ATYPICAL RELATIONS BETWEEN DEFAULT, DORSAL ATTENTION, AND FRONTOPARIETAL CONTROL NETWORKS IN MALES WITH AUTISM SPECTRUM DISORDER

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A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF ARTS

GRADUATE PROGRAM IN PSYCHOLOGY

YORK UNIVERSITY

TORONTO, ONTARIO

JANUARY 2025

Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by difficulties in social interaction and communication, and by restricted and repetitive behaviours. We used resting-state functional connectivity fMRI to investigate three intrinsic brain networks which subserve domains of behaviour known to be impacted in ASD; the antagonistic “default” and “dorsal attention” networks – which subserve internally and externally directed cognition, respectively – and the “frontoparietal control” network which flexibly couples with either default or dorsal attention networks in order to dynamically direct the locus of attention. Using a novel method to compare the hierarchical organization of networks between groups, we found atypical organization of the three networks in ASD, including a fractionation of the frontoparietal control network and attenuation of the anticorrelation between default and dorsal attention networks. These results suggest that ASD is associated with atypical hierarchical organization of large-scale intrinsic brain networks, potentially contributing to cognitive and behavioral symptoms.

Acknowledgements

Firstly, I want to thank my supervisor, Dr. Dale Stevens, for his guidance, patience and encouragement during both my bachelor's and master's degrees.

Secondly, I want to thank my committee members, Dr. Gary Turner, Dr. Lauren Sergio, and Dr. Magda Wojtowicz, for contributing their time and expertise, and providing thoughtful feedback.

Third, I want to thank my lab mates from the CAN Lab for creating a welcoming and neurodivergent friendly environment. I especially want to thank Naail Khan for coaching me in programming and statistics.

Fourth, I want to thank NSERC, OGS and VISTA for funding my graduate studies.

Finally, I want to thank my mother, Cindy Hartman, and my father, Dr. Lorne Hartman, for getting me to this point. Thank you for everything you've done to support me.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ADOS	Autism Diagnostic Observation Schedule
ASD	autism spectrum disorder
aTL	anterior temporal lobe
BA	Brodmann Area
BOLD	blood oxygen level dependent
daCC	dorsal anterior cingulate cortex
DAN	dorsal attention network
DMN	default mode network
EPI	echo-planar image
FEF	frontal eye field
fMRI	functional magnetic resonance imaging
FOV	field of view
FPCN	frontoparietal control network
GLM	general linear model
GSR	global signal regression
HF	hippocampal formation
IFG	inferior frontal gyrus
aINS	anterior insula
IPL	inferior parietal lobule
IQ	intelligence quotient
MFG	middle frontal gyrus

MNI	Montreal Neurological Institute
MPRAGE	magnetization prepared rapid gradient echo
MT	middle temporal motion complex
PCC	posterior cingulate cortex
PCS	precentral sulcus
PCu	precuneus
PFC	prefrontal cortex
PLS	partial least squares
ROI	region of interest
RRC	ROI-to-ROI connectivity matrices
RSFC	resting state functional connectivity
RVT	respiration volume per time
SFG	superior frontal gyrus
SOG	superior occipital gyrus
SPL	superior parietal lobule
STS	superior temporal sulcus
TD	typically developing
TE	time to echo
TPJ	temporal parietal junction
TR	time to repetition

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by difficulties in social interaction and communication, and by restricted and repetitive behaviours (American Psychiatric Association, 2013). The prevalence of ASD is 1 in 36, with males being four times more likely to be diagnosed than females (Maenner, 2023). Cognitively, ASD is widely understood to be associated with abnormalities of attentional allocation (Ames & Fletcher-Watson, 2010), executive functioning (St John et al., 2022) and theory of mind (Baron-Cohen, 2000; Polónyiová et al., 2024).

Neurologically, the specific abnormalities of brain function which underlie the condition remain poorly understood. A growing number of studies have attempted to investigate the neurobiology of ASD using functional connectivity fMRI, which measures the temporal correlation between blood-oxygenation-level-dependent (BOLD) signals of distributed brain regions in order to determine the degree to which they covary during a task or at rest (Di Martino et al., 2014; Hull et al., 2017; Rogers et al., 2007).

General Underconnectivity as a Theory of Autism?

Based on findings of reduced functional connectivity among regions of interest (ROI) in ASD during a sentence comprehension task, Just et al. (2004, p. 1817) formulated an "underconnectivity theory" which posits that "autism is a cognitive and neurobiological disorder marked and caused by underfunctioning integrative circuitry." Corresponding findings of underconnectivity in ASD were subsequently reported for tasks involving executive functioning

(Just et al., 2007), motor functioning (Mostofsky et al., 2009), visuomotor coordination (Villalobos et al., 2005), face processing (Kleinhans et al., 2008), working memory (Koshino et al., 2005), response inhibition (Kana et al., 2007), cognitive control (Solomon et al., 2009), self-representation (Lombardo et al., 2010) and tasks involving theory of mind (Mason et al., 2008).

This consistent finding of underconnectivity was previously described as the “first firm finding” in the neurophysiology of ASD (Hughes, 2007); however, numerous studies have since produced conflicting results. Thai et al. (2009) questioned the consensus around the general underconnectivity theory of ASD, noting that evidence in support of underconnectivity was primarily derived from comparing measures of task-related covariance between autistic participants and typically developing (TD) control participants. These measures are susceptible to indirect effects, such as increased demands on attentional resources, which are difficult to distinguish from deficits in the higher-level cognitive task being employed. For example, impairments in seemingly high-level face processing in ASD could potentially be accounted for by low-level visual processing deficits (Behrmann et al., 2006; Dakin & Frith, 2005). The interpretation of differential functional connectivity in ASD during task performance as being indicative of dysfunction in the neural systems which underlie those processes often fails to account for the possibility of more fundamental cognitive or perceptual deficits.

Intrinsic Functional Connectivity

Another avenue of investigation involves resting-state fMRI, in which participants are not presented with explicit task demands (Biswal et al., 1995; Fox & Raichle, 2007). This research paradigm has seen enormous growth in ASD research, in part due to the introduction of several data sharing initiatives, including the Autism Brain Imaging Data Exchange (ABIDE) database

(Di Martino et al., 2014). Resting-state functional connectivity (RSFC) analyses of resting-state fMRI scans in healthy participants have revealed RSFC across multiple dissociable functional brain networks. These networks largely overlap with those observed during task performance and have been used to map the brain's intrinsic architecture (Power et al., 2011; Sepulcre et al., 2010; Yeo et al., 2011).

A large number of studies on RSFC in ASD have focused on the default mode network (DMN), a set of brain regions including the medial (m) prefrontal cortex (PFC), posterior cingulate cortex (PCC), lateral and medial temporal lobes and posterior inferior parietal lobule (Gusnard et al., 2001). Initially, the DMN was referred to in the literature as a "task negative network" because its activation was typically suppressed during tasks which were interpreted as goal directed. However, subsequent research has shown the DMN to be activated during internally focussed cognition (Spreng et al., 2010) such as such as mind-wandering (Mason et al., 2008) self-reference (Gusnard et al., 2001), and self-oriented recollection and prospection (Schacter et al., 2007), which dispels the notion that the DMN is uninvolved in goal-directed cognition.

A related functional brain network is the dorsal attention network (DAN), which comprises the dorsolateral (dl) PFC, frontal eye fields (FEF), inferior precentral sulcus, middle temporal motion complex, and superior parietal lobule. The DAN is activated during externally focussed goal-directed cognition, and demonstrates anticorrelation with the DMN, such that activation in one network is associated with a concomitant decrease in the activation of the other both during a task and at rest (Fox et al., 2005; Spreng et al., 2010). However, Kennedy et al. (2006) found that individuals with ASD failed to demonstrate the appropriate deactivation of the DMN during externally directed tasks.

Anatomically interposed between the DMN and DAN is the frontoparietal control network (FPCN), comprising the rostrolateral prefrontal cortex, middle frontal gyrus, anterior insula/frontal operculum, dorsal anterior cingulate cortex, precuneus, and anterior inferior parietal lobule (Vincent et al., 2008). The FPCN has been shown to flexibly alternate coupling with the DMN and DAN during internally focussed vs. externally focussed cognition, respectively, suggesting that it is responsible for mediating the relationship between the other two networks in support of goal-directed cognitive processes (Spreng et al., 2010, 2013).

A graph analysis of network properties within and between the DMN, DAN, and FPCN has demonstrated that the FPCN comprises three dissociable types of nodes: DMN aligned nodes (left anterior inferior parietal lobule and left rostrolateral prefrontal cortex), DAN aligned nodes (bilateral dorsolateral prefrontal cortex and right middle frontal gyrus BA 9, rostrolateral prefrontal cortex, anterior insula and anterior inferior parietal lobule) and dual-aligned nodes (bilateral middle frontal gyrus BA 6, left middle frontal gyrus BA 9, left anterior insula, dorsal anterior cingulate cortex and medial superior prefrontal cortex).

Alterations in the composition and interaction of these three functional brain networks have been investigated across a number of cognitive domains, including aging (Setton et al., 2022; Spreng et al., 2016; Spreng & Schacter, 2012; Stevens et al., 2008), depression (Kaiser et al., 2015) and bilingualism (Grady et al., 2015; Stevens et al., 2023).

The majority of intrinsic functional connectivity studies of ASD have focused on the DMN, due to its central importance in cognitive modalities known to be impaired in ASD, such as prospection, social cognition, and theory of mind. The results of these studies have been inconsistent, variously reporting increased (CJ et al., 2013; Supekar et al., 2013), decreased (Assaf et al., 2010; Cherkassky et al., 2006; Jung et al., 2014; Kennedy & Courchesne, 2008a;

Monk et al., 2009; Washington et al., 2014; Weng et al., 2010; Wiggins et al., 2011), or mixed (Fishman et al., 2014; Funakoshi et al., 2016) patterns of RSFC.

Far fewer studies have focussed on the DAN and/or FPCN in ASD. Some studies have reported no difference in the composition or functional connectivity of the DAN (de Lacy et al., 2017; Kennedy & Courchesne, 2008b; Nomi & Uddin, 2015). Other studies have reported abnormalities of the DAN related to age, or the performance of a specific task; Farrant & Uddin (2016) reported that the dorsal and ventral attention networks were hyperconnected in autistic children and hypoconnected in autistic adults, and Fitzgerald et al. (2015) reported that the DAN demonstrated inverted patterns of functional connectivity compared to TD participants during valid and invalid trials of the Posner Cuing Task.

Several studies reference “salience”, “executive”, and “cingulo-opercular” networks, which we consider to be components of the FPCN. Results are inconsistent, with reports of both hyperconnectivity (Abbott et al., 2016) and hypoconnectivity (de Lacy et al., 2017) between the DMN and FPCN in ASD.

Methodological Considerations

Much of the inconsistency in the ASD literature may be the result of differences in data collection and analysis protocols. Functional connectivity can be measured in data acquired during a continuous resting-state, where participants lie awake in the scanner with eyes closed, open, or passively viewing a fixation point (Gusnard & Raichle, 2001), from data comprising concatenated rest blocks from a blocked task design, or from the residual time-courses generated by regressing task-evoked responses (Fair et al., 2007).

Task Regression

To evaluate the relative effect of differing methods of functional connectivity analysis in a population with ASD, Jones and colleagues (2010) examined data from an overt word generation task using data with task activation included, data with task activation removed via a single regressor, and data with task activation removed via individual regressors for each task condition. Apparent underconnectivity between most ROI pairs diminished with increasingly fine regression of task effects, indicating that residual task effects may confound studies using task-regressed data as a substitute for true resting-state data.

Indeed, Müller et al. (2011) conducted a literature review of functional connectivity studies of ASD, finding that studies which were consistent with general underconnectivity were largely task-based and restricted to specific ROIs, whereas those which examined task-unrelated activity across the whole brain were largely inconsistent with it. The authors stated that in the strictest sense “almost the entire literature supporting general functional underconnectivity in ASD might be considered misleading because it focuses on task-specific synchronization between brain regions that may or may not reflect underlying connectivity”.

Eye Condition

Another methodological confound concerns eye status during scans, which can confound the identification of a baseline state. Gusnard and Raichle (2001) have argued that baseline is achieved when participants lie awake with their eyes closed, or passively view a fixation point. However, evidence has accumulated that eyes-open and eyes-closed conditions are associated with significantly different patterns of neural activation, including differences in the amplitude and coherence of BOLD signal (Bianciardi et al., 2009), amplitude of low frequency fluctuations (Jao et al., 2013), the topological organization of functional brain networks (Xu et al., 2014), and frequency specific alterations in measures of regional homogeneity (Song et al., 2015).

Nair and colleagues (2018) examined the effect of eye condition on regional homogeneity analysis performed for both in-house data and low-motion subsamples of the ABIDE dataset, finding that eyes open was associated with local overconnectivity in posterior visual regions and local underconnectivity in the cingulate gyrus, whereas eyes closed was associated with the reverse finding (local underconnectivity in the posterior visual regions and local overconnectivity in the cingulate gyrus).

Global Signal Regression

A final concern is global signal regression (GSR). Globally coherent spontaneous fluctuations of BOLD signal have commonly been assumed to reflect diffuse physiological noise and are often regressed with a General Linear Model (GLM) during typical preprocessing procedures (Desjardins et al., 2001; Macey et al., 2004). However, as the global mean BOLD signal represents a composite of multiple nuisance variables and potentially large-scale coherent brain networks, GSR will both invariably underfit nuisance components and introduce components not native to each voxel's time-series (Saad et al., 2012). Moreover, as GSR recentres the distribution of correlation coefficients to zero, correlations with a given seed voxel will necessarily sum to a negative value, thereby introducing spurious anticorrelations (Murphy et al., 2009).

This is of particular concern when considering between-group contrasts, as locations exhibiting increasingly widespread and coherent differences will contribute correspondingly more to the global signal, and subsequently be more affected by its removal. In addition, where the mean correlation coefficient differs between groups, recentring of the distribution will result in a greater subtraction of correlation values from the group with the higher mean correlation, leading to a corresponding increase of values in regions which did not differ prior to GSR (Gotts et al., 2013).

Relations of the Default, Dorsal Attention, and Frontoparietal Control Networks in ASD

The ability of the FPCN to dynamically modulate the locus of attention by switching between coupling with the DMN and DAN is crucial to enabling goal-directed behaviours which require access to both internal stores of memory and the ability to execute actions in the world. Well documented cognitive and behavioural differences in ASD concern atypical executive functioning, allocation of attention, and theory of mind. We hypothesize that the hierarchical organization of DMN, DAN and FPCN in participants with ASD will be atypical; that the FPCN will be less coherent; and that the DMN and DAN will exhibit less characteristic anticorrelation.

Methods

Participants

Participants were previously recruited at the National Institutes of Health (NIH) Clinical Center, Nuclear Magnetic Resonance (NMR) Research Facility in Bethesda, Maryland. Participants included 25 young males with ASD (age range = 14-28) and 25 young male TD controls (age range = 14-28) with no history of psychiatric or neurological disorders. The TD participants were selected from a larger sample reported previously (Stevens et al., 2015, 2017) such that the groups did not differ significantly (p-values > .10) in age (mean age ± SD, ASD: 21 ± 4 yrs; TD: 22 ± 4 yrs), IQ (mean IQ ± SD, ASD: 115 ± 11; TD: 119 ± 12) as measured with the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2011), or mean head motion parameters. All participants were right-handed and had normal or corrected-to-normal visual acuity. The ASD participants were assessed using the Autism Diagnostic Observation Schedule (ADOS) by an experienced clinician, and all met the diagnostic criteria of the Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR) for ASD (American Psychiatric Association, 2000). Informed assent and/or consent of all participants, and/or where appropriate their parents or guardians, was obtained in accordance with a National Institutes of Health Institutional Review Board approved protocol. Participants were monetarily compensated for their participation.

Data Acquisition

Brain images were previously acquired on a 3 Tesla GE Signa whole-body MRI scanner with an 8-channel head coil. T1-weighted magnetization prepared rapid gradient echo (MPRAGE) anatomical images were acquired with the following parameters: 124 axial slices, slice thickness = 1.2 mm, field of view (FOV) = 24 cm, acquisition matrix = 256 x 256. T2*-weighted blood oxygen level dependent (BOLD) functional images were acquired with a gradient-echo EPI pulse sequence with the following parameters: repetition time (TR) = 3500 ms, echo time (TE) = 27 ms, flip angle = 90°, 42 interleaved contiguous axial slices per volume, slice thickness = 3.0 mm, FOV = 220 mm, acquisition matrix = 128 x 128, single-voxel volume = 1.7 x 1.7 x 3.0 mm^3). Each run lasted 8 minutes and 10 seconds, yielding 140 consecutive whole-brain volumes. Participants were instructed to lay motionless and awake in the scanner while maintaining visual fixation on a centrally located white cross on a gray background.

Preprocessing

Initial preprocessing was performed using the AFNI software package (Cox, 1996). The first four volumes of each run were discarded to allow for T1 equilibration effects. Functional data were despiked, slice-time corrected, and coregistered to the volume nearest the anatomical scan with third-order Lagrange polynomial interpolation. Images were subsequently affine warped to MNI152 stereotaxic space, resampled to 3 mm^3 isotropic voxels, and convolved with a Gaussian kernel with a full width at half maximum (FWHM) of 6 mm.

Physiological, motion, and hardware nuisance artifacts were eliminated using a modified version of the ANATICOR procedure (Jo et al., 2010) previously described in Stevens et al. (2015). T1 images were segmented into tissue compartments using the Freesurfer software package (Fischl et al., 2002). Draining-vessel, ventricular, and white matter masks were generated and eroded by one voxel along each of the three axes to prevent partial volume effects. The resulting masks were applied to the volume-registered echo-planar image, yielding a pure nuisance time-series for draining-vessels and ventricles, as well as local estimates of white-matter BOLD signal averaged within a 15mm radius sphere.

Additional regressors for cardiac pulsatility and respiratory artifacts monitored with a photoplethysmograph and pneumatic belt were generated using Retroicor (Glover et al., 2000) and for respiration volume per time (RVT) using RetroTS (Birn et al., 2008) in the AFNI Matlab library. The final set of nuisance covariates included a mean draining-vessel time-series, a mean ventricular time-series, a locally estimated white-matter time-series, six rigid-body motion parameter estimates (three translations and three rotations), and nine cardiac and respiratory signal regressors from Retroicor and RetroTS. All of the above were detrended with fourth-order polynomials and a least-squares model fitted time-series of each were subtracted from the voxel time-series.

We did not apply a band-pass filter, as temporal filtering is ineffective at eliminating signals above the Nyquist frequency (0.5 x 1/TR ≈ 0.143 Hz in this study), such as cardiac and respiratory signals, which may be aliased into the retained frequency spectrum (Gotts et al., 2013; Van Dijk et al., 2010). We also eschewed global signal regression, which has been shown to systematically distort functional connectivity results as discussed above (Gotts et al., 2013; Murphy et al., 2009; Saad et al., 2012, 2013).

Defining Network Nodes

Forty-three network node ROIs were previously defined by Spreng et al. (2013) using multivariate spatiotemporal PLS analysis (McIntosh & Lobaugh, 2004) of task-based regional peak activation within the DMN, DAN, and FPCN across three independent samples (Spreng et al., 2010; Spreng & Schacter, 2011) during numerical, visuospatial, and autobiographical planning tasks. In brief, each node comprised a 5 mm radius sphere centered on the mean peak maxima from a composite network map ($p < .005$), retaining only significant voxels from across the three samples (one voxel overlapping the left middle frontal gyrus (l-MFG) and left dorsolateral prefrontal cortex (l-dlPFC) was removed, and the right posterior inferior parietal lobule (r-pIPL) and right superior frontal gyrus (r-SFG) were significant in two of three samples but were included to maintain bilateral network composition).

The spatial distribution of activation patterns was topographically consistent with intrinsic measures of the respective networks. A small number of ROIs shifted affiliation between the FPCN and DMN, or FPCN and DAN, depending upon condition (i.e., rsfc or event-related). Notably, no ROIs shifted affiliation between the DMN and DAN.

Network Analyses

Network analyses were conducted in MATLAB (MathWorks, Natick, MA, USA) using Statistical Parametric Mapping 12 (Wellcome Department of Imaging Neuroscience, University College London, London, UK), CONN Toolbox 19.b (Whitfield-Gabrieli & Nieto-Castanon, 2012) and GraphVar 2.02b (Kruschwitz et al., 2015; Waller et al., 2018).

For each participant, the voxelwise timeseries were averaged within each of the forty-three ROI masks, and the corresponding Pearson's product-moment correlation coefficient was calculated for each pairwise correlation across all ROI pairs. The resultant distribution of correlation coefficients was Fisher *r*-to-*z* transformed and used to construct ROI-to-ROI connectivity (RRC) matrices, where each element in the matrix is the Fisher-transformed bivariate correlation coefficient for one pairwise connection.

Connectional modularity of the RRC matrix was established using complete-linkage clustering (Sørensen, 1948) with cluster distance defined by the covariance in BOLD fluctuations between pairs of ROIs or clusters, followed by a multivariate parametric GLM analysis of within- and between- cluster connectivity (Jafri et al., 2008). Typically, the farthest-neighbor distance between nodes is defined as a weighted combination of both functional covariance and an anatomical Euclidean distance metric; however, we chose to define distance entirely based on functional covariance.

We also assessed the betweenness centrality of the posterior middle frontal gyrus (BA 6) due to its importance as a connector node (Spreng et al., 2013). Betweenness centrality was selected over other network measures because of its ability to detect interconnector nodes (Rubinov & Sporns, 2010).

Seed-to-Voxel Analyses

Seed-based whole-brain voxelwise analyses were conducted in AFNI (Cox, 1996). In order to avoid excessive multiple comparisons, six seed ROIs were selected as being representative of their respective networks: the bilateral PCC, a core node of the DMN; the bilateral FEF, core nodes of the DAN; and two cytoarchitectonic subdivisions of the bilateral middle frontal gyrus (MFG), Brodmann areas 6 and 9, key nodes of the FPCN. These nodes are central to their respective networks and have high betweenness centrality scores, as opposed to, for example, bilateral HF (hippocampal formation) or MT (middle temporal motion complex), peripheral nodes of the DMN and DAN respectively, with low betweenness centrality.

For each participant, the timeseries was averaged across voxels within the given ROI mask and the corresponding Pearson's product-moment correlation coefficient was calculated for every other voxel time series in the brain. Paired samples Student's *t*-values (FDR-corrected, $p < 0.05$) were then calculated for the resultant distribution of correlation coefficients for each seed.

Quantitative Comparison of Hierarchical Clustering

Hierarchical agglomerative clustering was performed using the average linkage unweighted pair group method with arithmetic mean (Sokal & Michener, 1958). Dendrograms were generated in which pairwise sets of nodes with the greatest functional connectivity are combined into a cluster, and the means of each set of clusters were likewise paired. This process was continually iterated until a full dendrogram representing the hierarchical organization of functional connectivity was achieved.

In order to test whether ASD and TD groups were distinct in the hierarchical organization of DMN, DAN and FPCN, individual dendrograms were created for each participant and compared against those of every other participant. Baker's Gamma, alternatively known as the Goodman-Kruskal Index, is a measure of similarity between dendrograms defined as the rank correlation between the stages at which pairs of objects combine in each of the two trees (Baker, 1974).

A distribution of Baker's Gamma scores was generated for each participant compared to others in the same group, ASD or TD, which we term "within-group", and for each participant in the other group, which we term "between group." Independent samples t-tests were performed to establish whether Baker's Gamma scores were significantly higher within-group than between-group, which would indicate greater similarity in the hierarchical organization amongst members of the same group compared to between groups.

Results

Network Analyses

In the ASD group, ROIs were segregated into eight clusters compared to five in the TD group. Notably, the ASD group had two clusters that each comprised only two ROIs: one cluster comprised the left posterior IPL and the left TPJ, $F(1, 24) = 415.47$, and another cluster comprised the left anterior IPL and precuneus, $F(1, 24) = 418.95$. The pseudo F-statistic value, a ratio of the between-cluster variation to the within-cluster variation, for these clusters was significantly higher than the next largest cluster, $F(2, 23) = 139.17$. The highest pseudo F-statistic value in the TD group was $F(2, 23) = 221.88$ for a cluster containing the precuneus, left anterior IPL, bilateral SOG, left MT, and right FEF.

Next, we specified an agglomerative clustering solution with three components (see Figures 1 and 2). A visual inspection of the RRC matrix and chord diagrams revealed generally expected patterns of connectivity in the TD group: all ROIs with a DMN affiliated condition were present in one cluster, with the exception of the precuneus; another cluster solely contained ROIs with an FPCN affiliation; and the third cluster contained all nodes solely affiliated with the DAN, as well as a number of FPCN nodes and the precuneus. The ASD group revealed a different pattern of connectivity: a small DMN cluster comprising only the bilateral HF and right IFG, STS and aTL; a cluster containing a mix of DMN, FPCN, and dual-affiliated nodes; and a cluster containing a mix of DAN, FPCN, and dual-affiliated nodes.

In order to make anticorrelations between ROIs more apparent, we reweighted all cells in the RRC matrix with nonnegative T-values to zero and generated new chord plots representing negative correlations between nodes (see Figures 3 and 4).

The TD group demonstrated robust anticorrelation between DMN and DAN components. The dorsal medial, anterior medial, and ventral medial PFC, along with the PCC, left aTL, and right HF nodes of the DMN, were strongly anticorrelated with the bilateral dorsolateral PFC, SPL, and anterior IPL, and left inferior precentral sulcus (iPCS) and MT nodes of the DAN. Overall, we identified sixteen anticorrelated ROI pairs with a reliability of at least FDR-corrected $p < 0.05$, with an average value of $T = -2.358$. The ASD group demonstrated attenuated anticorrelation between the DMN and DAN clusters, with only four anticorrelations. Notably, two of these anticorrelated connections were only detected subthreshold at FDR-corrected $p = .06$ (amPFC and R-dlPFC; PCC and L-dlPFC), leaving only two reliable anticorrelated relationships with FDR-corrected $p < .05$ (L-aTL and R-aIPL; R-aTL and R-dlPFC).

Seed-to-Voxel Analyses

The only seed with between-group differences in correlations to survive a threshold of FDR-corrected $p < 0.05$ was the left FEF, with hyperconnectivity to the anterior cingulate and medial prefrontal cortex, and hypoconnectivity to the frontal operculum/insula and inferior/superior parietal lobule (Figure 5).

There were no significant whole-brain voxelwise between-group differences of the left MFG (BA 6) seed. However, the left MFG (BA 6) did show a significant increase in betweenness centrality in ASD compared to TD.

Quantitative Comparison of Hierarchical Clustering

Hierarchical organization of the networks measured by average linkage unweighted pair group method with arithmetic mean was statistically significantly different between ASD and TD. The

TD group strongly replicated prior literature, with the highest level three cluster solution corresponding to networks whose node affiliations largely mapped onto the expected resting-state affiliations for the DMN, DAN and FPCN networks (Figure 6.)

By contrast, the ASD group displayed a marked partitioning of the FPCN network in which roughly half of the nodes expected to be affiliated with the FPCN instead formed a distinct sub-cluster under the DMN, and the other half formed a distinct sub-cluster under the DAN (Figure 7).

Baker’s Gamma analysis of within- and between-group similarity in hierarchical organization confirmed our hypothesis that the members of each group would be on average more similar to members of their own group than to members of the other group, indicating that the groups have distinct hierarchical organization. The mean Baker’s Gamma of within- and between-group scores for the ASD group were 0.2452 and 0.2227, respectively, with the within- vs. between-group difference of $p = 0.0252$, 95% CI [0.0027, 0.0422]. The mean Baker’s Gamma of within- and between-group scores for the TD group were 0.2683 and 0.2218, respectively, with the within- vs. between-group difference of $p = 3.311\text{e-}06$, 95% CI [0.0269, 0.0659] (Figure 8).

A difference-of-differences [i.e., interaction between group (ASD vs. TD) and connectivity (within- vs. between-group)] analysis was performed by subtracting between-group from within-group Baker’s Gamma scores for each participant and comparing these differences across groups. The difference in means between groups was not significant ($p = 0.0548$) and the confidence interval included zero (95% CI [-0.0519, 0.0005]) meaning that the null hypothesis of no difference in means cannot be rejected. This indicates that group affiliation does not have an interaction effect with the difference between within- and between- group Baker’s Gamma scores.

Supplementary visualizations were created using complete-linkage clustering on group-level mean correlation matrices, where the pairwise distance between clusters equals the distance between the farthest elements in each cluster (Figures 9 and 10).

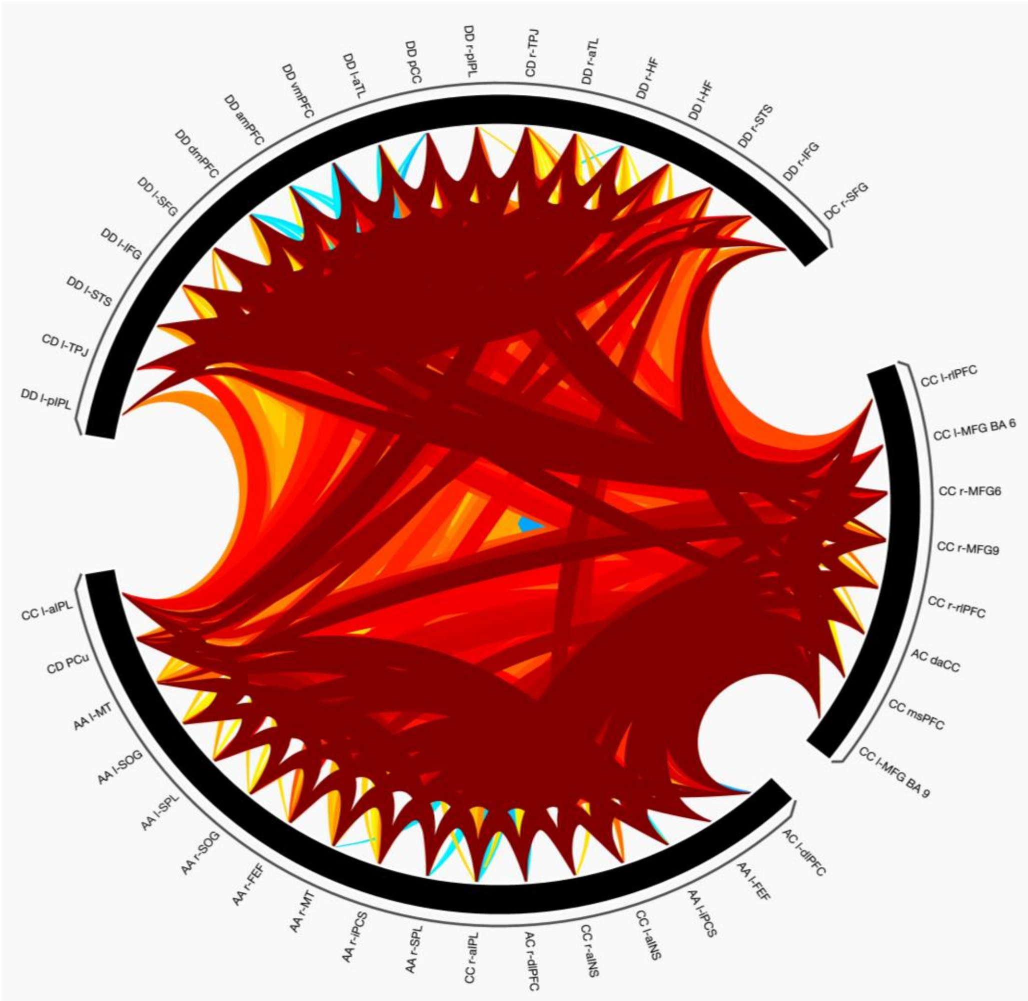

Figure 1: Chord diagram of ROI-to-ROI connectivity in TD

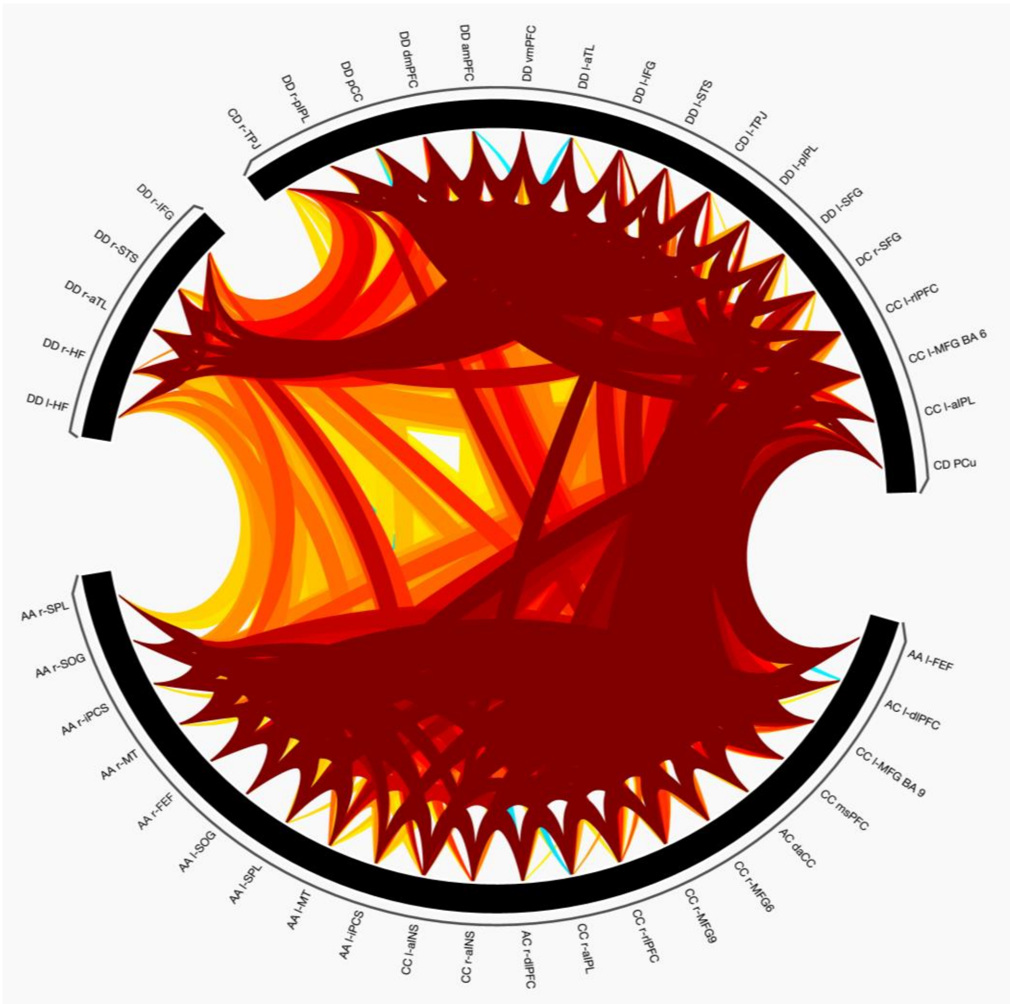

Figure 2: Chord diagram of ROI-to-ROI connectivity in ASD

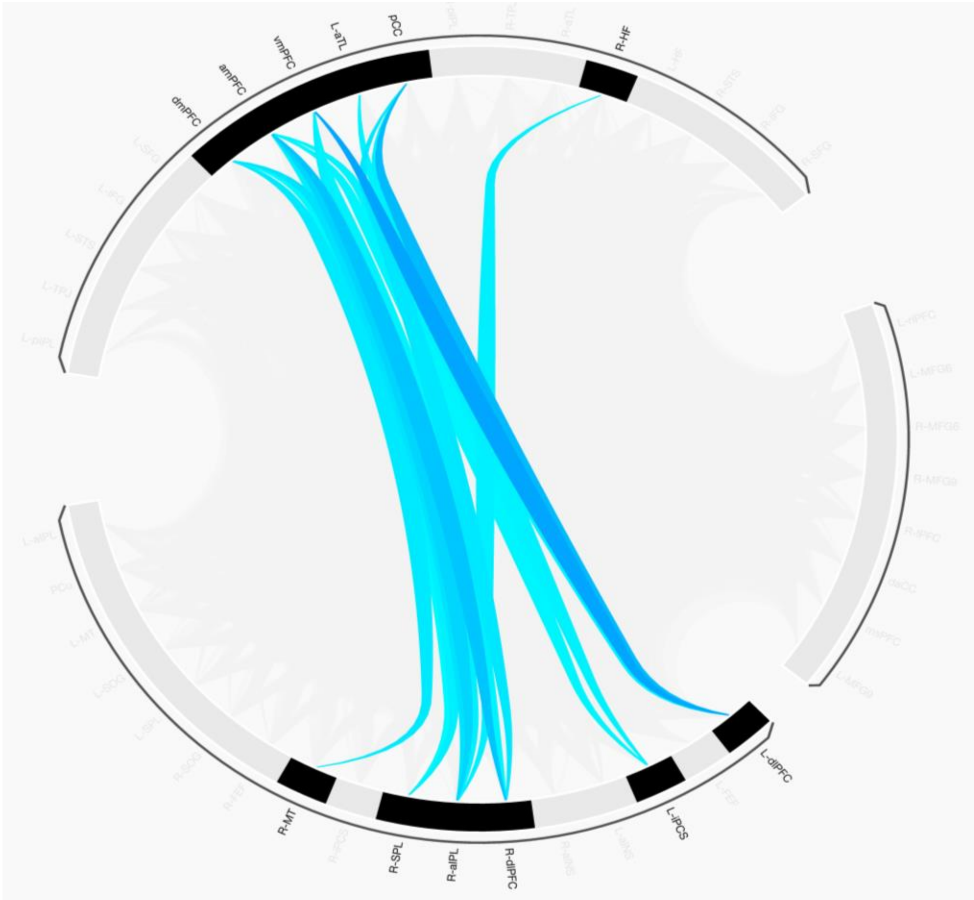

Figure 3: Chord plot of ROI-to-ROI negative correlations in TD

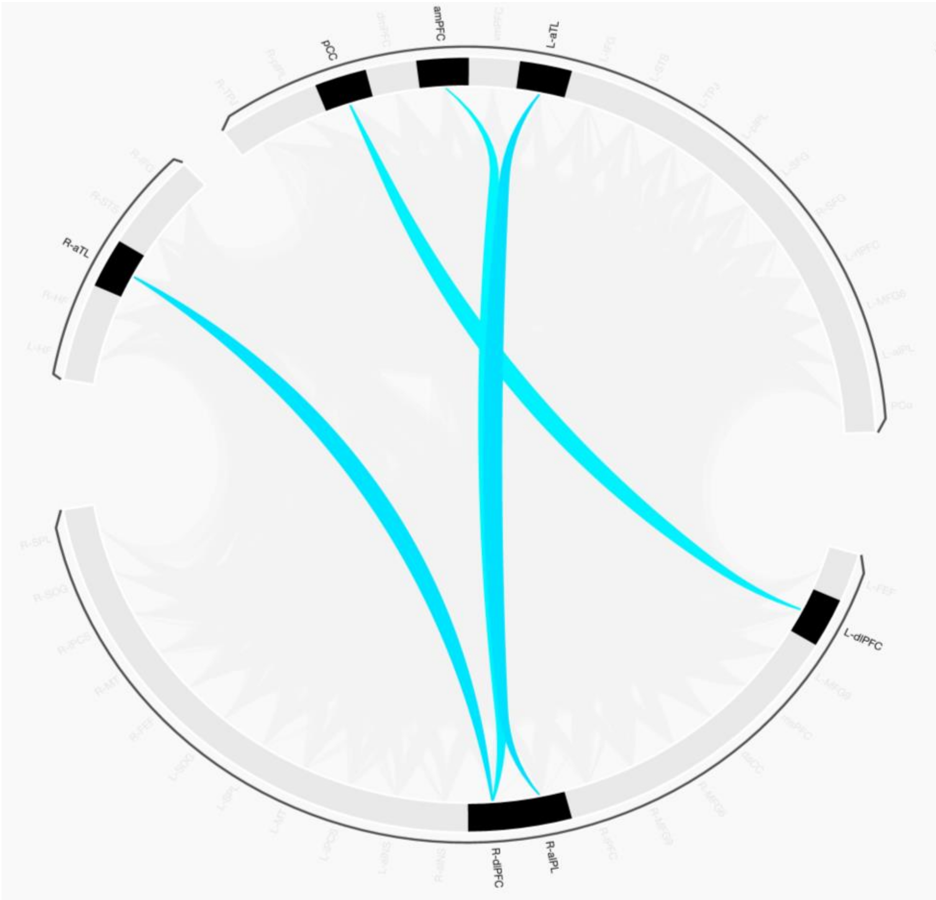

Figure 4: Chord plot of ROI-to-ROI negative correlations in ASD

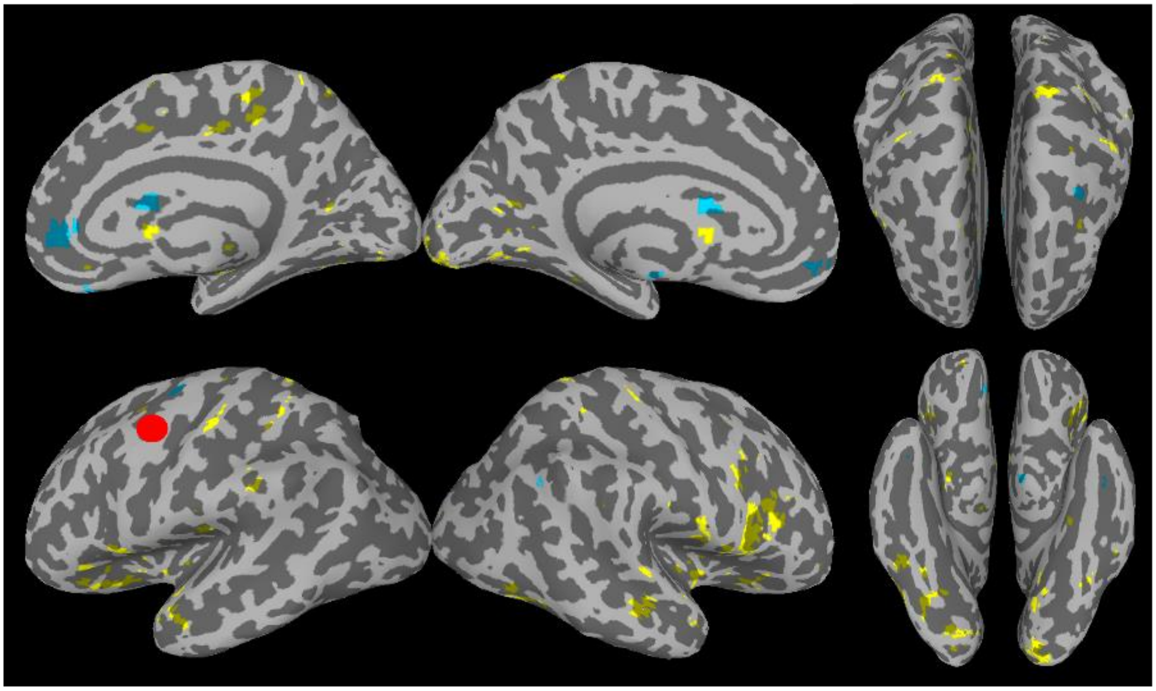

Figure 5: L-FEF seed-to-voxel whole-brain analysis, TD > ASD contrast projected onto a cortical surface map. Red = seed location, Blue = hypoconnectivity in ASD, Yellow = hyperconnectivity in ASD.

ASD > TD				
Hemis.	Region	x	y	z
R	ACC / mPFC	14	43	-1
L	ACC / mPFC	-10	55	7
L	aTL	-40	-10	-26
R	aTL	38	5	-31

Table 1. Select peak regions of between-group differences (ASD > TD). R, right; L, left; ACC, anterior cingulate cortex; mPFC, medial prefrontal cortex; aTL, anterior temporal lobe. Coordinates (*x*, *y*, *z*) are in MNI stereotaxic space.

TD > ASD				
Hemis.	Region	x	y	z
R	Putamen / Basal Ganglia	23	2	2
R	Fusiform Gyrus	32	-70	-10
L	Insula / Frontal Operculum	-55	10	-1
L	Superior Parietal Lobule	-22	-52	67
L	Putamen / Basal Ganglia	-22	5	-2
L	Cerebellum	-25	-53	-46
L	Ventral Visual Complex	-31	-65	-19

Table 2. Select peak regions of between-group differences (TD > ASD). R, right; L, left. Coordinates (*x*, *y*, *z*) are in MNI stereotaxic space.

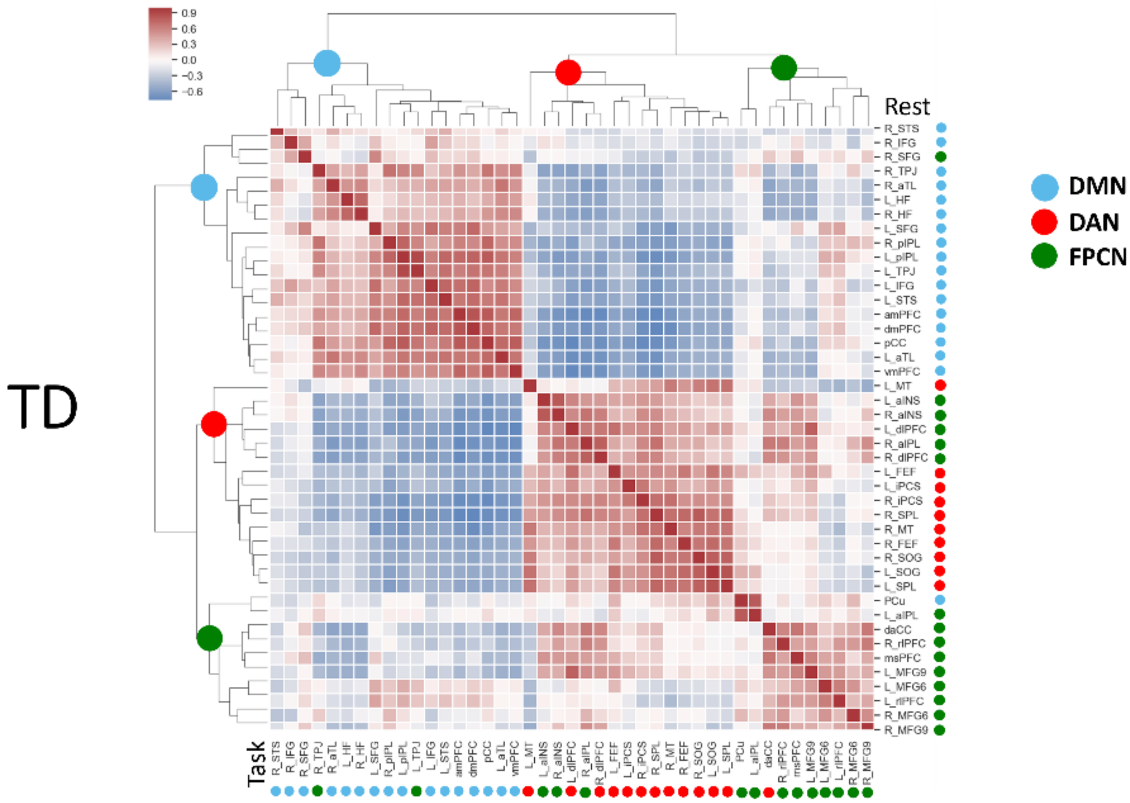

Figure 6: TD hierarchical clustering dendrogram overlayed on a correlation heatmap of the forty-three networks nodes. Blue dots = DMN, Red dots = DAN, Green dots = FPCN.

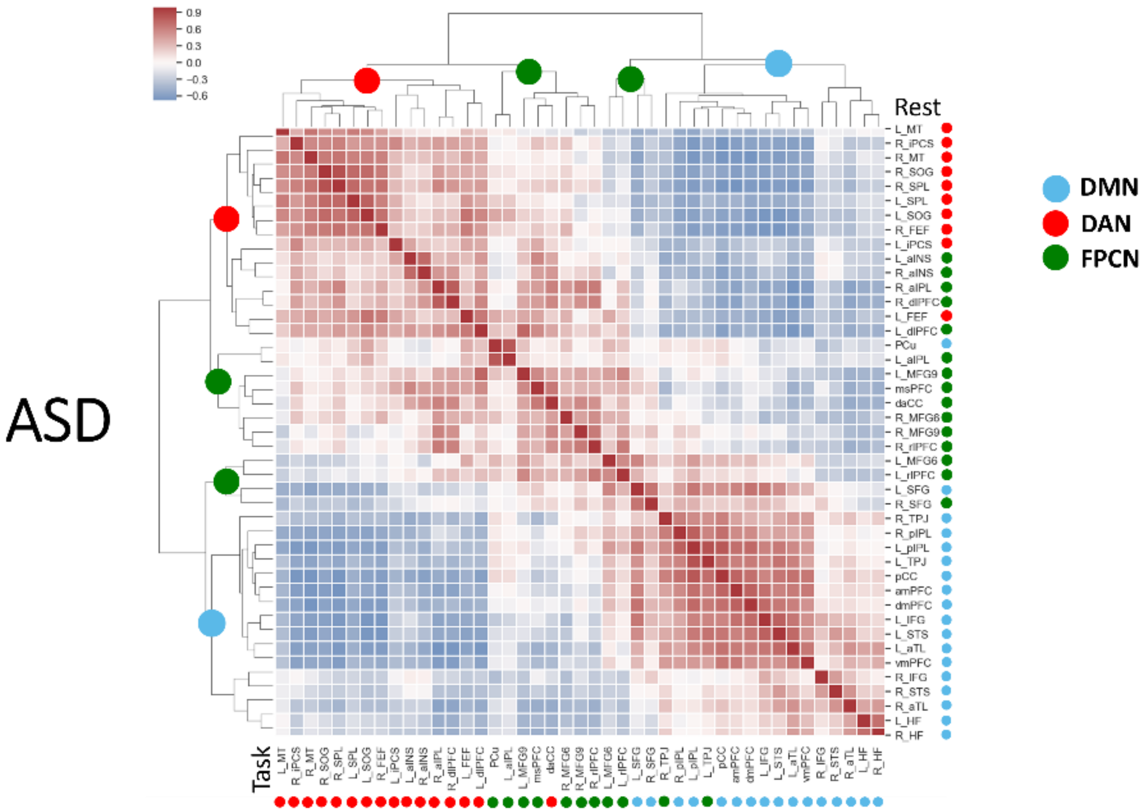

Figure 7: ASD hierarchical clustering dendrogram overlayed on a correlation heatmap of the forty-three networks nodes. Blue dots = DMN, Red dots = DAN, Green dots = FPCN.

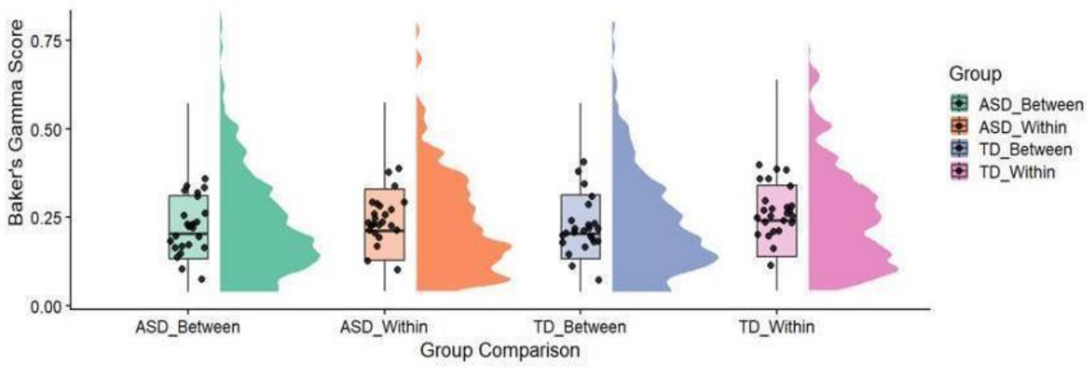

Figure 8: Within- and between-group Baker's Gamma scores for the ASD and TD groups. The boxplot displays the median and interquartile range of Baker's Gamma scores. Each dot represents a singular Baker's Gamma. Green, ASD between-group; orange, ASD within-group; blue, TD between group; pink, TD within-group; n.s., non-significant.

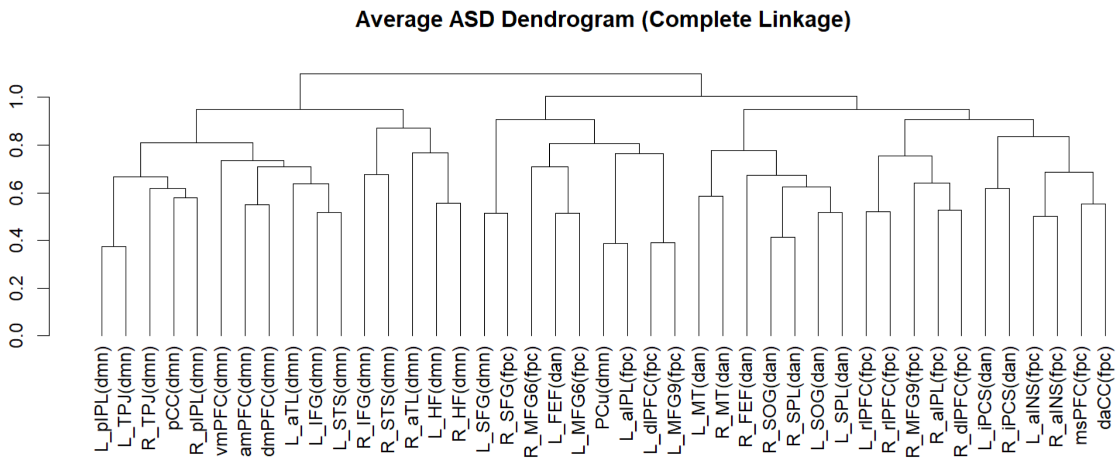

Figure 9: ASD group-level complete-linkage dendrograms showing the hierarchical organization of DMN, DAN and FCN network nodes.

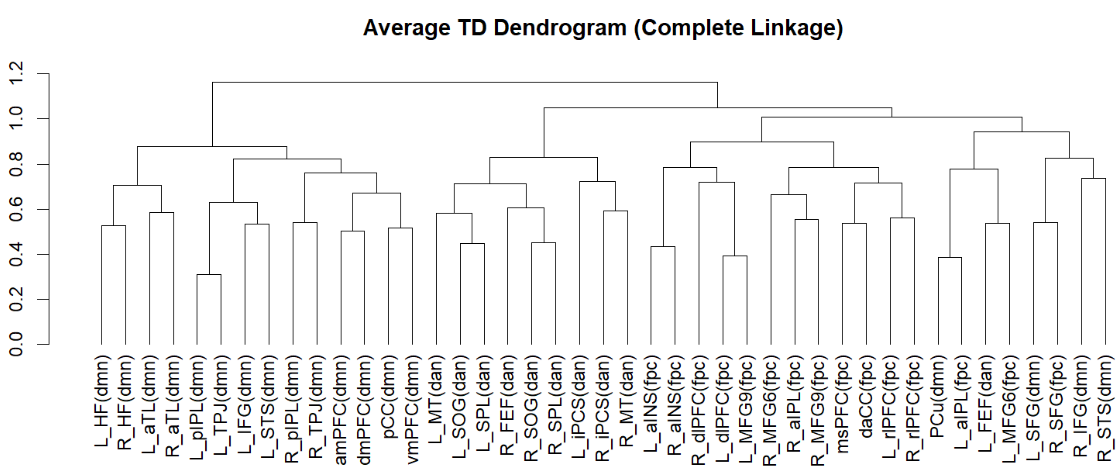

Figure 10: TD group-level complete-linkage dendrograms showing the hierarchical organization of DMN, DAN and FCN network nodes.

Discussion

Using a novel method to compare the hierarchical organization of intrinsic functional networks between ASD and TD groups, we found atypical organization of the three networks in ASD, including a fractionation of the FPCN, which dynamically switches coupling between the DMN and DAN, and reductions of the typical anticorrelation between DMN and DAN. In addition, we observed atypical connectivity of the L-FEF, a core DAN node. Increased betweenness-centrality of the core interconnector node L-MFG6 was also found.

We believe this study addresses a number of limitations in the current literature. As our study utilized true resting-state data, as opposed to regressed task data, we are confident that our results legitimately reflect the latent intrinsic architecture of brain. In addition, our rigorous accounting for motion artifacts via between-group motion matching and our application of a modified ANATICOR procedure has ensured that differences in functional connectivity were not merely the result of motion confounds. Eyes-open protocols have superior test-retest reliability for BOLD signal than eyes-closed protocols (Patriat et al., 2013; Zou et al., 2015). We also eschewed the use of two preprocessing methods which have been demonstrated to systematically affect functional connectivity results, namely bandpass filtering and global signal regression.

Hierarchical Clustering

Our unconstrained complete-linkage clustering solution indicated unusual segregation and integration of network components in ASD. In addition to the larger number of clusters in the ASD group compared to the TD group, two clusters with exceptionally high pseudo *F*-statistics, both including a portion of the IPL (L-pIPL and the L-TPJ; L-aIPL and precuneus). Notably, the pseudo *F*-statistics were nearly twice the highest value in the TD group, indicating that the above clusters are exceptionally tight-knit and highly separated (pseudo *F* describes the ratio of between- to within-cluster variance in agglomerative clustering procedures). The temporoparietal junction (TPJ) and precuneus (PCu) are both dual-affiliated nodes, with affiliations to the FPCN and DMN at task and rest, respectively, and the anterior and posterior portions of the IPL are solely affiliated with FPCN and DMN, respectively. While the correlation between the PCu and left anterior IPL at rest in the ASD group was expected – though not their separation from other clusters – the high degree of covariance between the left TPJ and left posterior IPL was unexpected, as the latter node is typically affiliated exclusively with the FPCN in TD participants.

When we specified a three-component clustering solution, a small DMN affiliated cluster containing the right hemisphere IFG, STS, aTL and bilateral hippocampal formation, which was also present during the unconstrained solution, remained intact. This small cluster was in stark contrast with the much larger DMN cluster observed in the TD group.

Most striking was the absence of a differentiated FPCN in the ASD group; unlike in the TD group, where a cluster comprised solely FPCN nodes, these nodes were roughly split between DMN and DAN clusters in the ASD group. These results indicate a lack of integration of the frontoparietal control network in ASD, and a greater tendency for nodes typically associated with the FPCN to instead affiliate with the other two networks. The ability of the FPCN to dynamically modulate the locus of attention by switching between coupling with the DMN and DAN is crucial to enabling goal-directed behaviours, and this fractionation of the FPCN may underly foundational cognitive and behavioural differences in ASD, including atypical executive functioning, allocation of attention, and theory of mind.

The regions in the small DMN cluster in the ASD group described above (IFG, STS, aTL) are known to have functional abnormalities associated with ASD. For instance, the IFG is considered to be critical for response inhibition and cognitive control (Hampshire et al., 2010; Swick et al., 2008), which are domains of impairment in ASD (Adams & Jarrold, 2012; Johnston et al., 2011). Compared to TD individuals, those with ASD show increased grey-matter volume (Eilam-Stock et al., 2016) and increased activation of the IFG during a go/no-go task (Schmitz et al., 2006). A number of age-related changes to the IFG are associated with ASD, including an increase of IFG activity in response to faces (Bastiaansen et al., 2011) and loss of functional connectivity of the IFG with the presupplementary motor area and right caudate during a go/no-go task (Lee et al., 2009). However, another study found decreased IFG volume (Nickel et al., 2018), although the effect was found to be mediated by comorbid ADHD, which is present in as many as one-third of ASD individuals (Leitner, 2014).

The STS has been characterized as a hub for social perception and cognition (Deen et al., 2015), and along with the medial prefrontal cortex and temporal poles (the most anterior portion of the aTL), has been implicated as constituting the core regions of a network involved in theory of mind (Carrington & Bailey, 2009), which has been shown to be hypoactive during a theory of mind task (i.e., inferring intentionality of moving geometric objects) in ASD (Castelli et al., 2002). Specific activation of the STS has been shown to be generally predictive of performance on theory of mind tasks in TD adults (Otsuka et al., 2009). In ASD, the STS has been found to exhibit a number of morphological and functional abnormalities, including decreased grey-matter volume, hypoactivation during both rest (Zilbovicius et al., 2006) and social tasks, including voice processing (Gervais et al., 2004), and eye-gaze processing (Pelphrey et al., 2005, 2007). Further, STS hypoconnectivity with frontoparietal regions was found to be predictive of atypical emotion recognition performance in ASD (Alaerts et al., 2014).

One of the most notable findings from our clustering analyses concerns the number of anticorrelated relationships observed between nodes of the default and dorsal attention networks. Commensurate with our expectations, the TD group demonstrated significant anticorrelation between the default and dorsal attention networks, with sixteen statistically significant negative between-network correlations. By contrast, the ASD group showed anticorrelation between only four node-pairs, two of which were subthreshold. The only two significant pairwise anticorrelations involved regions which are known to show atypical function in ASD (L-aTL and R-aIPL; R-aTL and R-dlPFC).

Numerous neuroimaging studies have examined the role of the aTL in encoding and integrating semantic information, although there is ongoing debate as to the modality of processing (Bonner & Price, 2013; Patterson et al., 2007; Peelen & Caramazza, 2012; Tyler et al., 2004; Visser et al., 2010). Morphological abnormalities of the anterior temporal lobes in ASD have been well documented (Abell et al., 1999; Ecker et al., 2012; Kwon et al., 2004; Rojas et al., 2006; Waiter et al., 2004), and fMRI studies have suggested atypical recruitment of this region across a range of cognitive tasks including irony processing (Wang et al., 2006), emotional introspection (Silani et al., 2008), theory of mind (Castelli et al., 2002), semantic processing (Gaffrey et al., 2007) and executive functioning (Gilbert et al., 2008). In particular, failure of the anterior portion of the left temporal lobe to specialize for language in early childhood has been hypothesized to represent a fundamental characteristic of ASD (Eyler et al., 2012).

The main connectivity route between the DAN and FPCN has been hypothesized to be the bilateral dlPFC (Spreng et al., 2013), which is affiliated with the DAN and FPCN during task and rest, respectively. This region has not been found to exhibit morphological abnormalities in ASD (Griebling et al., 2010), but post-mortem tissue examination has revealed abnormal microglial-neuronal organization (Morgan et al., 2012). In behavioural studies, participants with ASD reliably underperform on the Wisconsin Card Sorting Test (Liss et al., 2000; Rumsey, 1985; Rumsey & Hamburger, 1990; Sawa et al., 2013), a task which is known to be highly correlated with activation of the dlPFC (Berman et al., 1995; Nagahama et al., 1996), and repetitive transcranial magnetic stimulation of the dlPFC impairs performance on the Wisconsin Card Sorting Test in TD adults (Boschin et al., 2017).

Left Frontal Eye Field

The FEF is a key cortical region critically involved in volitional control over the locus of one's externally focussed attention, including the generation of volitional saccades, and is involved in visual fixation, pursuit, vergence, and a suite of associated cognitive processes such as attentional orienting, visual awareness, and perceptual modulation (Vernet et al., 2014).

Individuals with ASD demonstrate hypoactivation of the FEF during visually guided saccade tasks, but increased activation of a frontostriatal circuit including the dlPFC, caudate nucleus, medial thalamus, anterior and PCC, and right dentate nucleus (Takarae et al., 2007). In ASD, the FEF also shows hypoconnectivity with the dorsal anterior cingulate cortex, which is thought to exert top-down control on the FEF, and there is decreased inhibition-related activation of both the dorsal anterior cingulate cortex (dACC) and FEF (Agam et al., 2010).

Our seed-to-voxel analysis revealed hyper-connectivity of the left FEF to the anterior cingulate/medial prefrontal cortex and hypoconnectivity to the frontal operculum/insula, and inferior/superior parietal lobules.

The anterior cingulate cortex (ACC)/medial prefrontal cortex (mPFC) is a core area of the DMN (Spreng et al., 2009, 2010, 2013), and neuroimaging studies have implicated it in early social cognition (Grossmann, 2013) and associations between context and emotional responses (Euston et al., 2012). Abnormal functional connectivity of the mPFC is considered to be among the most replicated findings in the ASD literature across multiple studies utilizing different data collection protocols and analysis pipelines (Abbott et al., 2016; Assaf et al., 2010; Burrows et al., 2016; Doyle-Thomas et al., 2015; Monk et al., 2009; Nair et al., 2018; von dem Hagen et al., 2014; Washington et al., 2014), although the exact loci were not consistent. Neuroimaging and post-mortem studies have also identified morphological (Yang et al., 2016) and cytoarchitectonic abnormalities of the ACC in both children and adults with ASD (Simms et al., 2009; Uppal et al., 2014). A study utilizing a stimulus-oriented versus stimulus-independent executive functioning task found greater recruitment of the mPFC in ASD individuals compared to recruitment primarily of the occipital cortex in TD individuals (Gilbert et al., 2008). The authors argued that TD participants may be able to modulate activity in the early visual cortex according to the attentional demands of the task to a greater degree than ASD participants.

In studies that differentiate between salience and executive control networks, the dorsal portion of the ACC (dACC) is considered to be a salience network hub (Seeley et al., 2007), which acts as a pivot in switching between default and central executive networks (Sridharan et al., 2008). In our parcellation, the dACC was identified as a dual-affiliated DAN and FPCN node at task and rest, respectively.

Our results indicating hyper-connectivity of the left FEF with the mPFC in ASD may reflect a latent functional architecture in which the mPFC is generally overconnected to the FEF, associated with a deficit in properly attenuating the mPFC-FEF relationship as a function of task-specific attentional demands. However, this explanation does not account for the hemispheric specificity of our results, given that the right FEF did not demonstrate significant between-group differences.

We found hyper-connectivity of the left FEF with the frontal operculum/insula in ASD. Notably, the insula is considered to be the other core node of the salience network along with the anterior cingulate. The insula is more generally hypothesized to facilitate the detection of salient events and modulate switching between other distributed functional networks in order to facilitate access to attentional and memory resources (Menon & Uddin, 2010). An activation likelihood estimation (ALE) meta-analysis of social and non-social processing studies in ASD identified the insula as being hypoactive during social conditions ranging from face processing to theory of mind (Di Martino et al., 2009). It has been argued that the specific task demands for which the insula modulates switching are for whether information is related to external or internal stimuli (Uddin & Menon, 2009). Along with the dlPFC and the anterior insula, the right aIPL is a dual-aligned DAN/FPCN node that facilitates suppression of the DMN (Menon & Uddin, 2010), and shows hyper-connectivity with the left FEF in ASD.

Left Middle Frontal Gyrus (BA 6)

The left MFG (BA 6) demonstrated subthreshold (FDR-uncorrected, $p = .05$) hypoconnectivity with the inferior and superior parietal lobules, with no differences extending into the sulcus. These differences did not survive multiple comparison correction. L-MFG (BA 6) also demonstrated *increased* betweenness centrality in ASD compared to TD. This region typically expresses the highest betweenness centrality of correlations in healthy adults (Spreng et al., 2013) and has been characterized as a global hub using an anatomical labelling atlas (He et al., 2009). It has been argued that domain-specific information from either the DMN or DAN may enter the PFC via the MFG, and traverse the hierarchically organized caudal–rostral axis as contingent processing demands increase (Badre & D’Esposito, 2009; Christoff & Gabrieli, 2000).

Conclusions

Our results demonstrate that the relationships between DMN, DAN, and FPCN are different in ASD relative to TD individuals. In contrast to the TD group, the ASD group did not show a differentiated FPCN. As the FPCN is considered to be crucial for modulating the relationship between the default and dorsal attentions networks, the lack of a differentiated intrinsic FPCN during rest could indicate a latent functional architecture which is impaired at switching between internally and externally directed cognition. This is consistent with our finding of significantly reduced anticorrelation between nodes of the DMN and DAN, as the antagonistic relationship between the two reflects their opposing functional roles in cognition.

We also identified a detached subgroup of DMN nodes with unusually tight clustering in the ASD group, including the IFG, STS, and aTL, each of which is known to be structurally or functionally abnormal in ASD, and which subserve cognitive functions in the TD brain which are markedly impaired in ASD (e.g., response inhibition, social cognition, and semantic processing).

Our ROI analyses demonstrated differences in two regions: the left FEF and left middle frontal gyrus (BA 6). The left FEF was found to be hyperconnected to the medial prefrontal cortex, a region thought to mediate the binding between context and response in memory and decision making, and hypoconnected to the insula/frontal operculum, a region thought to be involved in the detection and discrimination of salient stimuli. The pattern of connectivity we identified in ASD could reflect a functional architecture where the FEF, responsible for modulating visual attention, cannot properly retrieve salient information, and is unable to effectively attenuate the typical FEF-mPFC relationship as a function of task specific attentional demands.

The left MFG (BA 6), which may convey domain-specific information from either the DMN or DAN to the prefrontal cortex, demonstrated increased betweenness centrality in ASD. Further work is needed to understand the functional relevance of this connectivity.

Future research might expand our approach to larger datasets, utilize individualized parcellations and functional localization, or examine the relationship between default, dorsal attention, and frontoparietal control networks during tasks to evaluate differences in the task evoked activation of the networks.

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