 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.

CONCLUSIONS: 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, Functional connectivity, Functional magnetic resonance imaging, Infant, Restricted and repetitive behavior

<https://doi.org/10.1016/j.bpsc.2018.09.008>

In the first 2 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 constitute some of the earliest emerging behavioral manifestations of autism spectrum disorder (ASD) and are observed as early as 12 months of age in infants in whom ASD is later diagnosed (1–4). Along with deficits in social communication and interaction, RRBs constitute 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

RRBs and Brain fc in Infants at Risk for Developing ASD

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 magnetic resonance imaging (MRI) 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.

In the present study, we aimed to characterize the relationship between subcategories of RRBs and 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, given that 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 (DMN), the frontoparietal control network (FPC), the salience network, and striatal regions of the subcortical network (38,45)—networks previously implicated with RRBs in studies in older participants, and 2) RBS-R subcategories previously combined into an alternative behavioral category (33,34) would be associated with overlapping patterns of functional network pairs.

METHODS AND MATERIALS

Participants

Participants were recruited as part of an ongoing, multisite, Autism Centers of Excellence Network study, the Infant Brain Imaging Study, which has collected a large infant sibling sample with prospective brain and 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, 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 no first-degree 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 control subjects (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 Infant Brain Imaging Study behavioral and structural MRI inclusion criteria (21) (see Supplement for details). Age groups did

Table 1. Demographics

	12-Month Age Group	24-Month Age Group	No. of Participants With Data Available at Both Time Points
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 Boys ^a	74	50	22
Age in Months, Mean (SD) ^a	12.5 (0.5)	24.6 (0.6)	–
Mullen Early Learning Composite Score, Mean (SD) ^a	98.0 (18.2)	99.8 (20.8)	–
RBS-R Score, Mean (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)	–

fcMRI, functional connectivity magnetic resonance imaging; HR–, high-risk, negative autism spectrum disorder diagnosis; HR+, high-risk, positive autism spectrum disorder diagnosis; LR–, low-risk, negative autism spectrum disorder diagnosis; RBS-R, Repetitive Behavior Scale-Revised.

^aNumbers reflect the group of participants providing both RBS-R and low motion fcMRI data.

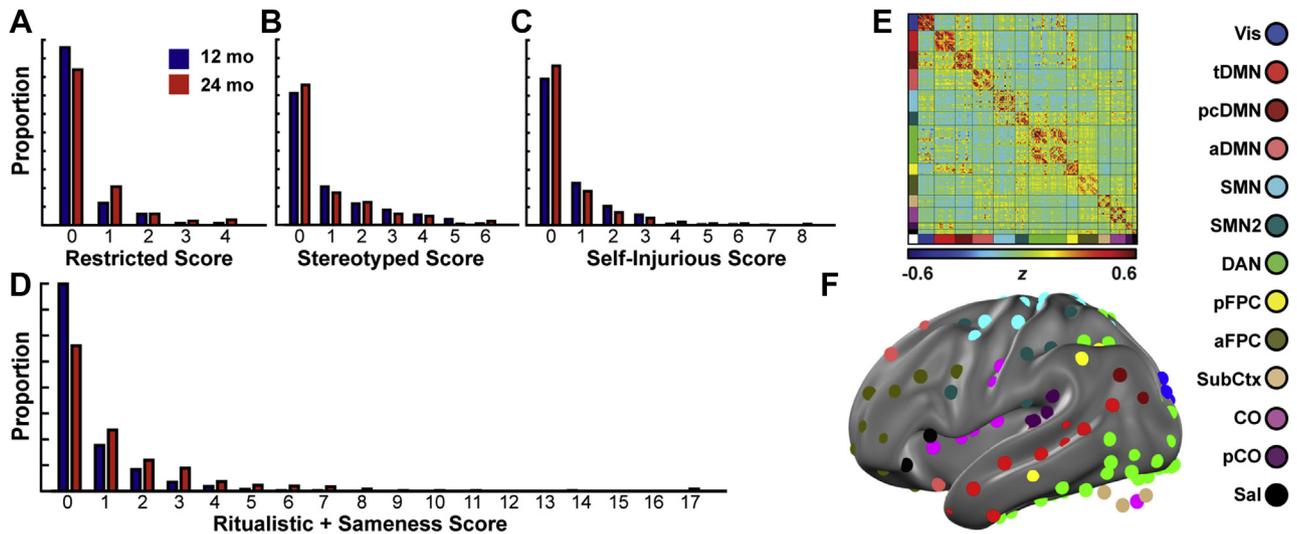


Figure 1. Restricted and repetitive behaviors and functional connectivity in infants. The number of items endorsed for each Repetitive Behavior Scale-Revised factor at both 12 months of age (blue) and 24 months of age (red). **(A)** The restricted behavior factor includes four items pertaining to limited 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 17 items relating to performing activities of daily living in a similar manner or resistance to change (e.g., arranging/ordering). See [Supplemental Table S1](#). **(E)** An Infomap-sorted mean functional connectivity magnetic resonance imaging matrix derived from the correlation structure between 230 functionally defined regions of interest. See [Supplemental Figure S1](#). **(F)** Left lateral view of the regions of interest on the brain surface, colored according to network assignment (see Methods and Materials for details). For clarity, regions of interest in the cerebellum are displayed without the cerebellar structure. aDMN, anterior default mode network; aFPC, anterior frontoparietal control network; CO, cingulo-opercular; DAN, dorsal attention network; pcDMN, posterior cingulate default mode network; pCO, posterior cingulo-opercular; pFPC, posterior frontoparietal control network; Sal, salience; SMN, somatomotor network; SMN2, somatomotor network 2; SubCtx, subcortex; tDMN, temporal default mode network; Vis, visual.

not significantly differ by proportion of children in whom ASD was later diagnosed (Fisher's exact test, $p = .36$), HR participants ($p = 1.0$), girls ($p = .47$), or cognitive development (Mullen composite standard score, Welch's t test, $p = .24$).

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 in 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 present study (4). This 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 Siemens MAGNETOM Tim Trio (Siemens Medical Solutions, Malvern, PA)

3T MRI scanners, each equipped with standard 12-channel head coils. All infants were scanned during natural sleep (43). Each of two to three acquisitions comprised 130 temporally contiguous frames spanning 5.4 minutes. See the Supplement for details.

Functional MRI Preprocessing and Fidelity Optimization

Data were preprocessed to reduce artifacts (i.e., blood oxygen level-dependent 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 fc, 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 [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 frame-to-frame displacement ≥ 0.2 mm were marked for censoring. See 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 voxelwise 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 included only for bandpass filtering and did not factor into correlation values. Finally, the data were spatially smoothed using a Gaussian kernel (6 mm full width at half maximum isotropic).

Definition of Regions of Interest and fc Computation

The derivation of 230 regions of interest (ROIs) for studies on this population was previously described (Supplemental Figure S1) (41,43). ROI-specific time courses were calculated by averaging the time courses of all voxels contained within 10-mm-diameter spheres. The fc values were calculated as the pairwise zero-lag Pearson correlation between each of the 26,335 pairs of ROI time courses 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 48 children with clean fcMRI data at both 12 and 24 months of age (see Supplement for details) (43). This model of the combined infant and toddler functional brain networks included 13 putative networks with naming informed by published adult networks (47): visual network (Vis), temporal DMN (tDMN), posterior cingulate DMN (pcDMN), anterior DMN, somatomotor network, somatomotor network 2, dorsal attention network (DAN), posterior FPC (pFPC), anterior FPC, subcortex (SubCtx), cingulo-opercular, posterior cingulo-opercular, and salience (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 Infant Brain Imaging Study sample of participants who contributed behavioral data ($n = 467$ at 12 months, $n = 379$ at 24 months; $n = 327$ had data at both time points) with the Wilcoxon signed rank test (α level of .0125 reflecting Bonferroni correction for the four behaviors tested). Using the matched fcMRI and 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 1A–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 $p \leq .05$, 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 (see Supplement for details) (43). A McNemar test was performed to determine whether patterns of brain-behavior relationships significantly differed between the 12-month and 24-month groups. Stringent, brain-wide empirical significance levels—reflecting the 1.25% false-positive rate—were determined using randomization (43). An α of .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 months ($n = 118$) 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, $p = .77$; stereotyped, $p = .72$; self-injurious, $p = .61$), whereas ritualistic/sameness behavior showed a significant age-related increase ($p = 1.8 \times 10^{-4}$) consistent with previous findings (4).

Restricted Behavior Associations With fc

The primary findings in relation to restricted behavior include only two of the possible 91 total network pairs: tDMN-DAN and tDMN-pFPC at 24 months (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 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 observed at 12 months: negative fc-restricted relationships in Vis-tDMN

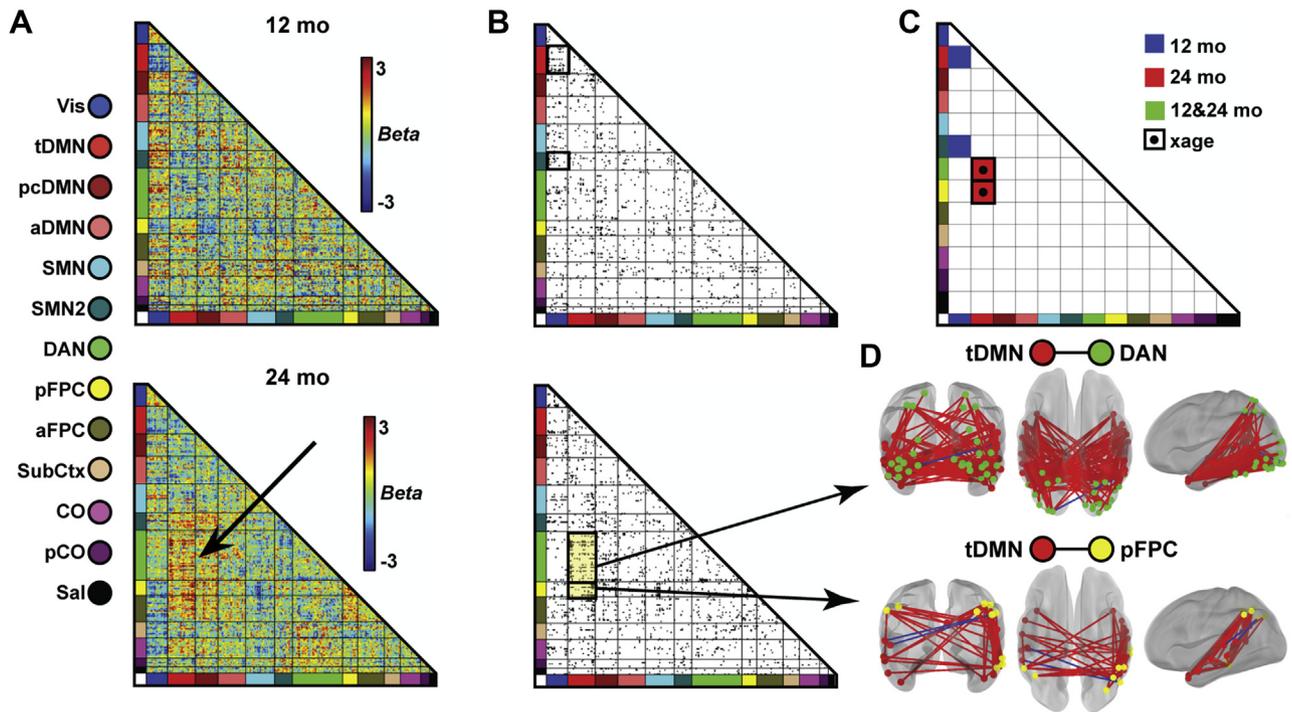


Figure 2. Connections showing a strong relationship to restricted behavior are concentrated in temporal default mode–dorsal attention network (tDMN–DAN) and temporal default mode–posterior frontoparietal control network (tDMN–pFPC) pairs at 24 months. **(A)** Strong positive and negative brain-behavior relationships cluster by sign, within a subset of network blocks (note the visually striking red clustering at 24 months but not at 12 months indicated by the arrow). **(B)** Functional connections showing a strong relationship to restricted behavior are defined as those with $p \leq .05$. Quantifying the level of clustering with enrichment analyses (see Methods and Materials 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 (blue box, 12 months; red box, 24 months) also exhibit significant differences across age groups (black circle; tested via McNemar χ^2): tDMN–DAN and tDMN–pFPC (see Supplemental Table S3). **(D)** For each primary result, region of interest pairs contributing to enrichment are visualized on a surface representation of the cortex. Ball color denotes functional network membership, and line color joining region of interest 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 functional connectivity underlying these brain-behavior relationships. aDMN, anterior default mode network; aFPC, anterior frontoparietal control network; CO, cingulo-opercular; pcDMN, posterior cingulate default mode network; pCO, posterior cingulo-opercular; Sal, salience; SMN, somato-motor network; SMN2, somatomotor network 2; SubCtx, subcortex; Vis, visual.

and positive fc–restricted relationships in Vis–somatomotor network 2.

Stereotyped Behavior Associations With fc

Primary findings include three network pairs: Vis–tDMN at 12 months, DAN–SubCtx at 24 months, 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 within tDMN–pFPC and DAN–SubCtx (Figure 3). Of tDMN–pFPC connections contributing enrichment, 83% showed primarily positive fc values, whereas 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 (Montreal Neurological Institute 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 Vis–Vis and negative fc–stereotyped relationships within Vis–pFPC and pcDMN–pFPC (Figure 3B).

Ritualistic/Sameness Behavior Associations With fc

Primary findings include higher ritualistic/sameness scores associated with less positive fc within Vis–tDMN at 12 months (with 82% of connections showing primarily negative fc) (Figure 4; Supplemental Figure S4) as well as less positive fc within Vis–pFPC at both 12 months 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 of 55) of connections at 12 months and 23% (9 of 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 within tDMN–pFPC at 24 months (Figure 4).

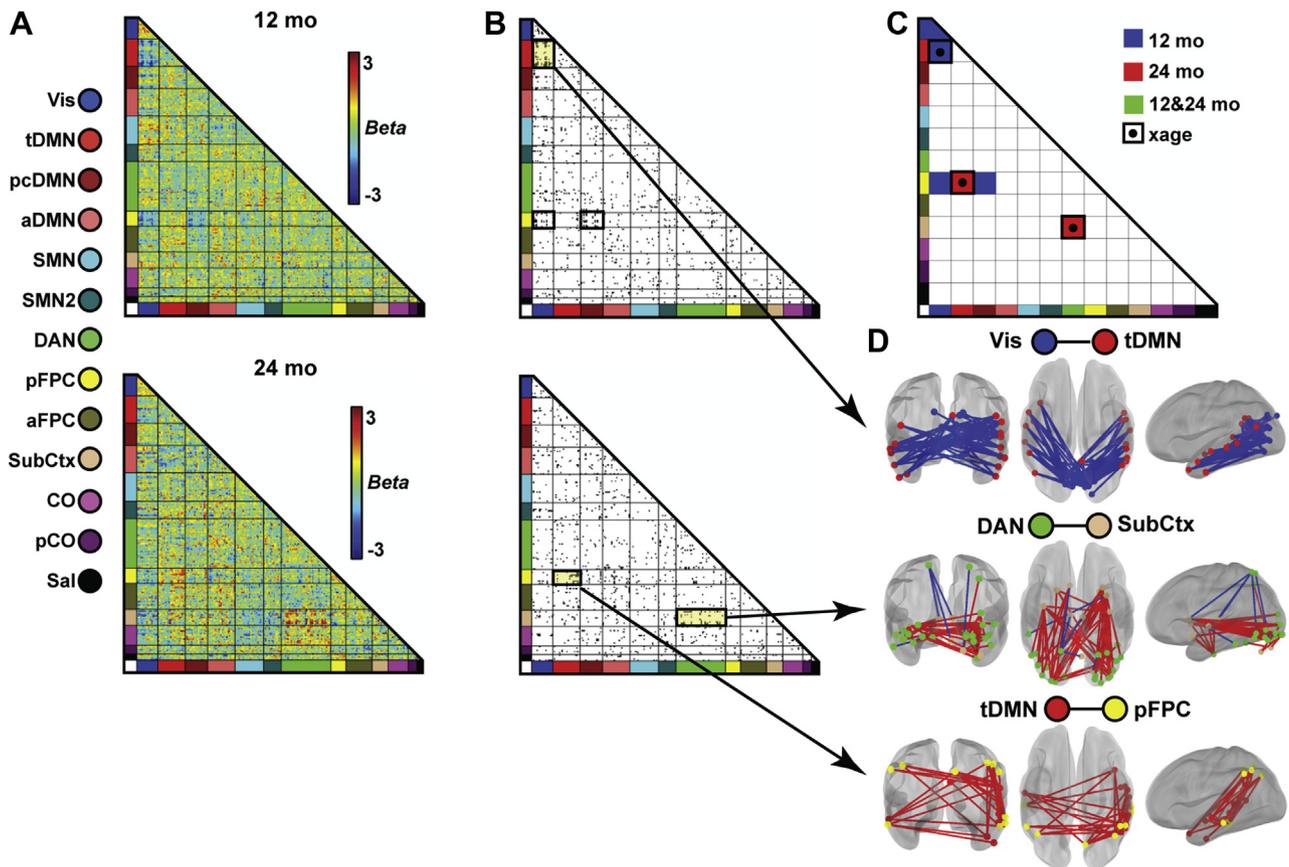


Figure 3. Strong functional connectivity (fc)–stereotyped relationships cluster within temporal default mode–visual network (tDMN–Vis) connections at 12 months and dorsal attention–subcortex (DAN–SubCtx) and temporal default mode–posterior frontoparietal control network (tDMN–pFPC) connections at 24 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 ($p \leq .05$) is restricted to a subset of network pairs (outlined in black). **(C)** Primary findings include tDMN–Vis enrichment at 12 months (but not 24 months) and DAN–SubCtx and tDMN–pFPC enrichment at 24 months (but not 12 months). See Supplemental Figure S3 for enrichment and McNemar (age group comparison) analyses. See Supplemental Table S3 for statistics. **(D)** At 12 months, the Vis–tDMN network pair showed primarily negative fc–stereotyped relationships, whereas at 24 months, 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. aDMN, anterior default mode network; aFPC, anterior frontoparietal control network; CO, cingulo–opercular; pcDMN, posterior cingulate default mode network; pCO, posterior cingulo–opercular; Sal, salience; SMN, somatomotor network; SMN2, somatomotor network 2.

Self-injurious Behavior Associations With fc

No primary-level findings were observed for fc–self-injurious behavior 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 tDMN–pFPC was associated with both stereotyped and restricted behaviors at 24 months (see 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 the following: 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, Vis–tDMN fc is significantly associated with both ritualistic/sameness and stereotyped behaviors (Figures 3, 4, and 6); 3) at 24 months of age, tDMN–pFPC fc is significantly associated with both stereotyped and restricted behaviors (Figures 2, 3, and 6); 4) at 24 months of age, tDMN–DAN fc is significantly associated with restricted behavior (Figure 2); and 5) at 24 months of age, DAN–SubCtx fc is significantly associated with stereotyped behavior (Figure 3).

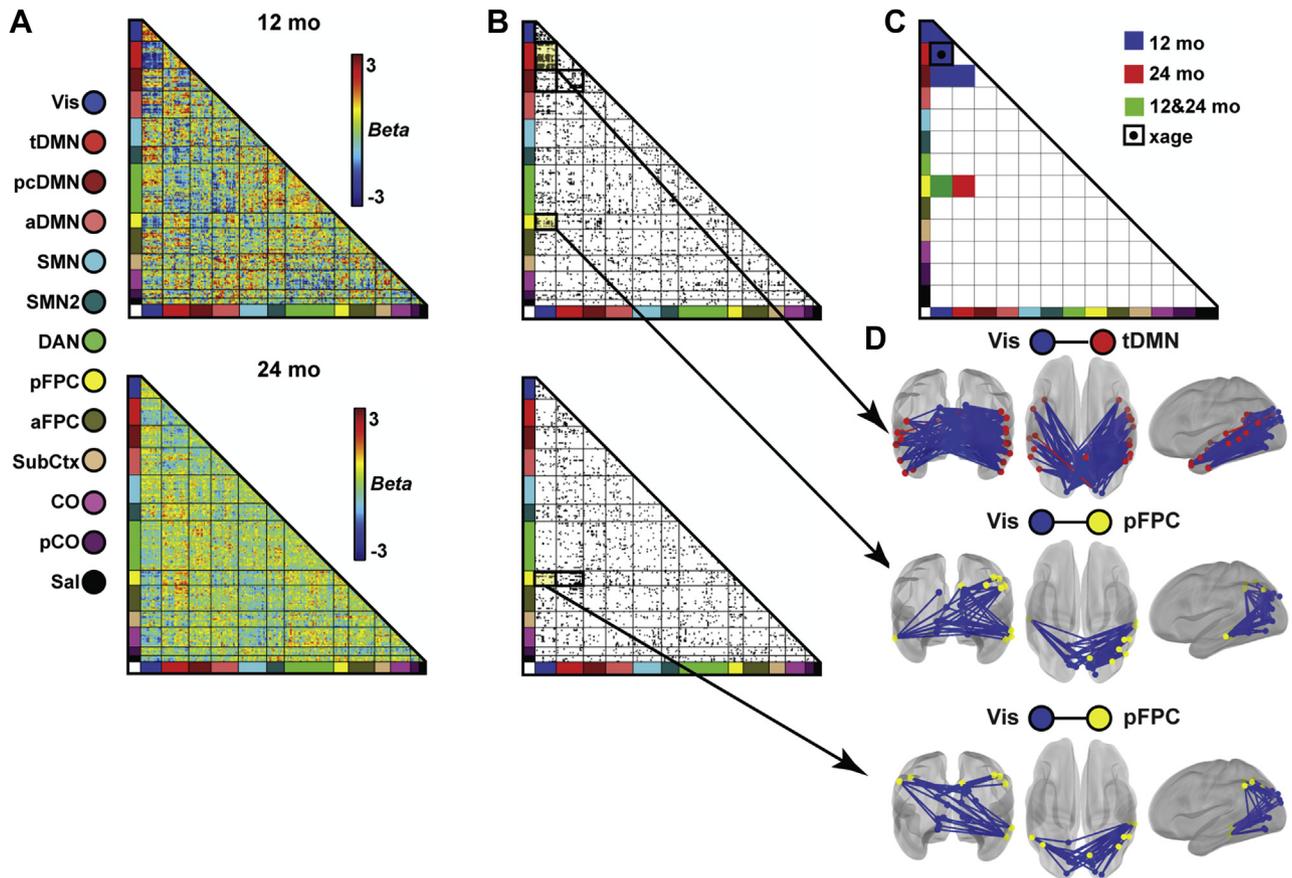


Figure 4. Strong functional connectivity (fc)–ritualistic/sameness relationships cluster within visual–temporal default mode network (Vis–tDMN) connections at 12 months and visual–posterior frontoparietal control network (Vis–pFPC) connections at 12 and 24 months. Analyses follow those outlined in Figure 2. **(A)** Note the particularly visually striking cluster of negative fc–ritualistic/sameness behavior relationships in the Vis–tDMN network pair at 12 months. **(B)** Significant clustering of strong brain–behavior associations ($p \leq .05$) is restricted to a subset of network pairs. **(C)** Primary findings included tDMN–Vis enrichment at 12 months but not 24 months (indicated with dot in a blue box) and Vis–pFPC pair enrichment at both 12 months and 24 months (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 months) and Vis–pFPC (at 12 and 24 months) 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. aDMN, anterior default mode network; aFPC, anterior frontoparietal control network; CO, cingulo–opercular; DAN, dorsal attention network; pcDMN, posterior cingulate default mode network; pCO, posterior cingulo–opercular; Sal, salience; SMN, somatomotor network; SMN2, somatomotor network 2; SubCtx, subcortex.

First, our results show that higher scores for restricted behavior—defined by a limited range of focus, interest, or activity—are associated with reduced antiphase correlations (less negative fc) between tDMN and DAN as well as more positive fc between tDMN and pFPC. Interactions between regions within DAN, DMN, and FPC 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 DMN and central executive networks [corresponding to our FPC (45)]. An anticorrelated relationship between DAN and DMN is well documented in both task and resting-state functional MRI studies in adults (62–64), with weaker anticorrelations predicting greater impairment in attention and inhibitory control (65) and providing a possible mechanism for limited cognitive flexibility. Further, resting-

state anticorrelated patterns between DAN and DMN have been observed to emerge over the first year of life and become increasingly anticorrelated by 24 months of age (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 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 within tDMN–pFPC and DAN–SubCtx at 24 months as well as less positive fc within 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,

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

posterior frontoparietal control network; SubCtx, subcortex; tDMN, temporal default mode network; Vis, visual.

primarily the putamen/lentiform nucleus and cerebellum, was uniquely associated with stereotyped behavior. These findings provide further empirical support for significant involvement of corticostriatal-thalamocortical circuitry in stereotypies (70–72). Further, atypical recruitment and regulation of visual cortical regions and atypical visual attention have been linked with RRB symptoms (73–75), and abnormalities in the control of visual attention have been shown to persist throughout infancy in children in whom ASD is later diagnosed (23,76–80).

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 within Vis-tDMN at 12 months as well as within Vis-pFPC at both 12 months and 24 months. Studies in older children have shown similar associations between greater ASD symptoms and reduced resting-state fc between the visual network and other large-scale functional networks, including motor and salience networks (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 order versus higher order (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. Of the 22 tDMN ROIs, 17 were located

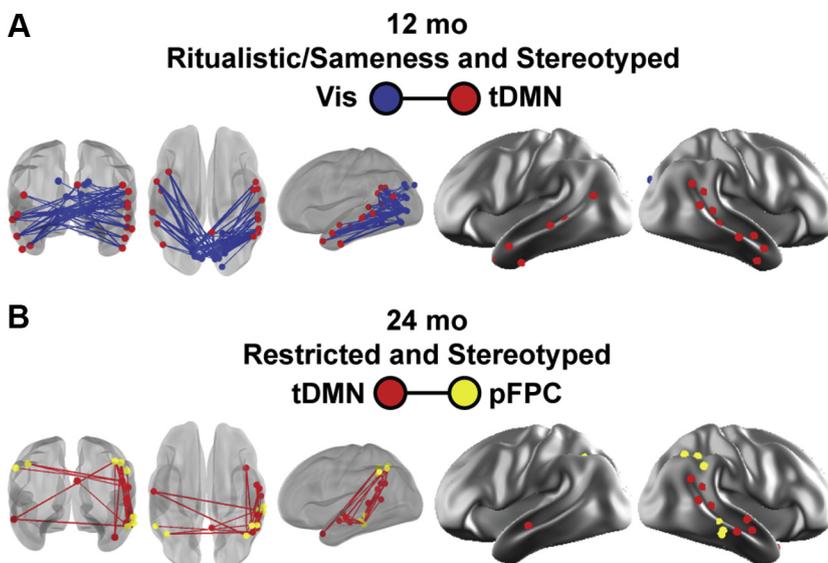


Figure 6. Regions of interest contributing to enrichment across behavior factors. Analyses revealed two network pairs, one at 12 months and one at 24 months, implicated with multiple behaviors. **(A)** Functional connections between visual (Vis) and temporal default mode network (tDMN) that showed a strong relationship to both stereotyped and ritualistic/sameness behavior at 12 months are visualized on the brain. **(B)** Functional connections between posterior frontoparietal control network (pFPC) and tDMN that showed a strong relationship to both restricted and stereotyped behavior at 24 months are visualized on the brain. The color of the region of interest denotes the functional network, and the color of the connecting bar denotes the sign of the brain-behavior relationship.

along each 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 and nearby temporal parietal junction region. The right posterior STS 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 to maximize sample size at each time point, cross-age comparisons involve some nonoverlapping 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-risk 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 2 years of life. This work sets the stage for future studies comparing brain-behavior relationships in larger age-specific, risk, and outcome subgroups. 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, an established approach to removing motion-induced artifacts from fcMRI data (50,95). Recent studies have established that global signal regression 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 owing 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) as well as for walking and gross motor behaviors (52). These nonoverlapping 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.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institutes of Health (Grant No. K01 MH103594 [to ATE], Grant No. R01 MH093510 [to JRP], Grant No. K01 MH101653 [to JJW], and Grant No. P30 NS098577 [to AZS]), National Institutes of Health Autism Centers of Excellence Network (Grant No. R01 HD055741 [to JPI]), Autism Speaks (Grant No. 6020 [to JPI]), Simons Foundation (Grant No. 140209 [to JPI]), U54 Intellectual and Developmental Disabilities Research Centers (Grant No. HD079124 to University of North Carolina [to JPI], Grant No. HD087011 to Washington University [to J. Constantino and BLS], Grant No. HD086984 to Children's Hospital of Philadelphia [to RTS], and Grant No. HD083091 to University of Washington [to AME]), and the McDonnell Center for Systems Neuroscience. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The Infant Brain Imaging Study (IBIS) Network is a National Institutes of Health-funded Autism Centers of Excellence project and consists of a consortium of eight universities in the United States and Canada. Clinical Sites: University of North Carolina (JPI [IBIS Network principal investigator], HCH, C. Chappell), University of Washington (SRD, AME, D. Shaw), Washington University (KNB, RCM, J. Constantino, JRP), Children's Hospital of Philadelphia (RTS, JPa), University of Alberta (LZ), and University of Minnesota (JTE); Data Coordinating Center: Montreal Neurological Institute (AE, D.L. Collins, G.B. Pike, V. Fonov, P. Kostopoulos, S. Das); Image Processing Core: New York University (GG) and University of North Carolina (MAS); Statistical Analysis Core: University of North Carolina (H. Gu).

JRP, JJW, JTE, and JPI were responsible for conceptualization. JTE, JJW, AME, LZ, CMA, AZS, KNB, MAS, and GG were responsible for data curation. CJM, ATE, and AT were responsible for formal analysis. CJM, ATE, JJW, JTE, AT, and JRP were responsible for investigation. CJM, ATE, SEP, AT, JRP, and BLS were responsible for methodology. JRP, JTE, JPI, KNB, LZ, AE, HCH, SJP, RTS, AME, and MAS were responsible for project administration. KNB, AE, HCH, SJP, RTS, JPI, and JRP were responsible for resources. CJM, ATE, AT, and JRP were responsible for software. KNB, AE, HCH, SJP, RTS, JPI, SEP, and JRP were responsible for supervision. CJM and ATE were responsible for visualization. CJM, ATE, JTE, JRP were responsible for writing original draft. CJM, ATE, JTE, AT, JJW, CMA, AME, LZ, KNB, RCM, NM, HCH, SJP, JPa, RTS, MAS, GG, BLS, SEP, JPI, and JRP were responsible for writing review and editing. JPI, JRP, ATE, and JJW were responsible for funding acquisition.

We thank the families and children for their time and participation. We thank Sarah Hoertel for key early analyses and for her help with guiding the brain-behavior analysis strategy, and we thank Leigh MacIntyre for managing the full Infant Brain Imaging Study database.

RRBs and Brain fc in Infants at Risk for Developing ASD

RCM receives acting, modeling, and speaking fees from Siemens Healthcare. AE is a founder and a member of the Board of Directors of Biospective Inc. All other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Departments of Psychiatry (CJM, AT, CMA, KNB, NM, BLS, JRP) and Neurology (BLS, SEP) and Mallinckrodt Institute of Radiology (ATE, AZS, KNB, RCM, BLS, SEP), Washington University School of Medicine; Departments of Psychological and Brain Sciences (SEP) and Biomedical Engineering (SEP), Washington University in St. Louis, St. Louis, Missouri; Biological Sciences Division (CJM), University of Chicago, Chicago, Illinois; Department of Educational Psychology (JJW) and Institute of Child Development (JTE), University of Minnesota, Minneapolis, Minnesota; Departments of Speech and Hearing Sciences (AME) and Radiology and Bioengineering (SRD), University of Washington, Seattle, Washington; Department of Pediatrics (LZ), University of Alberta, Edmonton, Alberta; McConnell Brain Imaging Center (AE), Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada; The Carolina Institute for Developmental Disabilities (HCH, MAS, JPI), University of North Carolina at Chapel Hill, Carboro, North Carolina; Department of Psychology (SJP), Temple University; Center for Autism Research (JPa, RTS), Children's Hospital of Philadelphia; Department of Psychiatry (JPa, RTS), University of Pennsylvania, Philadelphia, Pennsylvania; and Tandon School of Engineering (GG), New York University, Brooklyn, New York.

CJM and ATE contributed equally to this work as joint first authors.

JPI and JRP contributed equally to this work as joint senior authors.

Address correspondence to Claire J. McKinnon, B.A., Biological Sciences Division, University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637; E-mail: cmckinnon@uchicago.edu.

Received Aug 2, 2018; accepted Sep 1, 2018.

Supplementary material cited in this article is available online at <https://doi.org/10.1016/j.bpsc.2018.09.008>.

REFERENCES

- Ozonoff S, Macari S, Young GS, Goldring S, Thompson M, Rogers SJ (2008): Atypical object exploration at 12 months of age is associated with autism in a prospective sample. *Autism* 12:457–472.
- Kim SH, Lord C (2010): Restricted and repetitive behaviors in toddlers and preschoolers with autism spectrum disorders based on the Autism Diagnostic Observation Schedule (ADOS). *Autism Res* 3:162–173.
- Elison JT, Wolff JJ, Reznick JS, Botteron KN, Estes AM, Gu H, *et al.* (2014): Repetitive behavior in 12-month-olds later classified with autism spectrum disorder. *J Am Acad Child Adolesc Psychiatry* 53:1216–1224.
- Wolff JJ, Botteron KN, Dager SR, Elison JT, Estes AM, Gu H, *et al.* (2014): Longitudinal patterns of repetitive behavior in toddlers with autism. *J Child Psychol Psychiatry* 55:945–953.
- American Psychiatric Association (2013): *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, 5th ed. Washington, DC: American Psychiatric Association.
- Constantino JN, Zhang Y, Frazier T, Abbacchi AM, Law P (2010): Sibling recurrence and the genetic epidemiology of autism. *Am J Psychiatry* 167:1349–1356.
- Leekam SR, Prior MR, Uljarevic M (2011): Restricted and repetitive behaviors in autism spectrum disorders: A review of research in the last decade. *Psychol Bull* 137:562–593.
- Chen YH, Rodgers J, McConachie H (2009): Restricted and repetitive behaviours, sensory processing and cognitive style in children with autism spectrum disorders. *J Autism Dev Disord* 39:635–642.
- Wigham S, Rodgers J, South M, McConachie H, Freeston M (2015): The interplay between sensory processing abnormalities, intolerance of uncertainty, anxiety and restricted and repetitive behaviours in autism spectrum disorder. *J Autism Dev Disord* 45:943–952.
- Boyd BA, Baranek GT, Sideris J, Poe MD, Watson LR, Patten E, *et al.* (2010): Sensory features and repetitive behaviors in children with autism and developmental delays. *Autism Res* 3:78–87.
- Boyd BA, McBee M, Holtzclaw T, Baranek GT, Bodfish JW (2009): Relationships among repetitive behaviors, sensory features, and executive functions in high functioning autism. *Res Autism Spectr Disord* 3:959–966.
- Gabiels RL (2008): Is there a relationship between restricted, repetitive, stereotyped behaviors and interests and abnormal sensory response in children with autism spectrum disorders? *Res Autism Spectr Disord* 2:660–670.
- Rogers SJ, Ozonoff S (2005): Annotation: What do we know about sensory dysfunction in autism? A critical review of the empirical evidence. *J Child Psychol Psychiatry* 46:1255–1268.
- Wolff JJ, Swanson MR, Elison JT, Gerig G, Pruetz JR Jr, Styner MA, *et al.* (2017): Neural circuitry at age 6 months associated with later repetitive behavior and sensory responsiveness in autism. *Mol Autism* 8:8.
- Belmonte MK, Allen G, Beckel-Mitchener A, Boulanger LM, Carper RA, Webb SJ (2004): Autism and abnormal development of brain connectivity. *J Neurosci* 24:9228–9231.
- Just MA, Cherkassky VL, Keller TA, Minshew NJ (2004): Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain* 127:1811–1821.
- Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ (2007): Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry. *Cereb Cortex* 17:951–961.
- Cherkassky VL, Kana RK, Keller TA, Just MA (2006): Functional connectivity in a baseline resting-state network in autism. *Neuroreport* 17:1687–1690.
- Kana RK, Keller TA, Minshew NJ, Just MA (2007): Inhibitory control in high-functioning autism: Decreased activation and underconnectivity in inhibition networks. *Biol Psychiatry* 62:198–206.
- Minshew NJ, Williams DL (2007): The new neurobiology of autism: Cortex, connectivity, and neuronal organization. *Arch Neurol* 64:945–950.
- Wolff JJ, Gu H, Gerig G, Elison JT, Styner M, Gouttard S, *et al.* (2012): Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am J Psychiatry* 169:589–600.
- Delmonte S, Gallagher L, O'Hanlon E, McGrath J, Balsters JH (2013): Functional and structural connectivity of frontostriatal circuitry in autism spectrum disorder. *Front Hum Neurosci* 7:430.
- Elison JT, Paterson SJ, Wolff JJ, Reznick JS, Sasson NJ, Gu H, *et al.* (2013): White matter microstructure and atypical visual orienting in 7 month-olds at risk for autism. *Am J Psychiatry* 170:899–908.
- Hazlett HC, Gu H, Munsell BC, Kim SH, Styner M, Wolff JJ, *et al.* (2017): Early brain development in infants at high risk for autism spectrum disorder. *Nature* 542:348–351.
- Di Martino A, Yan CG, Li Q, Denio E, Castellanos FX, Alaerts K, *et al.* (2014): The autism brain imaging data exchange: Towards a large-scale evaluation of the intrinsic brain architecture in autism. *Mol Psychiatry* 19:659–667.
- Di Martino A, Kelly C, Grzadzinski R, Zuo XN, Mennes M, Mairena MA, *et al.* (2011): Aberrant striatal functional connectivity in children with autism. *Biol Psychiatry* 69:847–856.
- Padmanabhan A, Lynn A, Foran W, Luna B, O'Hearn K (2013): Age related changes in striatal resting state functional connectivity in autism. *Front Hum Neurosci* 7:814.
- Washington SD, Gordon EM, Brar J, Warburton S, Sawyer AT, Wolfe A, *et al.* (2014): Dysmaturation of the default mode network in autism. *Hum Brain Mapp* 35:1284–1296.
- Emerson RW, Adams CM, Nishino T, Hazlett HC, Wolff JJ, Zwaigenbaum L, *et al.* (2017): Functional neuroimaging in high-risk 6-month-old infants predicts a diagnosis of autism at 24 months of age. *Sci Transl Med* 9(393).
- Hahamy A, Behrmann M, Malach R (2015): The idiosyncratic brain: Distortion of spontaneous connectivity patterns in autism spectrum disorder. *Nat Neurosci* 18:302–309.
- Esbensen AJ, Seltzer MM, Lam KS, Bodfish JW (2009): Age-related differences in restricted repetitive behaviors in autism spectrum disorders. *J Autism Dev Disord* 39:57–66.

32. Bodfish JW, Symons FJ, Parker DE, Lewis MH (2000): Varieties of repetitive behavior in autism: Comparisons to mental retardation. *J Autism Dev Disord* 30:237–243.
33. Lam KS, Aman MG (2007): The Repetitive Behavior Scale-Revised: Independent validation in individuals with autism spectrum disorders. *J Autism Dev Disord* 37:855–866.
34. Mirenda P, Smith IM, Vaillancourt T, Georgiades S, Duku E, Szatmari P, *et al.* (2010): Validating the Repetitive Behavior Scale-revised in young children with autism spectrum disorder. *J Autism Dev Disord* 40:1521–1530.
35. Carcani-Rathwell I, Rabe-Hasketh S, Santosh PJ (2006): Repetitive and stereotyped behaviours in pervasive developmental disorders. *J Child Psychol Psychiatry* 47:573–581.
36. Mosconi MW, Kay M, D’Cruz AM, Seidenfeld A, Guter S, Stanford LD, *et al.* (2009): Impaired inhibitory control is associated with higher-order repetitive behaviors in autism spectrum disorders. *Psychol Med* 39:1559–1566.
37. Ravizza SM, Solomon M, Ivry RB, Carter CS (2013): Restricted and repetitive behaviors in autism spectrum disorders: The relationship of attention and motor deficits. *Dev Psychopathol* 25:773–784.
38. Traynor JM, Hall GBC (2015): Structural and functional neuroimaging of restricted and repetitive behavior in autism spectrum disorder. *Journal of Intellectual Disability Diagnosis and Treatment* 3:21–34.
39. Johnson MH (2001): Functional brain development in humans. *Nat Rev Neurosci* 2:475–483.
40. Fransson P, Aden U, Blennow M, Lagercrantz H (2011): The functional architecture of the infant brain as revealed by resting-state fMRI. *Cereb Cortex* 21:145–154.
41. Pruett JR Jr, Kandala S, Hoertel S, Snyder AZ, Elison JT, Nishino T, *et al.* (2015): Accurate age classification of 6 and 12 month-old infants based on resting-state functional connectivity magnetic resonance imaging data. *Dev Cogn Neurosci* 12:123–133.
42. Gao W, Lin W, Grewen K, Gilmore JH (2017): Functional connectivity of the infant human brain: Plastic and modifiable. *Neuroscientist* 23:169–184.
43. Eggebrecht AT, Elison JT, Feczko E, Todorov A, Wolff JJ, Kandala S, *et al.* (2017): Joint attention and brain functional connectivity in infants and toddlers. *Cereb Cortex* 27:1709–1720.
44. Backes C, Ruhle F, Stoll M, Haas J, Frese K, Franke A, *et al.* (2014): Systematic permutation testing in GWAS pathway analyses: Identification of genetic networks in dilated cardiomyopathy and ulcerative colitis. *BMC Genomics* 15:622.
45. Uddin LQ, Supekar K, Lynch CJ, Cheng KM, Odriozola P, Barth ME, *et al.* (2015): Brain state differentiation and behavioral inflexibility in autism. *Cereb Cortex* 25:4740–4747.
46. Smyser CD, Inder TE, Shimony JS, Hill JE, Degnan AJ, Snyder AZ, *et al.* (2010): Longitudinal analysis of neural network development in preterm infants. *Cereb Cortex* 20:2852–2862.
47. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE (2012): Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 59:2142–2154.
48. Van Dijk KR, Sabuncu MR, Buckner RL (2012): The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage* 59:431–438.
49. Satterthwaite TD, Elliott MA, Gerraty RT, Ruparel K, Loughhead J, Calkins ME, *et al.* (2013): An improved framework for confound regression and filtering for control of motion artifact in the pre-processing of resting-state functional connectivity data. *Neuroimage* 64:240–256.
50. Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE (2014): Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage* 84:320–341.
51. Mathias A, Grond F, Guardans R, Seese D, Canela M, Diebner HH (2004): Algorithms for spectral analysis of irregularly sampled time series. *J Stat Softw* 11:1–27.
52. Marrus N, Eggebrecht AT, Todorov A, Elison JT, Wolff JJ, Cole L, *et al.* (2018): Walking, gross motor development, and brain functional connectivity in infants and toddlers. *Cereb Cortex* 28:750–763.
53. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, *et al.* (2011): Functional network organization of the human brain. *Neuron* 72:665–678.
54. Cole MW, Reynolds JR, Power JD, Repovs G, Anticevic A, Braver TS (2013): Multi-task connectivity reveals flexible hubs for adaptive task control. *Nat Neurosci* 16:1348–1355.
55. Spreng RN, Sepulcre J, Turner GR, Stevens WD, Schacter DL (2013): Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain. *J Cogn Neurosci* 25:74–86.
56. Sridharan D, Levitin DJ, Menon V (2008): A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci U S A* 105:12569–12574.
57. Spreng RN, Stevens WD, Chamberlain JP, Gilmore AW, Schacter DL (2010): Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage* 53:303–317.
58. Gao W, Lin W (2012): Frontal parietal control network regulates the anti-correlated default and dorsal attention networks. *Hum Brain Mapp* 33:192–202.
59. Smallwood J, Brown K, Baird B, Schooler JW (2012): Cooperation between the default mode network and the frontal-parietal network in the production of an internal train of thought. *Brain Res* 1428:60–70.
60. Hellyer PJ, Shanahan M, Scott G, Wise RJ, Sharp DJ, Leech R (2014): The control of global brain dynamics: Opposing actions of frontoparietal control and default mode networks on attention. *J Neurosci* 34:451–461.
61. Scott G, Hellyer PJ, Hampshire A, Leech R (2015): Exploring spatiotemporal network transitions in task functional MRI. *Hum Brain Mapp* 36:1348–1364.
62. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005): The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 102:9673–9678.
63. Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL (2008): Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *J Neurophysiol* 100:3328–3342.
64. Corbetta M, Shulman GL (2002): Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* 3:201–215.
65. Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP (2008): Competition between functional brain networks mediates behavioral variability. *Neuroimage* 39:527–537.
66. Gao W, Gilmore JH, Shen D, Smith JK, Zhu H, Lin W (2013): The synchronization within and interaction between the default and dorsal attention networks in early infancy. *Cereb Cortex* 23:594–603.
67. Kennedy DP, Redcay E, Courchesne E (2006): Failing to deactivate: Resting functional abnormalities in autism. *Proc Natl Acad Sci U S A* 103:8275–8280.
68. Thakkar KN, Polli FE, Joseph RM, Tuch DS, Hadjikhani N, Barton JJ, *et al.* (2008): Response monitoring, repetitive behaviour and anterior cingulate abnormalities in autism spectrum disorders (ASD). *Brain* 131:2464–2478.
69. Uddin LQ, Supekar K, Lynch CJ, Khouzam A, Phillips J, Feinstein C, *et al.* (2013): Saliency network-based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry* 70:869–879.
70. Kim H, Lim CS, Kaang BK (2016): Neuronal mechanisms and circuits underlying repetitive behaviors in mouse models of autism spectrum disorder. *Behav Brain Funct* 12:3.
71. Lewis M, Kim SJ (2009): The pathophysiology of restricted repetitive behavior. *J Neurodev Disord* 1:114–132.
72. Stoodley CJ, D’Mello AM, Ellegood J, Jakkamsetti V, Liu P, Nebel MB, *et al.* (2017): Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice. *Nat Neurosci* 20:1744–1751.
73. Blaser E, Eglinton L, Carter AS, Kaldy Z (2014): Pupillometry reveals a mechanism for the autism spectrum disorder (ASD) advantage in visual tasks. *Sci Rep* 4:4301.

74. Jao Keehn RJ, Sanchez SS, Stewart CR, Zhao W, Grenesko-Stevens EL, Keehn B, *et al.* (2017): Impaired downregulation of visual cortex during auditory processing is associated with autism symptomatology in children and adolescents with autism spectrum disorder. *Autism Res* 10:130–143.
75. Murphy ER, Norr M, Strang JF, Kenworthy L, Gaillard WD, Vaidya CJ (2017): Neural basis of visual attentional orienting in childhood autism spectrum disorders. *J Autism Dev Disord* 47:58–67.
76. Elsabbagh M, Fernandes J, Webb SJ, Dawson G, Charman T, Johnson MH, *et al.* (2013): Disengagement of visual attention in infancy is associated with emerging autism in toddlerhood. *Biol Psychiatry* 74:189–194.
77. Gliga T, Bedford R, Charman T, Johnson MH, BASIS Team (2015): Enhanced visual search in infancy predicts emerging autism symptoms. *Curr Biol* 25:1727–1730.
78. Wass SV, Jones EJ, Gliga T, Smith TJ, Charman T, Johnson MH, *et al.* (2015): Shorter spontaneous fixation durations in infants with later emerging autism. *Sci Rep* 5:8284.
79. Jones W, Carr K, Klin A (2008): Absence of preferential looking to the eyes of approaching adults predicts level of social disability in 2-year-old toddlers with autism spectrum disorder. *Arch Gen Psychiatry* 65:946–954.
80. Jones W, Klin A (2013): Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism. *Nature* 504:427–431.
81. Nebel MB, Eloyan A, Nettles CA, Sweeney KL, Ament K, Ward RE, *et al.* (2016): Intrinsic visual-motor synchrony correlates with social deficits in autism. *Biol Psychiatry* 79:633–641.
82. Orekhova EV, Stroganova TA (2014): Arousal and attention re-orienting in autism spectrum disorders: Evidence from auditory event-related potentials. *Front Hum Neurosci* 8:34.
83. Thyé MD, Bednarz HM, Herringshaw AJ, Sartin EB, Kana RK (2018): The impact of atypical sensory processing on social impairments in autism spectrum disorder. *Dev Cogn Neurosci* 29:151–167.
84. Mooney EL, Gray KM, Tonge BJ, Sweeney DJ, Taffe JR (2009): Factor analytic study of repetitive behaviours in young children with pervasive developmental disorders. *J Autism Dev Disord* 39:765–774.
85. Bishop SL, Hus V, Duncan A, Huerta M, Gotham K, Pickles A, *et al.* (2013): Subcategories of restricted and repetitive behaviors in children with autism spectrum disorders. *J Autism Dev Disord* 43:1287–1297.
86. Pelphrey KA, Morris JP, McCarthy G (2005): Neural basis of eye gaze processing deficits in autism. *Brain* 128:1038–1048.
87. Calvert GA (2001): Crossmodal processing in the human brain: Insights from functional neuroimaging studies. *Cereb Cortex* 11:1110–1123.
88. Beauchamp MS, Lee KE, Argall BD, Martin A (2004): Integration of auditory and visual information about objects in superior temporal sulcus. *Neuron* 41:809–823.
89. Carrington SJ, Bailey AJ (2009): Are there theory of mind regions in the brain? A review of the neuroimaging literature. *Hum Brain Mapp* 30:2313–2335.
90. Redcay E (2008): The superior temporal sulcus performs a common function for social and speech perception: Implications for the emergence of autism. *Neurosci Biobehav Rev* 32:123–142.
91. Taylor KI, Moss HE, Stamatakis EA, Tyler LK (2006): Binding cross-modal object features in perirhinal cortex. *Proc Natl Acad Sci U S A* 103:8239–8244.
92. Corbetta M, Patel G, Shulman GL (2008): The reorienting system of the human brain: From environment to theory of mind. *Neuron* 58:306–324.
93. Travers BG, Kana RK, Klinger LG, Klein CL, Klinger MR (2015): Motor learning in individuals with autism spectrum disorder: Activation in superior parietal lobule related to learning and repetitive behaviors. *Autism Res* 8:38–51.
94. Constantino JN, Gruber CP, Davis S, Hayes S, Passanante N, Przybeck T (2004): The factor structure of autistic traits. *J Child Psychol Psychiatry* 45:719–726.
95. Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, *et al.* (2013): A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. *Neuroimage* 76:183–201.
96. Ciric R, Wolf DH, Power JD, Roalf DR, Baum GL, Ruparel K, *et al.* (2017): Benchmarking of participant-level confound regression strategies for the control of motion artifact in studies of functional connectivity. *Neuroimage* 154:174–187.
97. Tyszka JM, Kennedy DP, Paul LK, Adolphs R (2014): Largely typical patterns of resting-state functional connectivity in high-functioning adults with autism. *Cereb Cortex* 24:1894–1905.
98. Spoormaker VI, Schroter MS, Gleiser PM, Andrade KC, Dresler M, Wehrle R, *et al.* (2010): Development of a large-scale functional brain network during human non-rapid eye movement sleep. *J Neurosci* 30:11379–11387.
99. Graham AM, Pfeifer JH, Fisher PA, Lin W, Gao W, Fair DA (2015): The potential of infant fMRI research and the study of early life stress as a promising exemplar. *Dev Cogn Neurosci* 12:12–39.
100. Mitra A, Snyder AZ, Tagliazucchi E, Laufs H, Elison J, Emerson RW, *et al.* (2017): Resting-state fMRI in sleeping infants more closely resembles adult sleep than adult wakefulness. *PLoS One* 12:e0188122.
101. Boyd BA, McDonough SG, Bodfish JW (2012): Evidence-based behavioral interventions for repetitive behaviors in autism. *J Autism Dev Disord* 42:1236–1248.