

Evoked and intrinsic brain network dynamics in children with autism spectrum disorder



Lauren Kupis^{a,*}, Celia Romero^a, Bryce Dirks^a, Stephanie Hoang^a, Meaghan V. Parlade^a, Amy L. Beaumont^a, Sandra M. Cardona^a, Michael Alessandri^a, Catie Chang^{b,c,d}, Jason S. Nomi^a, Lucina Q. Uddin^{a,e,*}

^a Department of Psychology, University of Miami, Coral Gables, FL, USA

^b Department of Electrical Engineering and Computer Science, Vanderbilt University, Nashville, TN, USA

^c Department of Biomedical Engineering, Vanderbilt University, Nashville, TN, USA

^d Vanderbilt University Institute of Imaging Science, Vanderbilt University, Nashville, TN, USA

^e Neuroscience Program, University of Miami Miller School of Medicine, Miami, FL, USA

ARTICLE INFO

Keywords:

Attention
Cognitive flexibility
Social cognition
Salience network
Default mode network
Central executive network
Set-shifting

ABSTRACT

Objective: Brain dynamics underlie flexible cognition and behavior, yet little is known regarding this relationship in autism spectrum disorder (ASD). We examined time-varying changes in functional co-activation patterns (CAPs) across rest and task-evoked brain states to characterize differences between children with ASD and typically developing (TD) children and identify relationships with severity of social behaviors and restricted and repetitive behaviors.

Method: 17 children with ASD and 27 TD children ages 7–12 completed a resting-state fMRI scan and four runs of a non-cued attention switching task. Metrics indexing brain dynamics were generated from dynamic CAPs computed across three major large-scale brain networks: midcingulo-insular (M-CIN), medial frontoparietal (M-FPN), and lateral frontoparietal (L-FPN).

Results: Five time-varying CAPs representing dynamic co-activations among network nodes were identified across rest and task fMRI datasets. Significant Diagnosis \times Condition interactions were observed for the dwell time of CAP 3, representing co-activation between nodes of the M-CIN and L-FPN, and the frequency of CAP 1, representing co-activation between nodes of the L-FPN. A significant brain-behavior association between dwell time of CAP 5, representing co-activation between nodes of the M-FPN, and social abilities was also observed across both groups of children.

Conclusion: Analysis of brain co-activation patterns reveals altered dynamics among three core networks in children with ASD, particularly evident during later stages of an attention task. Dimensional analyses demonstrating relationships between M-FPN dwell time and social abilities suggest that metrics of brain dynamics may index individual differences in social cognition and behavior.

1. Introduction

Autism spectrum disorder (ASD) is a prevalent neurodevelopmental condition characterized by deficits in social communication and restricted and repetitive behaviors (American Psychiatric Association, 2013) (RRBs), and associated with atypical brain connectivity (Chen et al., 2017, 2018; Di Martino et al., 2011; Fishman et al., 2018; Keown et al., 2013; Müller and Fishman, 2018; Supekar et al., 2013; Mash et al., 2019). Despite decades of neuroimaging research exploring brain connectivity in ASD, a clear picture linking specific patterns of atypical

connectivity to cognitive and behavioral profiles in ASD has yet to emerge (Kana et al., 2014; Falahpour et al., 2016; Rane et al., 2015; Vissers et al., 2012). To date, brain functional connectivity (FC) and co-activation patterns among brain regions as measured with fMRI has primarily been studied using “static” measures (Falahpour et al., 2016; White and Calhoun, 2019). Static FC methods average the entire time series across an fMRI scan, missing the opportunity to characterize moment-to-moment changes in coupling between brain regions (Allen et al., 2014; Calhoun et al., 2014). Recent FC research has used time-varying dynamic approaches that examine how brain function may

* Corresponding authors at: University of Miami, P.O. Box 248185-0751, Coral Gables, FL 33124, USA.

E-mail addresses: lbk48@miami.edu (L. Kupis), luddin@miami.edu (L.Q. Uddin).

<https://doi.org/10.1016/j.nicl.2020.102396>

Received 6 June 2020; Received in revised form 26 July 2020; Accepted 19 August 2020

Available online 25 August 2020

2213-1582/ © 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

change over time (Chang and Glover, 2010) thereby better capturing flexible aspects of brain systems (Allen et al., 2014).

Various methods exist to study dynamic, time-varying changes in the brain, including dynamic functional connectivity (dFC) and time-varying co-activation pattern analysis (CAP) (see Uddin & Karlsgodt (Uddin and Karlsgodt, 2018) and Uddin (Uddin, 2020) for a review). Dynamic FC most commonly capitalizes on the ‘sliding window’ approach (Chang and Glover, 2010). Despite its increasing use (Lurie et al., 2020), a limitation of this approach is the examination of FC over a fixed window length over which connectivity may fluctuate (Lurie et al., 2020; Preti et al., 2017). Rather than relying on sliding windows, CAP methods identify critical co-activating patterns that recur over time (Liu and Duyn, 2013). CAP methods seek to identify co-activation patterns by averaging time points with similar spatial distributions of brain activity by using a *k*-means clustering algorithm applied either at the whole-brain or region-of-interest (ROI) level (Liu et al., 2018).

Application of time-varying dynamic analyses to resting-state and task-based fMRI has revealed *brain states*, or recurring patterns of activity or connectivity (Allen et al., 2014; Liu et al., 2018), that can be quantified using metrics such as dwell time, frequency of occurrence, and number of transitions between states. Emerging evidence suggests that flexible resting-state dynamics underlies behavioral adaptation, enhancing the ability of the brain to dynamically reconfigure (Allen et al., 2014; Bassett et al., 2011; Jia et al., 2014). Similarly, the degree of brain network reconfiguration during a cognitive task has been demonstrated to relate to cognitive flexibility, or the ability to selectively switch between mental processes and respond behaviourally (Braun et al., 2015; Dajani and Uddin, 2015). Additional work comparing rest and task-based fMRI data has led to discoveries of network commonalities between the two, but also task-specific network changes (Bolt et al., 2017; Cole et al., 2014).

Multiple studies indicate that dynamic brain states may be important for uncovering novel insights into various psychiatric disorders, including ASD (Buckley et al., 2015; Uddin et al., 2015; Barttfeld et al., 2012). State-specific changes across resting and task fMRI paradigms may provide a more precise characterization of brain connectivity abnormalities in ASD, yet little research to date has concurrently examined both task and resting-state fMRI dynamics in ASD (Uddin et al., 2015). For example, Barttfeld et al. (Barttfeld et al., 2012) found that changes in the pattern of functional connectivity between individuals with ASD and neurotypical individuals were state-dependent (interceptive and exteroceptive states). Additionally, the classification of static FC using a support vector machine algorithm based on the difference between states outperformed classification using connectivity of a single state (Barttfeld et al., 2012). The few resting-state fMRI studies of brain dynamics have found atypicalities in individuals with ASD using whole brain dFC. You et al. (You et al., 2013) found children with ASD had transitions between unconstrained resting states to sustained attention states characterized by widespread functional connectivity among frontal and parietal regions in addition to atypical modulation of distant connectivity during sustained attention relative to rest. Hypervariant dynamic connections have been identified in youth with ASD (Chen et al., 2017, 2018; Mash et al., 2019; Falahpour et al., 2016), with associations to symptom severity in the domains of both RRBs and social functioning (Chen et al., 2017, 2018; He et al., 2018). Decreased state transitions and longer dwell times have also been reported in children with ASD (de Lacy et al., 2017; Yao et al., 2016; Rashid et al., 2018). Crucially, higher levels of ASD symptoms are associated with longer dwell times and fewer transitions in globally disconnected states (Rashid et al., 2018; Watanabe and Rees, 2017). These results suggest that infrequent brain state switching and hypervariant dynamic connections might underlie the behavioral difficulties seen in ASD (Falahpour et al., 2016; Harlalka et al., 2019).

Previous work has focused on whole-brain time-varying changes, yet recent work has highlighted the importance of understanding transient patterns within specific large-scale brain networks (Circ

et al., 2017). Specific brain areas have been identified in subserving flexible behavior, including the midcingulo-insular network (M-CIN or salience network), which mediates switches between the lateral frontoparietal network (L-FPN or central executive network) and the medial frontoparietal network (M-FPN, or default mode network) (Uddin et al., 2015, 2019). In ASD, it has been demonstrated that weak modulation of brain states among these networks is associated with the severity of RRBs (Uddin et al., 2015). Using time-varying approaches, atypical dynamic interactions among these regions have additionally been related to social deficits (He et al., 2018). Further work has demonstrated that decreased switching between brain states among the M-FPN and L-FPN occurs within ASD populations and may be related to behavioral inflexibility (de Lacy et al., 2017). Despite emerging evidence that M-FPN, M-CIN, and L-FPN regions are critically involved in ASD pathology, no studies have directly compared task-related (evoked) and resting-state (intrinsic) time-varying relationships in ASD among these three core neurocognitive networks.

Here we examine co-activation patterns among six key nodes of the M-CIN, M-FPN, and L-FPN in children with and without ASD during both task and resting states for the first time. We hypothesized that children with ASD and typically developing (TD)/neurotypical children would exhibit differences in dynamic brain state metrics such as frequency of occurrence and dwell time across rest and task conditions. We further expected to find relationships between metrics of brain dynamics and parent-report measures of RRBs and social behaviors.

2. Methods

2.1. Participants

Participant enrollment included 35 children with ASD and 36 TD children recruited from the University of Miami and the University of Miami Center for Autism and Related Disabilities (CARD, <http://www.umcard.org/>). Exclusionary criteria included 1) less than 10 min of resting-state fMRI data 2) less than 4 usable task-fMRI runs 3) incidental findings. Subjects were additionally excluded if they had > 1 mm mean framewise displacement (FD) or failed a visual Quality Control inspection indicating that they had one or more visually identifiable artifacts including but not limited to: excessive motion, ringing, blurring, ghosting, wrapping, signal loss, and head coverage. This resulted in a final sample of 17 children with ASD ($M = 9.95$, $SD = 1.51$) and 27 TD children ($M = 9.79$, $SD = 1.88$) that did not differ significantly in gender, age, full scale IQ, and mean FD (p 's > 0.05) (Table 1) (Power et al., 2014).

All participants underwent an initial phone screening followed by 1) neuropsychological assessment at the University of Miami Autism Spectrum Assessment Clinic (ASAC, <http://www.umasac.org/>) within CARD, and a 2) mock MRI scanner training followed by functional and structural brain imaging and completion of questionnaire forms. ASD participants were also administered the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (Lord et al., 2012) by research-reliable examiners at the University of Miami ASAC. All participants were MRI compatible, able to perform the task, had a full-scale IQ > 65 as measured by the Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II) (Wechsler, 2011), and were right-handed. Inclusion criteria for ASD participants included a previous diagnosis of ASD based on the DSM-5 criteria (American Psychiatric Association, 2013) by a community neurologist, psychologist, or other medical/mental health professional and meeting the cut-off for autism or autism spectrum on the ADOS-2, Module 3. See Table 1 for participant information. This study was approved by the Institutional Review Board at the University of Miami and conducted in compliance with the Declaration of Helsinki. All participants provided written informed consent and received financial compensation for their participation.

Table 1
Participant Demographics.

	Diagnostic Group		
	TD (n = 27)	ASD (n = 17)	p value
	Mean (SD)	Mean (SD)	
N = 44			
Sex	18 M/9F	14 M/3F	0.343
Age	9.79 (1.88)	9.95 (1.56)	0.489
<i>range</i>	[7.08–12.92]	[8.17–12.67]	–
Race^a	0, 1, 1, 18, 4, 3	0, 1, 1, 13, 1, 1	0.843
Ethnicity, Hispanic/Latino	17	11	0.041
FSIQ^b	107.88 (10.77)	106.9 (16.48)	0.836
<i>range</i>	[90–133]	[74–132]	–
Motion^c			
<i>Rest FD</i>	0.146 (0.118)	0.148 (0.086)	0.958
<i>Task 1 FD</i>	0.145 (0.096)	0.110 (0.039)	0.160
<i>Task 2 FD</i>	0.151 (0.122)	0.143 (0.076)	0.813
<i>Task 3 FD</i>	0.195 (0.091)	0.227 (0.176)	0.420
<i>Task 4 FD</i>	0.197 (0.124)	0.221 (0.195)	0.618
SRS-2, T score	45.08 (4.57)	69.24 (12.34)	< 0.001
RBS-R, T score	2.148 (2.957)	15.941 (11.882)	< 0.001
ADOS-2			
<i>Social Affect</i>	–	8.56 (3.35)	–
<i>Restricted and Repetitive Behaviors</i>	–	2.00 (1.10)	–
<i>Comparison Score</i>	–	6.31 (1.54)	–

Note: FSIQ: Full Scale Intelligence Quotient; SRS-2: Social Responsiveness Scale, Second Edition; RBS-R: Repetitive Behaviors Scale-Revised; ADOS-2: Autism Diagnostic Observation Schedule-Second Edition

1. Numbers for each of the following racial categories presented in the following order: African American, Asian, Biracial, Caucasian, Other, Not Reported.
2. FSIQ: WASI-II full-scale IQ, 4 participants did not have WASI-II because WISC-V was administered within a year and had IQ > 65.
3. Power framewise displacement for raw rs-fMRI data calculated in dpabi.

2.2. Neuropsychological measures and assessments

The first session included a visit to the ASAC, where the WASI-II, a standardized measure of intelligence that provides three measures of IQ: Verbal, Performance, and Full (Wechsler, 2011), and ADOS-2, a standardized measure of communication, social interaction, play, and RRBs (Lord et al., 2012), were administered. These assessments were administered by licensed clinical psychologists who had previously achieved research-reliability on the ADOS-2.

Parents or caregivers completed the SRS-2 (Constantino and Gruber, 2012) and RBS-R (Lam and Aman, 2007), used to assess social abilities and RRBs continuously and quantitatively. The SRS-2 is a 65-item parent report measure that yields a total T-score indicating overall social ability. The RBS-R is a 44-item parent report measure that yields a total T-score indicating overall repetitive behaviors. The SRS-2 and RBS-R total raw scores were converted to age equivalent T-scores, with higher scores indicating more severe impairment (Constantino and Gruber, 2012; Lam and Aman, 2007).

2.3. fMRI data acquisition parameters

Children initially participated in a mock scan to adjust to the scanning environment and to practice the fMRI task. MRI data were acquired using a 3 T GE scanner with a 32-channel head coil. Functional images were collected using a gradient echo sequence (TR/TE/flip angle/FOV = 2 s/30 ms/75°/220 mm; orientation: 42 axial slices angled along the AC-PC; slice thickness: 3.4 mm no inter-slice skip, interleaved acquisition order and anterior-posterior encoding). At the beginning of the scanning session, participants completed a 10-min resting-state run consisting of 295 volumes. They were instructed to lie still with their eyes closed while remaining awake. The resting-state run was followed by four 122- vol task runs. The first 5 volumes of each run were discarded to account for gradient stabilization.

2.4. Non-cued attention switching task

Participants completed four runs of a task examining the ability to shift attention between stimulus dimensions (Casey et al., 2004; Britton et al., 2010). While in the scanner, participants viewed a display with three stimuli presented on a black background. One of the three objects differed from the other two in either shape (S), (e.g., square or circle) or color (C), (e.g., gray or white) (Fig. 1). Participants were instructed to identify the differing object by pressing a button corresponding to the unique object. They were not explicitly told how the objects differed (S or C). (See Supplement 1 for further details).

On each trial, three objects were presented for 1000 ms with a 1500 ms interstimulus interval (ISI). One object had a unique attribute, either shape (square or circle) or color (gray or white). Participants indicated the location of the unique object via a button press. The stimuli were presented in a blocked design with 12 trials per shape/color and 24 trials per mixed block. Each run lasted 4 min and 16 s (see Dirks et al. (Dirks et al., 2020) for further details).

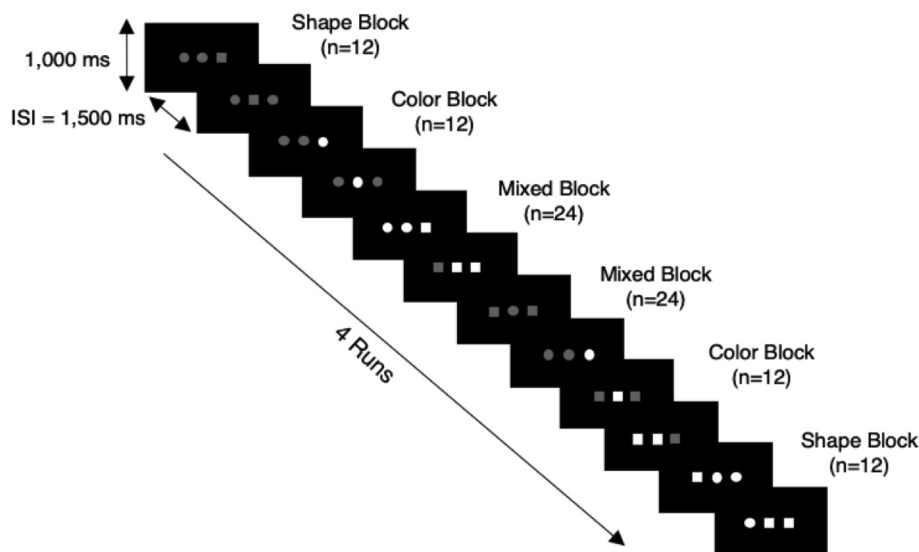


Fig. 1. Task Paradigm.

3. Data analysis

3.1. Behavioral data

Total accuracy was computed across all trials in each block and reported as the proportion of correct trials relative to the total number of trials the subject completed. Reaction time (RT) was calculated for each subject for correct trials only and computed as a total mean RT across all correct trials in each block (see [supplementary Table S1](#)). Accuracy and RT were analyzed using a 2 Diagnosis (ASD, TD) \times 4 Condition (task run 1, task run 2, task run 3, task run 4) mixed-model ANOVA.

3.2. fMRI data preprocessing and region-of-interest (ROI) selection

The resting-state run and four task runs were preprocessed separately using the Data Processing and Analysis for Brain Imaging (DPABI) version 3.1 toolbox (<http://rfmri.org/dpabi>) (Yan et al., 2016). The following steps were completed in the same order for all task and rest datasets: despiking (AFNI's 3dDespike), slice timing correction (Parker and Razlighi, 2019), realignment, brain extraction, segmentation, normalization to a standard SPM EPI template ($3 \times 3 \times 3$ mm), and smoothing (FWHM = 6 mm). Despiking identifies voxelwise TR outliers > 2.5 standard deviations of the time series and replaces them with an adjusted value based on the mathematical formula: $s' = c1 + (c2-c1) \cdot \tanh((s-c1)/(c2-c1))$ where $c1 = 2.5$, $c2 = 4$, $s =$ original TR value, $s' =$ replaced TR value. Despiking was chosen over other censoring methods to preserve temporal continuity in the rest and task data.

Six ROIs were selected, including the right fronto-insular cortex (rFIC) and anterior cingulate cortex (ACC) of the M-CIN; right dorsolateral prefrontal cortex (rDLPFC) and right posterior parietal cortex (rPPC) of the L-FPN; and the ventromedial prefrontal cortex (VMPFC) and posterior cingulate cortex (PCC) of the M-FPN. Coordinates delineating these ROIs in a previous study were used (Table S2) (Uddin et al., 2011).

3.3. Independent component analysis (ICA) denoising

Each subject's rest and task fMRI datasets were individually denoised by hand-classifying ICA components after running FSL's Melodic ICA algorithm with automatic dimensionality estimation. Components identified as noise (e.g. those containing artifacts such as white matter, cerebrospinal fluid, head motion, or proportionally large amounts of high-frequency information) were regressed out of the data prior to subsequent post-processing using the `fsl_regfilt` command (Griffanti et al., 2017; Jenkinson et al., 2012).

3.4. Post-ICA processing and analysis

After ICA denoising, the average time series were extracted from 6-mm radius spheres of six ROIs in key nodes of the M-CIN, M-FPN, and L-FPN. Time courses were then linearly detrended, low pass filtered (0.01–0.1 Hz), and subjected to regression of the Friston 24 head motion parameters (6 motion parameters of each volume, the preceding volume, and the 12 corresponding squared items) (Friston et al., 1996), white matter, and CSF, as calculated in the DBAPI toolbox (Yan et al., 2016).

3.5. Co-activation pattern (CAP) analysis

Time series extracted from the six ROIs during task and resting-state runs were converted to z statistics and then concatenated into a single group matrix (787 TR \times 44 subjects) following previous studies (Hutchison and Morton, 2015; Denkova et al., 2019). The concatenated matrix was subjected to k -means clustering. Testing values of $k = 2$ –20,

the optimal value of $k = 5$ was determined using the elbow criterion by applying a least-squares fit line to the cluster validity index, defined as the ratio of within-cluster to between-cluster differences (Figure S1) (Allen et al., 2014; Damaraju et al., 2014). A CAP analysis was conducted using k -means clustering (squared Euclidean distance) using the optimal k of 5 on the group concatenated time series of the 6 ROIs across all subjects (Liu et al., 2013). CAP metrics were then calculated separately for each of the five conditions (rest run, task run 1, task run 2, task run 3, task run 4) and for all task runs combined (task all = task runs 1–4). The CAP metrics computed included a) dwell time (DT), calculated as the average number of TRs that a participant stayed in a given brain state in each condition b) frequency of occurrence of brain states, calculated as a percent over time that the brain state occurred throughout the duration of each condition, and c) the number of transitions, calculated as the number of switches between brain states.

3.6. Statistical analysis

DT and frequency of occurrences were subjected to a 2 Diagnosis (ASD, TD) \times 5 Condition (rest run, task run 1, task run 2, task run 3, task run 4) mixed model ANOVA. DT and frequency of occurrences were additionally subjected to a 2 Diagnosis (ASD, TD) \times 2 Condition (rest run, task all) mixed model ANOVA. Post-hoc two-tailed t -tests were conducted to identify differences in the means for each of the runs. Number of transitions during rest were subjected to a t -test, and task run transitions were analyzed using a 2 Diagnosis (ASD, TD) \times 4 Condition (task run 1, task run 2, task run 3, task run 4) mixed model ANOVA. (See [Supplement 1](#) for details regarding analyses of confounding variables).

3.7. Brain-behavior analysis

The relationship between brain state metrics and social and repetitive behaviors were assessed by calculating Pearson correlations between the CAP metrics (DT, frequency of occurrences, and transitions) and SRS-2 and the RBS-R T-scores in dimensional analyses across all subjects. We additionally calculated partial Pearson correlations between DT and SRS-2 while controlling for age.

4. Results

4.1. Time-varying resting-state and task fMRI

CAP analyses revealed five brain states that dynamically occurred during rest and task runs (Fig. 2). CAP 1 was characterized by co-activation among the nodes of the L-FPN. CAP 2 was characterized by co-activation among the nodes of the M-CIN. CAP 3 was characterized by co-activation among the nodes of the M-CIN and the nodes of the L-FPN. CAP 4 was characterized by co-activation among the nodes of the M-FPN, the L-FPN, and M-CIN. CAP 5 was characterized by co-activation among the nodes of the M-FPN.

4.2. Behavioral

For RT, a mixed model ANOVA revealed there was a significant linear effect of Condition ($F(1,34) = 13.580$, $p = 0.001$). Pairwise comparisons between runs showed that the RTs for task run 1 were significantly higher (slower) than both task run 3 and 4 (p 's < 0.05). There were no significant differences between RTs of task runs 1 and 2, 2 and 3, and 2 and 4 (p 's > 0.05). There were no significant interactions for RT, and RT did not significantly differ by diagnostic group (p 's > 0.05) (Fig. 3A).

Mean accuracy was greater than 90% for each run in both ASD and TD groups (See [supplementary Table S1](#)). A mixed model ANOVA revealed that there were no significant main effects or interactions for accuracy (p 's > 0.05) (Fig. 3B).

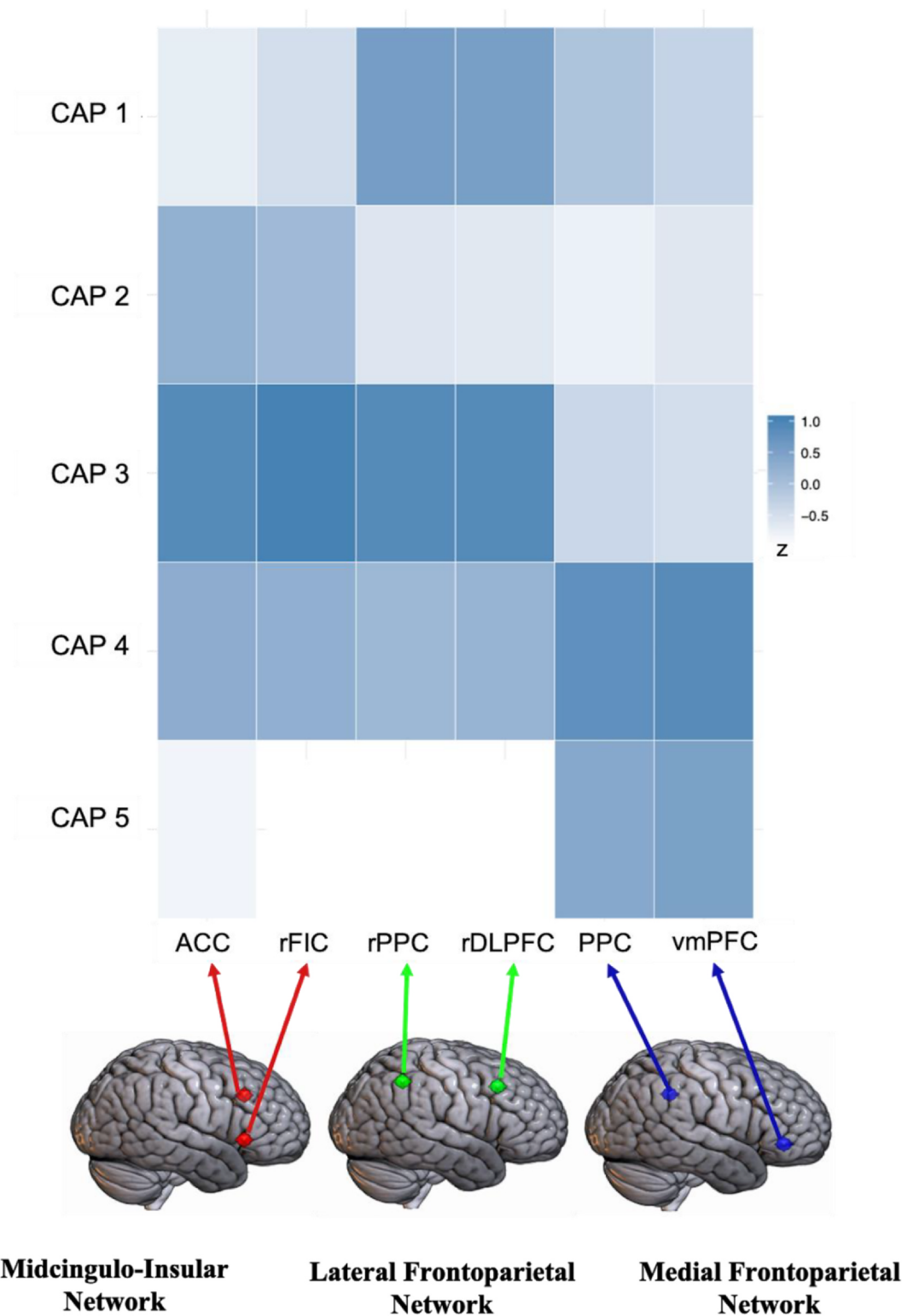


Fig. 2. Time series from 6 regions of interest (ROIs) were extracted across rest and task runs for both children with ASD and TD children, and z-scored and concatenated into a single matrix. The matrix was subjected to *k*-means clustering and CAP analysis using a *k* of 5. The intensity of colors in the CAP matrix indicate the z-scored activation value of the ROIs within each centroid.

4.3. CAP frequency of occurrence

A mixed model ANOVA revealed a significant linear interaction for the frequency of occurrence of CAP 1, the state with co-activation among nodes of the L-FPN, [$F(1,42) = 6.512, p = 0.014$], (Fig. 3C). Thus, the occurrences of CAP 1 were similar between groups during

rest, and children with ASD initially had fewer occurrences of CAP 1 during the first two task runs but then showed more occurrences of CAP 1 in the last two task runs compared with TD children. Post-hoc *t*-tests were conducted on each run, revealing a significant difference between diagnostic groups within task run 4 ($p = 0.021$). No other run comparisons were significant (p 's > 0.05), (Figure S3). A post-hoc

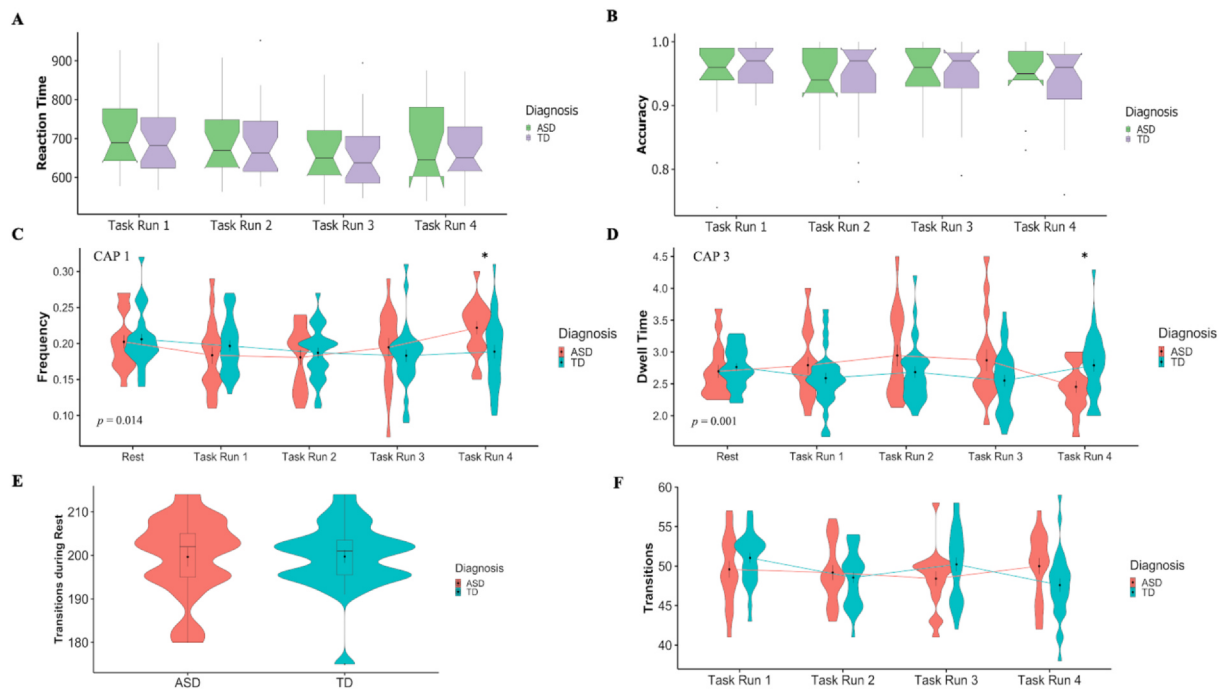


Fig. 3. Behavioral data and CAP frequency, dwell time, and transitions during rest and task states. A) Box plot of RT in children with ASD and TD children. There were no significant differences between groups in RT (p 's > 0.05). B) Box plot of Accuracy in children with ASD and TD children. There were no significant differences between groups in accuracy (p 's > 0.05). C) Frequency of occurrence of CAP 1, characterized by co-activation of L-FPN nodes, was greater in Task Run 4 for children with ASD than TD children. D) Dwell time of CAP 3, characterized by co-activation of M-CIN and L-FPN nodes, was shorter in Task Run 4 for children with ASD than TD children. E) Transitions between CAPs during rest were not significantly different between groups. F) Transitions between CAPs during task performance were not significantly different between groups when high motion subjects were removed. Results from mixed model ANOVA are shown inside graphs with significant interactions (C and D). * = p < 0.05 from post-hoc t -test.

regression model comparing frequency of occurrences between ASD and TD for task run 4 while controlling for head motion during task run 4 was significant ($p = 0.035$). Thus, head motion did not influence the group differences observed in task run 4. A post-hoc mixed model ANOVA was conducted excluding four high motion subjects, and a significant linear interaction was still observed, [$F(1,38) = 6.526, p = 0.015$].

There was a significant cubic main effect of Condition for the frequency of occurrences of CAP 3, [$F(1, 42) = 6.25, p = 0.016$], however there was no significant main effect of Diagnosis [$F(1, 42) = 0.001, p = 0.976$]. There was a significant quadratic main effect of Condition for the frequency of occurrences of CAP 5, [$F(1, 42) = 6.346, p = 0.016$], however there was no significant main effect of Diagnosis [$F(1, 42) = 0.324, p = 0.572$]. There were no significant main effects or interactions for CAP 2 and CAP 4 (p 's > 0.05).

Additionally, there were no significant main effects or interactions for the 2 Diagnosis (ASD, TD) \times 2 Condition (rest run, task all) mixed model ANOVAs for CAPs 1–5 (p 's > 0.05).

4.4. CAP dwell time

A mixed model ANOVA revealed a significant quadratic main effect of Condition for DT of CAP 1, [$F(1,42) = 22.316, p < 0.001$], however there was no significant main effect of Diagnosis [$F(1, 42) = 0.574, p = 0.453$]. There was a significant quadratic main effect of Condition for the DT of CAP 2, [$F(1, 42) = 11.368, p = 0.002$], however there was no significant main effect of Diagnosis [$F(1, 42) = 0.875, p = 0.355$]. There was a significant quadratic interaction for DT of CAP 3, where the M-CIN is coupled with the L-FPN [$F(1, 42) = 12.785, p = 0.001$] (Fig. 3D). These results demonstrate that the DT of CAP 3 was similar between groups during rest, and children with ASD initially spend more time in CAP 3 for task runs 1–3, then spend less time in CAP 3 for task run 4 compared with TD children. Post-hoc t -tests were

conducted on each condition to compare diagnostic groups and revealed a significant difference in task run 4 ($p = 0.034$) (Figure S4). No other condition comparison was significant (p 's > 0.05). A post-hoc regression model comparing DT between ASD and TD for task run 4 while controlling for head motion was significant ($p = 0.029$). A post-hoc mixed model ANOVA was conducted excluding four high motion subjects, and a significant quadratic interaction was still observed [$F(1,38) = 8.625, p = 0.006$]. There were no significant main effects or interactions for CAP 4 and CAP 5 (p 's > 0.05).

2 Diagnosis (ASD, TD) \times 2 Condition (rest run, task all) mixed model ANOVAs for CAPs 1–5 revealed main effects of Condition for CAP 1, [$F(1, 42) = 22.366, p < 0.001$], CAP 2, [$F(1, 42) = 29.003, p < 0.001$], and CAP 4, [$F(1, 42) = 7.745, p = 0.008$] and CAP 5, [$F(1, 42) = 9.387, p = 0.004$]. CAP 3 did not exhibit a significant main effect ($p = 0.389$). There were no main effects of Diagnosis for any of the CAPs (p 's > 0.05).

4.5. CAP transitions

A mixed model ANOVA revealed a significant cubic interaction for the number of transitions [$F(1, 42) = 4.124, p = 0.049$], indicating TD children have more transitions in task run 1, but have fewer in task run 2, then more in task run 3 and again fewer in task run 4 compared to children with ASD (Fig. 3E). However, there was no significant main effect of Diagnosis [$F(1, 42) = 0.008, p = 0.930$]. A post-hoc mixed model ANOVA using a low motion sample ($N = 40$) revealed the interaction was no longer significant [$F(1, 38) = 3.360, p = 0.075$]. We conducted t -tests comparing ASD and TD groups on the resting-state run (Fig. 3F), on each task run separately, and on the task runs combined, and found no significant differences between the diagnostic groups (p 's > 0.05) (Table S6).

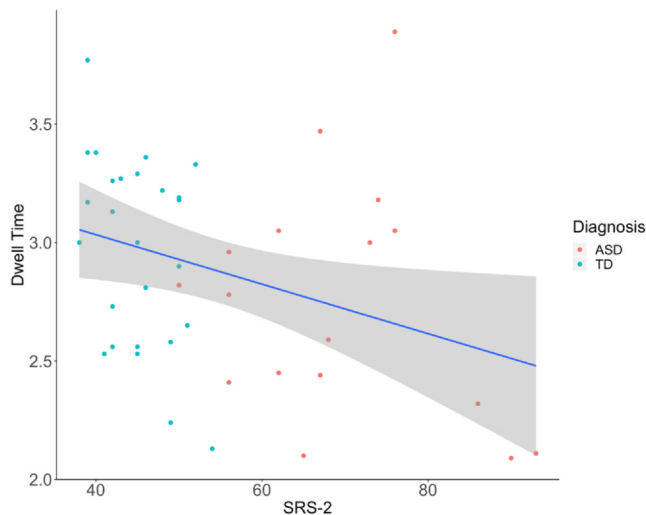


Fig. 4. Pearson correlation between resting-state CAP 5, the M-FPN CAP, and symptom severity indexed by the Social Responsiveness Scale (SRS-2) (Constantino and Gruber, 2012).

4.6. Brain-behavior results

Pearson correlations between SRS-2 and RBS-R total T-scores with each CAP metric revealed a significant correlation between SRS-2 and DT during CAP 5 in the rest condition ($r = -0.337$, $p = 0.027$) (uncorrected) (Fig. 4). No other significant correlations were observed between SRS-2, RBS-R, and any other CAP metrics for CAP 5, nor any metrics for CAPs 1–4 (p 's > 0.05). Partial Pearson correlations between SRS-2 and DT while controlling for age revealed that the correlation between SRS-2 and DT during CAP 5 in the rest condition was still significant ($r = -0.341$, $p = 0.027$). We additionally found a significant correlation between SRS-2 and DT during CAP 3 in the task 4 condition ($r = -0.472$, $p = 0.002$) (uncorrected). No other correlations were significant (p 's > 0.05).

5. Discussion

Here, we investigate brain dynamics among three neurocognitive networks ubiquitously present in the functional neuroimaging literature (Uddin, 2015). The M-CIN, comprising the anterior insula and anterior cingulate cortices, is thought to enable dynamic switching between the M-FPN (comprising medial prefrontal and posterior cingulate cortices and involved in internally oriented cognition) and the L-FPN (comprising lateral prefrontal and posterior parietal cortices and involved in goal-directed behaviors) (Goulden et al., 2014; Fox et al., 2006). A large literature supports the role of the M-CIN as a mediator of incoming stimuli, guiding appropriate behavioral responses (Uddin, 2015; Goulden et al., 2014; Menon and Uddin, 2010; Uddin and Menon, 2009). Specific regions of the M-CIN such as the ACC have also been shown to have varying modulatory interactions with brain regions during rest and task conditions (Di et al., 2020). While atypical patterns of brain activation and connectivity of these networks have previously been documented in ASD (Uddin et al., 2013), very few studies have examined network configurations as they change between rest and task states (Uddin et al., 2015). Characterizing dynamic changes in the brain lends insight into these alterations, but most studies to date have focused on whole-brain dynamics using sliding window dynamic functional connectivity approaches that have limitations including the use of an arbitrary window length (Allen et al., 2014; Uddin, 2020). Inflexibility among these networks has been shown to underlie core symptoms of ASD (Uddin et al., 2015), yet no previous studies have examined time-varying patterns of co-activation among these networks during intrinsic and evoked states in children with the disorder. Here

we used CAP, a method that relies on fewer model assumptions than the sliding window approach, for the first time to characterize brain dynamics among the M-CIN, L-FPN, and M-FPN during a resting-state scan and four runs of an attention task in children with ASD and TD children.

Using CAP, we found evidence for five recurring brain states involving dynamic patterns among M-CIN, M-FPN, and L-FPN nodes during task and resting states. CAP 1 and CAP 2 states exhibited co-activation patterns within L-FPN and within M-CIN, respectively. CAP 3 was characterized by a co-activation among both the M-CIN and L-FPN, a state commonly associated with cognitive task performance (Corbetta and Shulman, 2002) and sometimes referred to as “task-positive” networks (Di and Biswal, n.d.). Together, these results suggest the M-CIN and L-FPN may function independently or simultaneously as needed in the service of task demands or during resting conditions. CAP 4 was characterized by co-activation among all three networks, a brain state which is consistent with evidence from prior studies (Marshall et al., 2020). CAP 5 was a state in which strong M-FPN node co-activation was observed. M-FPN, typically referred to as the “task-negative” network, recently has been revealed to play a role in specific task conditions (Krieger-Redwood et al., 2016; Mars et al., 2012; Spreng et al., 2014; Vatanserver et al., 2015) potentially during minimally demanding cognitive tasks (Vatanserver et al., 2015). Taken together, these five CAPs display patterns that are consistent with the role of the M-CIN in mediating both the L-FPN and M-FPN, and suggests dynamic interactions among the networks during both task and resting-states (Goulden et al., 2014).

For CAPs 1 and 3, distinct group differences were identified in dynamic metrics of frequency of occurrences and dwell time. Interestingly, in the last two task runs children with ASD exhibited more frequent occurrences of CAP 1 and spent less time in CAP 3 during task run 4 compared to TD children. Greater frequency of occurrences of the L-FPN and less dwell time of simultaneous M-CIN and L-FPN co-activation during the last task runs in children with ASD suggests they rely more on the L-FPN when needing to exert greater effort to reach the same behavioral outcomes as children with TD. Previous work has shown that high functioning individuals with ASD may perform a task at an above-average level, as shown here, but may require more detailed-focused processing (Happé and Frith, 2006). This type of behavior has been previously associated with overly stable brain dynamics in adults with ASD (Watanabe and Rees, 2017). The lack of behavioral differences found in this study suggests that children with ASD performed at a high level across all four task runs, and this behavior is supported by altered changes in dynamic fluctuations across the networks from the early to the later phases of the task.

The observed disruption in the coordination of the L-FPN and M-CIN nodes, evident in the last task runs, is consistent with emerging evidence using dynamic methods of disruptions in between-network connectivity in children with ASD (de Lacy et al., 2017). Similarly, coordination among all three neurocognitive networks has been previously shown to dynamically occur less frequently during intrinsic states in children with ASD compared to TD children, indicating a reduced co-activation of the M-CIN with nodes of the M-FPN and L-FPN (Marshall et al., 2020). Although our finding is across evoked states, our results are consistent with the prior study suggesting the nodes of the M-CIN have reduced coordination with the nodes of the L-FPN, primarily during the last task runs. A disruption in the coordination of networks may underlie cognitive and behavioral inflexibility seen in children with ASD (Uddin et al., 2015; Bartfeld et al., 2012). Additionally, dynamics assessed during evoked states may reveal unique network re-configurations under varying task demands, and differential employment of cognitive effort in ASD (Cheng et al., 2018). Dynamic analyses can track differential brain responses in ASD across changing task demands over time. The current findings imply that CAP metrics computed across multiple task runs can be more revealing of neural profiles in autism than differences between task and rest contexts, which have been the focus of previous similar works (Uddin et al.,

2015). However, further studies are needed to support this interpretation. There were no group differences in transitions observed, primarily after removing subjects with excessive motion. This is contradictory to a growing dynamic functional connectivity literature suggesting that transitions between states are altered in ASD (Uddin, 2020; de Lacy et al., 2017; Watanabe and Rees, 2017). Our results may be influenced by our limited sample size and the relatively short duration of our task and rest scans; future studies including larger sample sizes and longer scan times are needed to further explore this issue. Additionally, our lack of significant findings for transitions may be attributed to our analysis of three neurocognitive networks rather than whole-brain analyses, as conducted in previous studies (Uddin, 2020; de Lacy et al., 2017; Watanabe and Rees, 2017).

The only significant relationship between the brain dynamic metrics and behavior was identified in the M-FPN. Greater dwell time in the M-FPN was associated with better social abilities as indexed by the SRS-2. This is in line with previous research linking the M-FPN with social ability in ASD (He et al., 2018; Padmanabhan et al., 2017) and in the general population (Mars et al., 2012; Li et al., 2014). The dynamic analyses presented here provide new insight into the relationship between the M-FPN and social behaviors. Our findings indicate that children who exhibit greater M-FPN engagement during resting states are those who are higher functioning in the social domain. This is in line with a large literature implicating the M-FPN in thinking about others (Uddin et al., 2007).

During task performance, we observed no behavioral differences in reaction time and accuracy between children with ASD and TD children. In both groups, accuracy remained elevated across the four task runs (Accuracy > 90%), indicating there was not an underlying behavioral change across the four task runs to account for the brain dynamic changes we observed. As previously reported, high accuracy and a lack of behavioral differences between groups indicate that this task was relatively easy for both children with ASD and TD children to complete (Dirks et al., 2020). Nevertheless, children with ASD recruited brain regions involved in executive control to a greater extent than TD children by task run 4, indicating that they exerted greater cognitive effort to reach the same level of performance as TD children. This suggests that children with ASD may neurally compensate to reach the same level of behavioral performance as TD children across the duration of a task (Livingston and Happé, 2017).

5.1. Limitations

There are a few limitations important to note in the present study. Our sample size was limited as we maintained strict requirements including a visual Quality Control inspection, a full 10 min of resting-state fMRI, and completion of all four task runs. While these requirements increased power related to our study aims, they reduced our sample size, as several children were excluded due to our strict criteria. Future work with larger sample sizes is needed to confirm and extend the results presented here. Lastly, other large-scale networks including the dorsal attention network (DAN)/dorsal frontoparietal network (D-FPN) have also been shown to interact with the three networks investigated here, depending on context (Dixon et al., 2018). Future studies should further expand on the current work by investigating the D-FPN and its dynamic relationship to the L-FPN, M-CIN and M-FPN in children with ASD.

5.2. Conclusions

This study investigated brain dynamic metrics concurrently during rest and an attention task in children with ASD and TD children. Group differences between children with ASD and TD children were evident in brain states consisting of the L-FPN and M-CIN specifically during the fourth task run, suggesting atypical between-network coordination in children with ASD during prolonged periods of task engagement.

Atypical between-network coordination may underlie neural compensation in children with ASD, enabling comparable behavioral performance as TD children. Finally, greater M-FPN dwell time was associated with stronger social abilities, indicating that the dynamics of this network may be important in our understanding of social dysfunction in both ASD and the general population.

CRedit authorship contribution statement

Lauren Kupis: Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Celia Romero:** Data curation, Writing - review & editing. **Bryce Dirks:** Data curation, Writing - review & editing. **Stephanie Hoang:** Visualization, Writing - review & editing. **Meaghan V. Parladé:** Resources, Supervision, Writing - review & editing. **Amy L. Beaumont:** Resources, Supervision, Writing - review & editing. **Sandra M. Cardona:** Resources, Supervision, Writing - review & editing. **Michael Alessandri:** Resources, Supervision, Writing - review & editing. **Catie Chang:** Methodology, Supervision, Writing - review & editing. **Jason S. Nomi:** Data curation, Supervision, Writing - original draft, Writing - review & editing. **Lucina Q. Uddin:** Conceptualization, Supervision, Writing - original draft, Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by grants from the Canadian Institute for Advanced Research, a Gabelli Senior Scholar Award from the University of Miami, R01MH107549 from the National Institute of Mental Health (LQU), and an NIMH award (R03MH121668) and NARSAD Young Investigator Award (JSN). The authors would like to thank Jennifer Britton for providing the task used in the study.

Presentation information

This study was presented as an abstract at the University of Miami Graduate and Postgraduate Research Symposium; March 5, 2020; Coral Gables, Florida and presented virtually at the Organization for Human Brain Mapping; June 24–July 2, 2020.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2020.102396>.

References

- Allen, E.A., Damaraju, E., Plis, S.M., Erhardt, E.B., Eichele, T., Calhoun, V.D., 2014. Tracking whole-brain connectivity dynamics in the resting state. *Cereb. Cortex* 24 (3), 663–676.
- American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub.
- Barttfeld, P., Wicker, B., Cukier, S., et al., 2012. State-dependent changes of connectivity patterns and functional brain network topology in autism spectrum disorder. *Neuropsychologia* 50 (14), 3653–3662.
- Bassett, D.S., Wymbs, N.F., Porter, M.A., Mucha, P.J., Carlson, J.M., Grafton, S.T., 2011. Dynamic reconfiguration of human brain networks during learning. *Proc. Natl. Acad. Sci. U S A* 108 (18), 7641–7646.
- Bolt, T., Nomi, J.S., Rubinov, M., Uddin, L.Q., 2017. Correspondence between evoked and intrinsic functional brain network configurations. *Hum. Brain Mapp.* 38 (4), 1992–2007.
- Braun, U., Schäfer, A., Walter, H., et al., 2015. Dynamic reconfiguration of frontal brain networks during executive cognition in humans. *Proc. Natl. Acad. Sci. U S A* 112 (37), 11678–11683.

- Britton, J.C., Rauch, S.L., Rosso, I.M., et al., 2010. Cognitive inflexibility and frontal-cortical activation in pediatric obsessive-compulsive disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 49 (9), 944–953. <https://doi.org/10.1016/j.jaac.2010.05.006>.
- Buckley, A.W., Scott, R., Tyler, A., et al., 2015. State-dependent differences in functional connectivity in young children with autism spectrum disorder. *EBioMedicine* 2 (12), 1905–1915.
- Calhoun, V.D., Miller, R., Pearlson, G., Adali, T., 2014. The chronnectome: time-varying connectivity networks as the next frontier in fMRI data discovery. *Neuron* 84 (2), 262–274.
- Casey, B.J., Davidson, M.C., Hara, Y., et al., 2004. Early development of subcortical regions involved in non-cued attention switching. *Devel. Sci.* 7 (5), 534–542. <https://doi.org/10.1111/j.1467-7687.2004.00377.x>.
- Chang, C., Glover, G.H., 2010. Time–frequency dynamics of resting-state brain connectivity measured with fMRI. *Neuroimage* 50 (1), 81–98.
- Chen, H., Nomi, J.S., Uddin, L.Q., Duan, X., Chen, H., 2017. Intrinsic functional connectivity variance and state-specific under-connectivity in autism. *Hum. Brain Mapp.* 38 (11), 5740–5755.
- Chen, H., Wang, J., Uddin, L.Q., et al., 2018. Aberrant functional connectivity of neural circuits associated with social and sensorimotor deficits in young children with autism spectrum disorder. *Autism Res.* 11 (12), 1643–1652.
- Cheng, L., Zhu, Y., Sun, J., et al., 2018. Principal states of dynamic functional connectivity reveal the link between resting-state and task-state brain: an fMRI study. *Int. J. Neural Syst.* 28 (07), 1850002. <https://doi.org/10.1142/s0129065718500028>.
- Ciric, R., Nomi, J.S., Uddin, L.Q., Satpute, A.B., 2017. Contextual connectivity: a framework for understanding the intrinsic dynamic architecture of large-scale functional brain networks. *Sci. Rep.* 7 (1), 6537.
- Cole, M.W., Bassett, D.S., Power, J.D., Braver, T.S., Petersen, S.E., 2014. Intrinsic and task-evoked network architectures of the human brain. *Neuron* 83 (1), 238–251.
- Constantino, J.N., Gruber, C.P., 2012. *Social Responsiveness Scale Second Edition (SRS-2): Manual*.
- Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. *Nat. Rev. Neurosci.* 3 (3), 201–215.
- Dajani, D.R., Uddin, L.Q., 2015. Demystifying cognitive flexibility: Implications for clinical and developmental neuroscience. *Trends Neurosci.* 38 (9), 571–578.
- Damaraju, E., Allen, E.A., Belger, A., et al., 2014. Dynamic functional connectivity analysis reveals transient states of dysconnectivity in schizophrenia. *Neuroimage Clin.* 5, 298–308.
- de Lacy, N., Doherty, D., King, B.H., Rachakonda, S., Calhoun, V.D., 2017. Disruption to control network function correlates with altered dynamic connectivity in the wider autism spectrum. *Neuroimage Clin.* 15, 513–524.
- Denkova, E., Nomi, J.S., Uddin, L.Q., 2019. Dynamic brain network configurations during rest and an attention task with frequent occurrence of mind wandering. *Hum. Brain Mapp.* <https://doi.org/10.1002/hbm.24721>.
- Di, X., Biswal, B.B., n.d. Modulatory interactions between the default mode network and task positive networks in resting-state. doi: 10.7287/peerj.preprints.124.
- Di Martino, A., Kelly, C., Grzadzinski, R., et al., 2011. Aberrant striatal functional connectivity in children with autism. *Biol. Psychiatry* 69 (9), 847–856.
- Di, X., Zhang, H., Biswal, B.B., 2020. Anterior cingulate cortex differently modulates frontoparietal functional connectivity between resting-state and working memory tasks. *Hum. Brain Mapp.* 41 (7), 1797–1805.
- Dirks, B., Romero, C., Voorhies, W., Kupis, L., Nomi, J.S., Dajani, D.R., Odriozola, P., Burrows, C.A., Beaumont, A.L., Cardona, S.M., Parlade, M.V., Alessandri, M., Britton, J.C., Uddin, L.Q., 2020. Neural responses to a putative set-shifting task in children with autism spectrum disorder. *Autism Res.*
- Dixon, M.L., De La Vega, A., Mills, C., et al., 2018. Heterogeneity within the frontoparietal control network and its relationship to the default and dorsal attention networks. *Proc. Natl. Acad. Sci. U S A.* 115 (7), E1598–E1607.
- Falahpour, M., Thompson, W.K., Abbott, A.E., et al., 2016. Underconnected, but not broken? Dynamic functional connectivity MRI shows underconnectivity in Autism is linked to increased intra-individual variability across time. *Brain Connect.* 6 (5), 403–414.
- Fishman, I., Linke, A.C., Hau, J., Carper, R.A., Müller, R.-A., 2018. Atypical functional connectivity of amygdala related to reduced symptom severity in children with Autism. *J. Am. Acad. Child Adolesc. Psychiatry* 57 (10), 764–774.e3.
- Fox, M.D., Corbetta, M., Snyder, A.Z., Vincent, J.L., Raichle, M.E., 2006. Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proc. Natl. Acad. Sci. U S A.* 103 (26), 10046–10051.
- Friston, K.J., Williams, S., Howard, R., Frackowiak, R.S.J., Turner, R., 1996. Movement-related effects in fMRI time-series. *Magn. Reson. Med.* 35 (3), 346–355.
- Goulden, N., Khusnulnisa, A., Davis, N.J., et al., 2014. The salience network is responsible for switching between the default mode network and the central executive network: replication from DCM. *Neuroimage* 99, 180–190.
- Griffanti, L., Douaud, G., Bijsterbosch, J., et al., 2017. Hand classification of fMRI ICA noise components. *NeuroImage* 154, 188–205. <https://doi.org/10.1016/j.neuroimage.2016.12.036>.
- Happé, F., Frith, U., 2006. The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *J. Autism Dev. Disord.* 36 (1), 5–25. <https://doi.org/10.1007/s10803-005-0039-0>.
- Harlalka, V., Bapi, R.S., Vinod, P.K., Roy, D., 2019. Atypical flexibility in dynamic functional connectivity quantifies the severity in autism spectrum disorder. *Front. Hum. Neurosci.* 13, 6.
- He, C., Chen, Y., Jian, T., et al., 2018. Dynamic functional connectivity analysis reveals decreased variability of the default-mode network in developing autistic brain. *Autism Res.* 11 (11), 1479–1493.
- Hutchison, R.M., Morton, J.B., 2015. Tracking the brain's functional coupling dynamics over development. *J. Neurosci.* 35 (17), 6849–6859.
- Jenkinson, M., Beckmann, C.F., Behrens, T.E.J., Woolrich, M.W., Smith, S.M., 2012. FSL. *NeuroImage* 62 (2), 782–790. <https://doi.org/10.1016/j.neuroimage.2011.09.015>.
- Jia, H., Hu, X., Deshpande, G., 2014. Behavioral relevance of the dynamics of the functional brain connectome. *Brain Connect.* 4 (9), 741–759.
- Kana, R.K., Uddin, L.Q., Kenet, T., Chugani, D., Müller, R.-A., 2014. Brain connectivity in autism. *Front. Hum. Neurosci.* 8, 349.
- Keown, C.L., Shih, P., Nair, A., Peterson, N., Mulvey, M.E., Müller, R.-A., 2013. Local functional overconnectivity in posterior brain regions is associated with symptom severity in autism spectrum disorders. *Cell Rep.* 5 (3), 567–572.
- Krieger-Redwood, K., Jefferies, E., Karapanagiotidis, T., et al., 2016. Down but not out in posterior cingulate cortex: deactivation yet functional coupling with prefrontal cortex during demanding semantic cognition. *NeuroImage* 141, 366–377. <https://doi.org/10.1016/j.neuroimage.2016.07.060>.
- Lam, K.S., Aman, M.G., 2007. The repetitive behavior scale-revised: independent validation in individuals with autism spectrum disorders. *J. Autism Dev. Disord.* 37 (5), 855–866.
- Li, W., Mai, X., Liu, C., 2014. The default mode network and social understanding of others: what do brain connectivity studies tell us. *Front. Hum. Neurosci.* 8. <https://doi.org/10.3389/fnhum.2014.00074>.
- Liu, X., Chang, C., Duyn, J.H., 2013. Decomposition of spontaneous brain activity into distinct fMRI co-activation patterns. *Front. Syst. Neurosci.* 7. <https://doi.org/10.3389/fnsys.2013.00101>.
- Liu, X., Duyn, J.H., 2013. Time-varying functional network information extracted from brief instances of spontaneous brain activity. *Proc. Natl. Acad. Sci. U S A.* 110 (11), 4392–4397.
- Liu, X., Zhang, N., Chang, C., Duyn, J.H., 2018. Co-activation patterns in resting-state fMRI signals. *Neuroimage* 180 (Pt B), 485–494.
- Livingston, L.A., Happé, F., 2017. Conceptualising compensation in neurodevelopmental disorders: reflections from autism spectrum disorder. *Neurosci. Biobehav. Rev.* 80, 729–742. <https://doi.org/10.1016/j.neubiorev.2017.06.005>.
- Lord, C., Rutter, M., DiLavore, P., Risi, S., Gotham, K., Bishop, S., 2012. *Autism diagnostic observation schedule—2nd edition (ADOS-2)*. Western Psychological Corporation, Los Angeles, CA.
- Lurie, D.J., Kessler, D., Bassett, D.S., et al., 2020. Questions and controversies in the study of time-varying functional connectivity in resting fMRI. *Netw. Neurosci.* 4 (1), 30–69.
- Mars, R.B., Neubert, F.-X., Noonan, M.P., Sallet, J., Toni, I., Rushworth, M.F.S., 2012. On the relationship between the “default mode network” and the “social brain”. *Front. Hum. Neurosci.* 6. <https://doi.org/10.3389/fnhum.2012.00189>.
- Marshall, E., Nomi, J.S., Dirks, B., Romero, C., Kupis, L., Chang, C., Uddin, L.Q., 2020. Co-activation pattern analysis reveals altered salience network dynamics in children with autism spectrum disorder. *Hum. Brain Mapp.* 41 (1), 1–11. <https://doi.org/10.1002/hbm.24721>.
- Mash, L.E., Linke, A.C., Olson, L.A., Fishman, I., Liu, T.T., Müller, R.-A., 2019. Transient states of network connectivity are atypical in autism: a dynamic functional connectivity study. *Hum. Brain Mapp.* 40 (8), 2377–2389.
- Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. *Brain Struct. Funct.* 214 (5–6), 655–667.
- Müller, R.-A., Fishman, I., 2018. Brain connectivity and neuroimaging of social networks in Autism. *Trends Cogn. Sci.* 22 (12), 1103–1116.
- Padmanabhan, A., Lynch, C.J., Schaer, M., Menon, V., 2017. The default mode network in Autism. *Biol. Psychiatry: Cognitive Neurosci. Neuroimage* 2 (6), 476–486. <https://doi.org/10.1016/j.bpsc.2017.04.004>.
- Parker, D.B., Razlighi, Q.R., 2019. The benefit of slice timing correction in common fMRI preprocessing pipelines. *Front. Neurosci.* 13, 821.
- Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage* 84, 320–341.
- Preti, M.G., Bolton, T.A., Van De Ville, D., 2017. The dynamic functional connectome: state-of-the-art and perspectives. *Neuroimage* 160, 41–54.
- Rane, P., Cochran, D., Hodge, S.M., Haselgrove, C., Kennedy, D.N., Frazier, J.A., 2015. Connectivity in Autism: a review of MRI connectivity studies. *Harv. Rev. Psychiatry* 23 (4), 223–244.
- Rashid, B., Blanken, L.M.E., Muetzel, R.L., et al., 2018. Connectivity dynamics in typical development and its relationship to autistic traits and autism spectrum disorder. *Hum. Brain Mapp.* 39 (8), 3127–3142.
- Spreng, R.N., DuPre, E., Selarka, D., et al., 2014. Goal-congruent default network activity facilitates cognitive control. *J. Neurosci.* 34 (42), 14108–14114.
- Supekar, K., Uddin, L.Q., Khousam, A., et al., 2013. Brain hyperconnectivity in children with autism and its links to social deficits. *Cell Rep.* 5 (3), 738–747.
- Uddin, L.Q., 2015. Salience processing and insular cortical function and dysfunction. *Nat. Rev. Neurosci.* 16 (1), 55–61.
- Uddin, L.Q., 2020. Brain mechanisms supporting flexible cognition and behavior in adolescents with autism spectrum disorder. *Biol. Psychiatry*. <https://doi.org/10.1016/j.biopsych.2020.05.010>.
- Uddin, L.Q., Karlsgodt, K.H., 2018. Future directions for examination of brain networks in neurodevelopmental disorders. *J. Clin. Child Adolesc. Psychol.* 47 (3), 483–497.
- Uddin, L.Q., Iacoboni, M., Lange, C., Keenan, J.P., 2007. The self and social cognition: the role of cortical midline structures and mirror neurons. *Trends Cognitive Sci.* 11 (4), 153–157. <https://doi.org/10.1016/j.tics.2007.01.001>.
- Uddin, L.Q., Menon, V., 2009. The anterior insula in autism: under-connected and under-examined. *Neurosci. Biobehav. Rev.* 33 (8), 1198–1203.
- Uddin, L.Q., Supekar, K.S., Ryali, S., Menon, V., 2011. Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. *J. Neurosci.* 31 (50), 18578–18589. <https://doi.org/10.1523/jneurosci.4465-11.2011>.
- Uddin, L.Q., Supekar, K., Lynch, C.J., et al., 2013. Salience network-based classification

- and prediction of symptom severity in children with Autism. *JAMA Psychiatry*. 70 (8), 869. <https://doi.org/10.1001/jamapsychiatry.2013.104>.
- Uddin, L.Q., Supekar, K., Lynch, C.J., et al., 2015. Brain state differentiation and behavioral inflexibility in Autism. *Cereb. Cortex*. 25 (12), 4740–4747.
- Uddin, L.Q., Yeo, B.T.T., Spreng, R.N., 2019. Towards a universal taxonomy of macro-scale functional human brain networks. *Brain Topogr.* 32 (6), 926–942.
- Vatansever, D., Menon, D.K., Manktelow, A.E., Sahakian, B.J., Stamatakis, E.A., 2015. Default mode dynamics for global functional integration. *J. Neurosci.* 35 (46), 15254–15262. <https://doi.org/10.1523/jneurosci.2135-15.2015>.
- Vissers, M.E., Cohen, X.M., Geurts, H.M., 2012. Brain connectivity and high functioning autism: a promising path of research that needs refined models, methodological convergence, and stronger behavioral links. *Neurosci. Biobehav. Rev.* 36 (1), 604–625.
- Watanabe, T., Rees, G., 2017. Brain network dynamics in high-functioning individuals with autism. *Nat. Commun.* 8, 16048.
- Wechsler, D., 2011. Wechsler Abbreviated Scale of Intelligence-Second Edition. NCS Pearson, San Antonio, TX.
- White, T., Calhoun, V.D., 2019. Dissecting static and dynamic functional connectivity: example from the autism spectrum. *J. Exp. Neurosci.* 13.
- Yan, C.-G., Wang, X.-D., Zuo, X.-N., Zang, Y.-F., 2016. DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging. *Neuroinformatics*. 14 (3), 339–351.
- Yao, Z., Hu, B., Xie, Y., et al., 2016. Resting-state time-varying analysis reveals aberrant variations of functional connectivity in Autism. *Front. Hum. Neurosci.* 10, 463.
- You, X., Norr, M., Murphy, E., et al., 2013. Atypical modulation of distant functional connectivity by cognitive state in children with Autism Spectrum Disorders. *Front. Hum. Neurosci.* 7. <https://doi.org/10.3389/fnhum.2013.00482>.