

Structural and Functional Properties of Social Brain Networks in Autism and

Social Anxiety

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ABSTRACT

The default mode network (DMN) is active in the absence of task demands and during self-referential thought. Considerable evidence suggests that the DMN is involved in normative aspects of social cognition, and as such, disruptions in the function of DMN would be expected in disorders characterized by alterations in social function. Consistent with this notion, work in autism spectrum disorder (ASD) and social anxiety disorder (SAD) has demonstrated altered activation of several core regions of the DMN relative to neurotypical controls. Despite emergent evidence for alterations within the same brain systems in SAD and ASD, as well as a behavioral continuum of social impairments, no study to date has examined what is unique and what is common to the brain systems within these disorders. Therefore, the primary aim of the current study is to precisely characterize the topology of neural connectivity within the DMN in SAD and ASD and neurotypical controls in order to test the following hypotheses through functional and structural connectivity analyses of the DMN. Our analyses demonstrate increased coactivation of the dorsomedial prefrontal cortex in ASD and SAD compared to controls, as well as over and under connectivity in structural brain connectivity in ASD. These results may reflect general deficits in social function at rest, and disorder specific alterations in structural connectivity in ASD.

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Introduction

Social cognition broadly refers to the processes by which an organism encodes, stores, manipulates, updates and applies information about others (Saxe, 2006), and likely evolved to accomplish specific tasks related to competing and cooperating with conspecifics (Tomasello, Carpenter, Call, Behne & Moll, 2005). Social cognition is further operationalized as the ability to understand and evaluate one's own thoughts and actions within the social world (metacognition), as well the understanding of another's mental state to the content of another's mental state (Schmitz, Kawahara-Baccus, & Johnson, 2004). The neural bases of social cognition, including the structural and functional properties of relevant brain networks have been documented in increasing detail (Gallese, Keysers, & Rizzolatti, 2004), and have consistently highlighted a role for the brain's default mode network (DMN) in supporting normative aspects of social cognition, such as self-referential processing (Buckner, Andrews-Hanna, & Schacter, 2008; Uddin, Iacoboni, Lange & Keenan, 2007; Spreng & Grady, 2010). Research on the DMN within the context of psychiatric and neurodevelopmental disorders has shown alterations in the connective properties of these networks. The purpose of the current study is to evaluate neural connectivity in the DMN in individuals with noted social impairment.

Impairments in social cognitive processes are widely observed across a number of psychological and neurodevelopmental disorders. In particular, both autism spectrum disorders (ASD) and social anxiety disorder (SAD) are characterized by deficits in social function, including deficits in self-referential processing, emotion recognition, and difficulty interpreting social cues. SAD and ASD have distinct behavioral components as well; for example,

individuals with ASD have impairments in social communication and building social relationships, whereas individuals with SAD fear social situations where they may be evaluated negatively (American Psychiatric Association, 2013). Current symptom-based classification of psychological disorders may be insufficient to conceptualize social deficits noted across disorders (Insel, 2014). The approach recently codified by the National Institute for Mental Health (NIMH), the Research Domain Criteria (RDoC; Insel et al., 2010), may be more appropriate for investigating social deficit as a dimension rather than categorical. The RDoC approach takes into account multiple units of analysis, which are combined to understand how symptoms of psychological disorders may be deconstructed into underlying processes and then rebuilt perforce, thus more accurately reflecting underlying genes, physiology and behaviors rather than imperfect diagnostic categories.

This approach is potentially a powerful model for understanding disorders that share commonalities in major symptom clusters, such as the noted social cognitive deficits in ASD and SAD. Despite the conceptual and empirical overlap in SAD and ASD (Richey et al., 2012; White, Bray & Ollendick, 2012), very little research has been conducted to understand the underlying neural processes that give rise to social cognitive deficits in these seemingly discrepant diagnostic categories. There is converging evidence that these deficits in social cognition may manifest in resting state networks.

The role of the DMN in normal social cognition is increasingly appreciated. Buckner and colleagues (2008) propose that the DMN contributes to social judgment and self-reflection. Given the evidence that deficits in social cognition manifest in the DMN, we focused on this well-studied network to examine both disorder *specific* and *social-cognitive general* differences. The DMN is active in the absence of task demands and can be reliably identified through resting-

state fMRI (Buckner et al., 2008; Raichle & Snyder, 2001). Resting state brain data reveal functional connections between brain regions and are thought to relate to behavior recorded outside of the scanner and are likely antecedent to the aberrant activation observed in psychological disorders observed during tasks (Seeley et al., 2007; Biswal Zerrin Yetkin, Haughton, & Hyde, 1995; Grecius et al., 2003; Beckmann, DeLuca, Devlin, & Smith, 2005; Fox, Snyder, Vincent, Corbetta, Van Essen, & Raichle, 2005; Liao et al., 2010).

Regions associated with resting-state functional connectivity often show agreement with structural, white-matter connectivity (Grecius, Sepukar, Menon, & Doherty, 2009; Skudlarski, Jagannathan, Calhoun, Hampson, Skudlarska, & Pearlson., 2008; Honey et al., 2009; van den Heuval, Stam, Kahn, & Pol, 2009). Diffusion tensor imagining (DTI) is a common and noninvasive way to measure white-matter connectivity. DTI measures the flow of water molecules through the brain and can be used to detect myelination and connectivity between regions. Fractional anisotropy (FA) is the most commonly utilized metric of DTI, and can index the flow of water through white matter structures (Travers et al., 2012). FA is measured from 0 to 1, where values closer to 0 indicate that water may flow equally in all directions, and values closer to one suggest longer and narrower connections.

In ASD, researchers have reported decreased connectivity in ASD relative to controls. For example, there is noted decreased functional connectivity in the medial prefrontal cortex (mPFC) in region-of-interest (Kennedy and Courschene, 2008), and independent component analyses (von dem Hagen et al., 2013). Researchers have found decreased functional connectivity between the posterior cingulate cortex and mPFC through seed-based analyses (Eilam-Stock et al., 2014; Doyle-Thomas et al., 2015). Other groups have identified hyperconnectivity in ASD relative to controls (Uddin et al., 2013; Anderson et al., 2011; Lynch et

al., 2013). Although perfect agreement has not been achieved regarding the connectivity profile of DMN in autism, it does appear clear that decreased connectivity in the DMN is associated with increased core features of the disorder (Washington et al., 2014; Anderson et al., 2011). With regards to structural connectivity, Uddin and colleagues (2010) found support for structural connectivity between regions underlying the DMN in neurotypical controls, including between angular gyrus (AG) and hippocampal and parahippocampal regions.

In SAD, a growing literature has implicated specific alterations in DMN connectivity profiles, relative to controls. Liu and colleagues (2015) used multivariate pattern analysis (MVPA) to differentiate SAD patients from control participants. With 82.5% classification accuracy, they found that PCC, precuneus (PCUN), and angular gyrus (AG) contributed the greatest weights to the classifier. During tasks, individuals with SAD had less deactivation of the PCC and PCUN (Gentili et al., 2008). This was supported in an ICA analysis between participants with ASD and controls (Liao et al., 2010). They also found increased activation of the dorsomedial prefrontal cortex (dmPFC) in SAD relative to controls.

Basic neuroscience work in SAD has revealed evidence that brain structure and function associated with the DMN may underlie behavioral manifestations of the disorder (Liao, et al., 2011; Phan et al., 2009; Gentili et al., 2008). Structurally, a number of white matter tracts may mediate pathways relating attentional and emotional processes (Phan et al., 2009). Additionally, brain-behavior associations in SAD revealed that symptom severity is related to increased functional connectivity in a resting state network involved in top-down attentional processing (the dorsal attention network), but relationships between SAD symptomatology and functional connectivity within the DMN have yet to be investigated (Ding et al., 2011; Liao, 2010). Individuals with SAD additionally show aberrations in activation in brain regions associated with

social cognitive processes, (e.g., the medial prefrontal cortex and superior temporal sulcus) compared to normal controls (Tillfors, Furmack, Marteinsdottir & Fredrikson, 2002; Gentili, 2008).

The work outlined above has facilitated understanding of the role of DMN in ASD and SAD separately, however the fact that they have occurred exclusively in parallel is potentially limiting because such approaches cannot rule out the possibility of clinical epiphenomena driving the observed differences between DSM-IV(or 5)-diagnosed patients and control subjects. The RDoC broadly suggests that understanding of psychological disorders is potentially constrained by available, albeit imperfect, diagnostic criteria (Insel et al., 2010; Berenbaum, 2013; Cuthbert & Kozack, 2013). This process-focused, transdiagnostic research approach acknowledges that clusters of symptoms may be attributable to a lower-order latent construct that may occur within one disorder, but these symptoms more likely reflect a mechanism implicated across multiple disorders (Cuthbert & Insel, 2013; Berenbaum, 2013). An increasingly accepted method for understanding symptoms across diagnoses is to identify a symptom that is believed to be common to multiple disorders specifically for the purpose of measuring the underlying process at increasingly fine levels of resolution (e.g., behavior, circuits, cells, genes, molecules). As a prime example, in ASD and SAD, much is known about the neural substrates underlying the social deficits specific to each disorder; however, very little work has been done to (1) compare neurofunctional features that may be common to both disorders, (2) identify features of both that are distinct from typical development and (3) identify neurofunctional features that are unique to each disorder.

The current study uses a transdiagnostic approach as codified in the RDoC to characterize how symptom clusters (particularly social disability symptoms) can be traced to common and

distinct neurobiological mechanisms within SAD and ASD. Accordingly, the main purpose of this study is to define the intrinsic structural and functional properties of a candidate social-cognitive network (the default mode network) in the brain across two psychiatric disorders that are both characterized by social dysfunction. In the context of this approach, we focus on the connective properties of DMN that are expected to be (1) common to ASD and social anxiety, relative to controls (2) unique in ASD, relative to social anxiety and controls (3) unique in social anxiety, relative to ASD and controls.

Specific Aims

The overall goal of this study is to simultaneously characterize the structural (white matter) and functional (grey matter) connective properties of the default mode network. To do this, we used a data-fusion method that combines structural and functional neuroimaging methods, in order to simultaneously evaluate the intrinsic connective properties of the brain at the level of white matter (WM) and grey matter (GM). This approach therefore allows concurrent characterization of the major fiber tracts connecting portions of the cortical sheet that belong to an identified network. In combination with diagnostic and behavioral data, we identified changes in the connective properties to variation in symptomatology in a transdiagnostic (3-group) design. The aims of the proposed study are:

1. Examine the connective properties of the DMN in adults without any prior history of social impairment compared to individuals with a confirmed diagnosis of a psychological disorder (ASD or SAD).

2. Compare the structural and functional connectivity of the DMN in ASD, versus SAD, in order to assess features of this network that are unique to each.
3. Relate self-reported social-cognitive vulnerabilities and rating on clinical interviews to connectivity metrics.

Hypotheses

As related to the specific aims above, the hypotheses of the study are:

- 1) Functional connectivity in social brain networks will show differential functional connectivity, such that a) individuals with ASD will show differential connectivity of the DMN relative to controls, b) individuals with SAD will show differential connectivity of the DMN relative to controls, and c) individuals with SAD will show differential connectivity of DMN relative to individuals with ASD.
- 2) Structural connectivity underlying functional brain regions will vary as a function of group classification, such that FA values will systematically differentiate individuals from ASD from those with SAD, as well as both ASD and SAD from controls.
- 3) Behavioral indices of social function will be related to a) structural connectivity, b) functional connectivity within the DMN, c) and vary as a function of group membership.

Methods

Participants

Fifteen neurotypical controls, fourteen participants with SAD, and fourteen participants with ASD were recruited through ongoing projects. One participant with ASD was excluded

from imaging analyses due to technical difficulties in image acquisition at the scanner, resulting in 13 participants with ASD with complete neuroimaging data. Additional individuals with an Autism Spectrum Disorder were recruited from the Virginia Tech Center for Autism. Participants were individually matched on gender, age, and FSIQ.

Inclusion criteria for all participants included an FSIQ above 85, and a diagnosis of ASD, SAD, or no clinical diagnoses for the neurotypical control group. Exclusion criteria for all participants included: an FSIQ below 85, and being younger than 18 years old or older than 55 years old. Individuals with a history of epilepsy, head trauma, or implanted metal in their body, and other contraindications to MRI (e.g., pacemakers, cochlear implants, metal in eyes, aneurysm clips) were also excluded.

Participants in ASD group were administered the Autism Diagnostic Observation Schedule – 2 (ADOS-2), as assessed by a research-trained assessor to confirm diagnoses. All participants were administered the Anxiety Disorders Schedule – IV (ADIS-IV) by a trained graduate student in order to determine the presence of absence of SAD. For participants in the SAD group, SAD was required to be the principle diagnosis, although other comorbid anxiety disorders and depression were allowed, as defined by a clinical severity rating (CSR) of >1, relative to any other diagnosis with CSR >4. The typical sample included only individuals that do not meet clinical threshold on any psychological disorder. The application of these screening criteria indicated that 11 participants with ASD also met criteria for SAD. Table 1 illustrates participant characteristics in the three groups.

Procedures

This study was conducted in either three or four sessions. For the first session of the study, eligibility for participants was determined by phone, in which MRI safety was assessed. Upon confirming eligibility based on this initial screen, the participant was invited into the lab to undergo a psychological screening session and to complete a self-reported measure of social anxiety. Eligible participants (meeting the criteria named immediately above) were then invited to participate in the MRI portion of the study.

Clinical interviews and assessments

Anxiety Disorders Interview Scale (ADIS).

The ADIS (Brown, DiNardo & Barlow, DiNardo, 1996) is a structured interview that measures anxiety disorders according to DSM-IV criteria. This assessment permits differential diagnosis between anxiety disorders. This interview also yields a severity rating ranging from 0 (i.e., no disorder present) to 8 (i.e., patient is in need of hospitalization).

Autism Diagnostic Observation Scale – 2 (ADOS-2).

The ADOS-2 (Lord et al., 2012) is a semistructured assessment utilized to evaluate individuals suspected of having ASD. Module 4 is used with adults who have fluent speech, as was the case with all ASD participants in this study.

Wechsler Abbreviate Scales of Intelligence (WASI).

The WASI (Wechsler, 1999) is a standardized and reliable measure for intelligence. The full test consists of four subtests: vocabulary, similarities, block design, and matrix reasoning. The test is validated on individuals aged 6-89 and takes between 30-45 minutes to administer the four subtests.

Behavioral measures

Leibowitz Social Anxiety Scale (LSAS).

The LSAS comprises 24 items related to dimension of social anxiety (Liebowitz, 1987). The LSAS features subscales for fear and avoidance of social interactions and performance situations and has good psychometric properties (Heimberg, Mueller, Holt, Hope, & Liebowitz, 1992). LSAS scores were not available for six participants in the autism group and these cases are therefore excluded from relevant analyses.

Neuroimaging Data Acquisition

Scanning was performed on a Siemens TrioTim 3T scanner system with 50-mT/m gradients (Siemens, Erlangen, Germany). Head movement was restricted by using foam cushions. A high-resolution T1-weighted (anatomical) scan was collected using a 16-channel head coil. Thirty high resolution images were acquired using a 3D fast SPGR pulse sequence (TR = 2600ms; TE = 3.02 ms; FOV = 25.6 cm; image matrix = 256^2 ; voxel size = 1mm³) and used for coregistration with the functional data. These structural images were aligned in the near axial plane defined by the anterior and posterior commissures (AC/PC). Whole brain functional images consisted of 30 slices parallel to the AC-PC plane using a BOLD-sensitive gradient-echo EPI sequence with higher-order shimming, at TR of 2000 ms (TE: 30 ms; FOV: 22 cm; isotropic voxel size: $3.43 \times 3.43 \times 4.00$; flip angle 90°). The resting-state sequence began with 4 discarded RF excitations to allow for steady state equilibrium. Resting state scans consisted of 150 images. Three b0 images and 13 diffusion weighted images with $b= 1000\text{s/mm}^2$ were acquired for the diffusion weighted data. The imaging parameters are TR=10300ms, TE=96ms, FOV=2048mm².

Data Analysis

Functional Connectivity Analysis.

Resting state fMRI (rsfMRI) data were used to define DMN on the basis of intrinsic connectivity via independent components analysis (ICA). The ICA approach is based on FSL's Multivariate Exploratory Linear Optimized Decomposition (MELODIC; Beckmann et al., 2005). This statistical approach multiplies separate signals into independent, uncorrelated spatiotemporal components (Comon, 1994), via Multi-Sessional Temporal Concatenation in FSL MELODIC (www.fmrib.ox.ac.uk/fsl/melodic2/index.html). First, for each subject, the group-average set of spatial maps were used as spatial regressors in a multiple regression into the subject's 4D space-time dataset. This results in a set of subject-specific timeseries, one per group-level spatial map. Next, those timeseries are regressed in the temporal domain into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map.

Structural Connectivity Analysis.

In order to evaluate the structural connectivity of the DMN, an atlas-based structural map based on a robust probabilistic approach was used to probabilistically identify voxels in the DMN. Specifically, the spatial mask reported by Smith and colleagues (2009) was applied to identify DMN. We opted to use a probabilistic approach rather than subject-specific ICA component maps of the DMN because this approach is agnostic to preexisting differences in resting state differences in resting state connectivity inherent to diagnostic status. Given that functional connectivity has been found to underlie structural connectivity (Grecius et al., 2009), and we hypothesized group differences in resting state connectivity, the meta-analytic approach

seemed more appropriate. This approach was taken rather than using the individual ICA maps from the output of MELODIC in order to maintain independence of the two different data streams. Using output from the MELODIC ICA components may have introduced systematic bias into individual level maps, thus preventing a fair test of the hypothesis that structural differences exist across groups. For example, conducting structural connectivity analyses based on may have resulted in unequal ROIs between groups, thereby introducing systematic differences in WM tracts, thereby biasing results. Using the Smith et al., (2009) template allowed us to avoid these biases and assess structural connectivity between groups more fairly. As such, this change represents a deviation from the proposed methodology for this study.

After identification of DMN, according to the procedure outlined above, 3dROIMaker created 6 non-overlapping regions-of-interest (ROIs) by spatial clustering and thresholding each casewise map, the: Left Temporal Region, Right Temporal Region, Left Parietal Region, Right Parietal Region, Posterior Cingulate Cortex (PCC), Anterior Cingulate Cortex (ACC). The regions reported in this paper are the: Left and Right Parietal Region, ACC, and PCC. These ROIs were used as the basis for probabilistic tractography connecting each pairwise ROI. Diffusion weighted images were evaluated using the following procedures (Taylor & Saad, 2013). Tensors were estimated through AFNI's 3dDWItoDT processing step. 3dTrackID was utilized to estimate tracts between pairs of ROIs. Probabilistic tractography was used to perform Monte Carlo simulations of whole brain tractography and to utilize uncertainty in estimated DT ellipsoids to find WM voxels associated with pairs of assigned GM ROIs. Contiguous voxels that connect a pair of GM ROIs formed a WM ROI. Tractography reveals the number of likely tracts that run through a specific voxel, thereby estimating the likelihood that the voxel belongs to a specific WM tract. FACTID was used to create tracts by following tracts both through the e1

orientation, and also by testing corners, edges, and diagonals. Mean and standard deviation of functional anisotropy (FA) were calculated. Tracts were drawn according to the following procedures. If FA values were above 0.2 and the angle between e1 and successive voxels is above 60° the tract is assumed to continue. FA values are reported for connections between the four regions of interest, resulting in six possible tracts: Left Parietal Region <--> Posterior Cingulate Cortex; Left Parietal Region <--> Anterior Cingulate Cortex; Left Parietal Region <--> Right Parietal Region; Posterior Cingulate Cortex <--> Anterior Cingulate Cortex; Right Parietal Region <--> Posterior Cingulate Cortex; and the Right Parietal Region <--> Anterior Cingulate Cortex. Tensors were not estimated for 10 participants (3 ASD, 2 SAD, and 5 controls). By using the methodology described above, 10 participants were excluded from the analyses because tensors were not created for them. Participants missing from these analyses are reported in Appendix A. It is not uncommon for tensors to fail to be established between regions in a metaanalytic approach (e.g., Grecius et al., (2009) excluded 5 of 23 subjects, while using a more liberal FA threshold than we used here). As such, there are 5 participants with ASD (1 female), 10 control participants (2 females), and 12 participants with SAD (3 female) included in the DTI analyses.

Brain-behavior relationships.

To measure brain-behavior relationships, we measured the relationship between functional connectivity and social anxiety clinical severity on ADIS by including ADIS severity as a centered covariate of the DMN ICA component. The relationship between structural connectivity and behavior was assessed by correlating FA values with clinical severity on ADIS and LSAS scores.

Results

Resting State Connectivity.

To test the hypothesis that the DMN would show differential functional connectivity, across the three groups, three initial group-level contrasts were performed on the ICA component reflecting DMN (Figure 1) across these groups (i.e., ASD > TD; SAD > TD; ASD > SAD; Figures 2-4 depict group level maps of the DMN). Using a *p* value threshold of 0.05, there were no significant effects for these contrasts. A post-hoc analysis was performed to test the potential differences between the combined patient groups versus controls using the contrast [0.5,0.5,-1], respectively. In this analysis, the clinical groups showed significantly greater coactivation of the dorsal medial prefrontal cortex (dmPFC) in the DMN compared to the control group (Figure 5; Table 2).

Structural Connectivity.

To test the hypothesis that the structural connectivity underlying the DMN varies between groups, we performed ANOVAs on FA values between regions by group. Significant differences were found in the connectivity between the Right Parietal Region <--> Anterior Cingulate Cortex $F(2,30) = 5.661, p = 0.008$ and Left Parietal Region <--> Posterior Cingulate Cortex $F(2,30) = 4.528, p = 0.019$. No other significant differences were found (all $ps > .38$). Post hoc t-tests were conducted to determine the nature of the effects observed in the ANOVA. In the Right Parietal Region <--> Anterior Cingulate Cortex connectivity contrast, we found a significant difference between the ASD and Control group ($p = 0.0387$), and the ASD and SAD groups ($p = 0.039$), but not between the SAD and control group ($p = 1$). A summary of mean FA scores is presented in Table 2 and Figure 6.

Brain Behavior Relationships.

To test whether functional connectivity is related to social functioning, we tested social anxiety as a centered covariate in the DMN ICA component. With a statistical threshold of $p < .05$, we did not find a significant relationship between ADIS scores and the DMN. In order to test the hypothesis that brain structural connectivity is related to measures of social functioning, we correlated FA values with LSAS scores and ADIS social anxiety scores. None of the correlations between FA connectivity and social anxiety measures were significant (all $ps > .3$, $rs < .2$).

Discussion

The objective of this study was to investigate disorder specificity and domain generality of social disability in resting state brain networks in a sample of adults with social anxiety, autism, or no clinical condition. Given the conceptual overlap in symptomology of the social deficits in ASD and SAD, it was hypothesized that there would be similar patterns of connectivity within these two groups. It was also hypothesized that disorder specific connectivity would be evident, given differences in presentation between the disorders (e.g., increased self-evaluation in SAD versus difficulty understanding social cues in ASD). We further hypothesized that measures of social functioning would be related to functional and structural connectivity. When investigating functional connectivity, we found that the dorsomedial prefrontal cortex showed increased functional connectivity within the default mode network when comparing both clinical groups to controls. Given that we did not find any functional connectivity differences between the two clinical groups themselves, the dmPFC may be a marker of general social deficits.

The dmPFC is implicated in emotion regulation and self-referential judgment (Kelley, Macrae, Wyland, Cagler, Inati, & Heatherton, 2002; Liao et al., 2010). In ASD, the role of the dmPFC has been somewhat controversial. A review implicated increased dmPFC activation in self monitoring (Travera et al., 2012), although Kennedy and Courschene (2008) found decreased activation of the dmPFC relative to controls in the DMN. In SAD, the dmPFC has shown increased activation in adults with social anxiety disorder in the DMN compared to controls (Liao et al., 2010). Given this conflicting literature, it is important to note that 11 of our participants with ASD also met criteria for SAD. Thus, one explanation for our discrepant findings might be that increased activation of the dmPFC is partly attributable to comorbid social anxiety in the ASD group. Prior research has found that as many as 50% of adults with ASD also meet criteria for SAD (Maddox & White, 2015). However, no study to date has examined the effect of this comorbidity on the brain. It is therefore possible that general contradictory results of functional connectivity in ASD are due to unexplored comorbid conditions. This study may illuminate the need to examine comorbidities within ASD on the neural level.

With regard to our hypothesis of altered structural connectivity across groups, we found increased connectivity within the ASD group in connections between the Right Parietal Region and the ACC. We also observed decreased connectivity in the connections between the Left Parietal Region and the PCC. This is concordant with literature reporting mixed results of over- and under-connectivity in ASD in non-midline structures (Yerys et al., 2015; Lynch et al., 2013; von dem Hagen, et al., 2013). Contrary to our hypothesis that the SAD group would show altered structural connectivity compared to the TD group, the SAD group evidenced no alterations of structural connectivity compared to controls. This indicates that increased structural connectivity may be a biomarker of social deficits specific to ASD.

There are a few possible reasons we did not observe differences between the SAD and TD group in structural connectivity. One reason may lie in the properties inherent to DTI, and more specifically FA. For example, in areas where many fiber tracts cross FA is reduced (Weeden et al., 2008). A secondary measure, such as mean diffusivity, could have provided a measure of tissue barriers to the tracts in all directions, which may have provided a more robust indicator of structural integrity. Another potential reason we did not observe structural differences concordant with functional differences may be attributable to the meta-analytic mask procedure. For example, our template DMN brain from Smith and colleagues (2009) did not include the mPFC as a region, and it was therefore impossible to examine structural differences underlying connections to and from the dmPFC. Had we applied individual level maps derived from the ICA analyses we may have observed altered structural connectivity between SAD and TD.

When relating structural differences to measure of social anxiety, we found no significant effects. To date, there is no research on structural alterations in the DMN in SAD. Some research has identified reduced FA in a large white matter tract in the brain, the uncinate fasciculus in SAD (Phan et al., 2009; Liao et al., 2011). Additionally, one study found increased structural connectivity between the mPFC and corpus callosum in SAD compared to controls, although this altered connectivity was not related to LSAS scores. Taken together, this may indicate that symptoms of social anxiety do not contribute to altered structural connectivity in the DMN.

A number of limitations of the current study should be noted. We do not have a continuous measure of social functioning, such as the Social Responsiveness Scale, on all of our participants (Constantino & Gruber, 2007). Such a measure would have enabled us to

investigate general social functioning, rather than disorder specific, contributions to structural and functional connectivity. Additionally, many of our participants with ASD did not complete the LSAS, and so we do not have self-report information on these participants perceived struggles with social situations. It is therefore possible that what was observed by a graduate student clinician may not match the internal experience of the participants with ASD with regard to social anxiety. It is unclear how one's self-perception may influence functional and structural connectivity. In terms of functional connectivity, the current approach did not allow for comparison of functional connectivity with behavioral measures of social anxiety. When considering structural connectivity, we also only used one measure, FA, which may not fully capture the complexities of the microstructure of the brain.

These results may hold significance for clinical treatment of social disorders. A transdiagnostic understanding of how symptoms might be linked to alterations in the neurofunctional properties of social cognition networks would potentially accelerate discovery in treatment development by promoting rational treatment development. Our finding that the dmPFC is coactive during a mind wandering, task-free condition among participants with social deficits, but not in controls, may indicate potential avenues for treatment. The dmPFC has been implicated as underlying emotion regulation. With this in mind, one potential mechanism subserving these social deficits may be emotion regulation. Treatment of ASD often targets specific symptoms and ranges from speech to social skills to cognitive skills without insight into the neural structures subserving the mechanisms of social deficits (Reichow & Wolery, 2009; Dawson & Bernier, 2013). It may be the case that, in individuals with ASD and comorbid anxiety, treatment focused on emotion regulation may alleviate associated symptoms of ASD. In SAD, emotion regulation has been investigated as an underlying mechanism, and treated in

adults with SAD through cognitive behavioral therapy (Goldin, Ziv, Jazaieri, Weeks, Heimberg, & Gross, 2014). Future work should be conducted to examine the relationship between neural markers of social deficits across disorders and treatments related to biomarkers. It will also be important to explore the relationship between comorbid SAD in ASD.

References

- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
- Anderson, J. S., Nielsen, J. A., Froehlich, A. L., DuBray, M. B., Druzgal, T. J., Cariello, A. N., ... & Lainhart, J. E. (2011). Functional connectivity magnetic resonance imaging classification of autism. *Brain*, 134(12), 3742-3754.
- Berenbaum, H. (2013). Classification and psychopathology research. *Journal of abnormal psychology*, 122(3), 894.
- Beckmann, C. F., DeLuca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 360(1457), 1001-1013.
- Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic resonance in medicine*, 34(4), 537-541.
- Brown, T. A., DiNardo, P., Barlow, D. H., & DiNardo, P. A. (1996). Anxiety disorder interview schedule adult version (ADIS-IV).
- Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network. *Annals of the New York Academy of Sciences*, 1124(1), 1-38.
- Comon, P. (1994). Independent component analysis, a new concept?. *Signal processing*, 36(3), 287-314.

Constantino JN, Gruber CP (2007) The SRS manual. Western Psychological Services, Los Angeles.

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC medicine*, 11(1), 126.

Cuthbert, B. N., & Kozak, M. J. (2013). "Constructing constructs for psychopathology: The NIMH research domain criteria": Correction to Cuthbert and Kozak (2013).

Dawson, G., & Bernier, R. (2013). A quarter century of progress on the early detection and treatment of autism spectrum disorder. *Development and psychopathology*, 25(4pt2), 1455-1472.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, 102(27), 9673-9678.

Ding, J., Chen, H., Qiu, C., Liao, W., Warwick, J. M., Duan, X., ... & Gong, Q. (2011). Disrupted functional connectivity in social anxiety disorder: a resting-state fMRI study. *Magnetic resonance imaging*, 29(5), 701-711.

Doyle-Thomas, K. A., Lee, W., Foster, N. E., Tryfon, A., Ouimet, T., Hyde, K. L., ... & Anagnostou, E. (2015). Atypical functional brain connectivity during rest in autism spectrum disorders. *Annals of neurology*, 77(5), 866-876.

Eilam-Stock, T., Xu, P., Cao, M., Gu, X., Van Dam, N. T., Anagnostou, E., ... & Fan, J. (2014).

Abnormal autonomic and associated brain activities during rest in autism spectrum disorder. *Brain*, 137(1), 153-171.

Gallese, V., Keysers, C., & Rizzolatti, G. (2004). A unifying view of the basis of social cognition. *Trends in cognitive sciences*, 8(9), 396-403.

Gentili, C., Gobbini, M. I., Ricciardi, E., Vanello, N., Pietrini, P., Haxby, J. V., & Guazzelli, M. (2008). Differential modulation of neural activity throughout the distributed neural system for face perception in patients with Social Phobia and healthy subjects. *Brain Research Bulletin*, 77(5), 286-292.

Goldin, P. R., Ziv, M., Jazaieri, H., Weeks, J., Heimberg, R. G., & Gross, J. J. (2014). Impact of cognitive-behavioral therapy for social anxiety disorder on the neural bases of emotional reactivity to and regulation of social evaluation. *Behaviour research and therapy*, 62, 97-106.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences*, 100(1), 253-258.

Greicius, M. D., Supekar, K., Menon, V., & Dougherty, R. F. (2009). Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cerebral cortex*, 19(1), 72-78.

- Heimberg, R. G., Mueller, G. P., Holt, C. S., Hope, D. A., & Liebowitz, M. R. (1993). Assessment of anxiety in social interaction and being observed by others: The Social Interaction Anxiety Scale and the Social Phobia Scale. *Behavior Therapy*, 23(1), 53-73.
- Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., & Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences*, 106(6), 2035-2040.
- Insel, T. R. (2014). The NIMH Research Domain Criteria (RDoC) Project: Precision Medicine for Psychiatry. *American Journal of Psychiatry*, 171(4), 395-397.
- Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., ... & Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, 167(7), 748-751.
- Kennedy, D. P., & Courchesne, E. (2008). Functional abnormalities of the default network during self-and other-reflection in autism. *Social Cognitive and Affective Neuroscience*, 3(2), 177-190.
- Kelley, W. M., Macrae, C. N., Wyland, C. L., Caglar, S., Inati, S., & Heatherton, T. F. (2002). Finding the self? An event-related fMRI study. *Journal of cognitive neuroscience*, 14(5), 785-794.
- Liebowitz, M. R. (1987). Social phobia. *Modern problems of pharmacopsychiatry*.
- Liao, W., Chen, H., Feng, Y., Mantini, D., Gentili, C., Pan, Z., ... & Zhang, W. (2010). Selective aberrant functional connectivity of resting state networks in social anxiety disorder. *Neuroimage*, 52(4), 1549-1558.

- Liao, W., Xu, Q., Mantini, D., Ding, J., Machado-de-Sousa, J. P., Hallak, J. E., ... & Chen, H. (2011). Altered gray matter morphometry and resting-state functional and structural connectivity in social anxiety disorder. *Brain research*, 1388, 167-177.
- Liu, F., Guo, W., Fouche, J. P., Wang, Y., Wang, W., Ding, J., ... & Chen, H. (2015). Multivariate classification of social anxiety disorder using whole brain functional connectivity. *Brain Structure and Function*, 220(1), 101-115.
- Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. (2012). *Autism diagnostic observation schedule: ADOS-2*. Torrance: Western Psychological Services.
- Lynch, C. J., Uddin, L. Q., Supekar, K., Khouzam, A., Phillips, J., & Menon, V. (2013). Default mode network in childhood autism: posteromedial cortex heterogeneity and relationship with social deficits. *Biological psychiatry*, 74(3), 212-219.
- Maddox, B. B., & White, S. W. (2015). Comorbid Social Anxiety Disorder in Adults with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, 1-12.
- Phan, K. L., Orlichenko, A., Boyd, E., Angstadt, M., Coccaro, E. F., Liberzon, I., & Arfanakis, K. (2009). Preliminary evidence of white matter abnormality in the uncinate fasciculus in generalized social anxiety disorder. *Biological psychiatry*, 66(7), 691-694.
- R Development Core Team (2008). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org>.
- Raichle, M. E., & Snyder, A. Z. (2007). A default mode of brain function: a brief history of an evolving idea. *Neuroimage*, 37(4), 1083-1090.

- Reichow, B., & Wolery, M. (2009). Comprehensive synthesis of early intensive behavioral interventions for young children with autism based on the UCLA young autism project model. *Journal of autism and developmental disorders*, 39(1), 23-41.
- Richey, J. A., Rittenberg, A., Hughes, L., Damiano, C. R., Sabatino, A., Miller, S., ... & Dichter, G. S. (2012). Common and distinct neural features of social and non-social reward processing in autism and social anxiety disorder. *Social cognitive and affective neuroscience*, nss146.
- Saxe, R. (2006). Uniquely human social cognition. *Current opinion in neurobiology*, 16(2), 235-239.
- Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., ... & Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of neuroscience*, 27(9), 2349-2356.
- Schmitz, T. W., Kawahara-Baccus, T. N., & Johnson, S. C. (2004). Metacognitive evaluation, self-relevance, and the right prefrontal cortex. *Neuroimage*, 22(2), 941-947.
- Skudlarski, P., Jagannathan, K., Calhoun, V. D., Hampson, M., Skudlarska, B. A., & Pearlson, G. (2008). Measuring brain connectivity: diffusion tensor imaging validates resting state temporal correlations. *Neuroimage*, 43(3), 554-561.
- Spreng, R. N., & Grady, C. L. (2010). Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *Journal of Cognitive Neuroscience*, 22(6), 1112-1123.

Taylor, P. A., & Saad, Z. S. (2013). FATCAT:(An Efficient) Functional And Tractographic Connectivity Analysis Toolbox. *Brain connectivity, 3*(5), 523-535.

Tillfors, M., Furmark, T., Marteinsdottir, I., & Fredrikson, M. (2002). Cerebral blood flow during anticipation of public speaking in social phobia: a PET study. *Biological Psychiatry, 52*(11), 1113-1119.

Tomasello, M., Carpenter, M., Call, J., Behne, T., & Moll, H. (2005). Understanding and sharing intentions: The origins of cultural cognition. *Behavioral and brain sciences, 28*(05), 675-691.

Travers, B. G., Adluru, N., Ennis, C., Tromp, D. P., Destiche, D., Doran, S., ... & Alexander, A. L. (2012). Diffusion tensor imaging in autism spectrum disorder: a review. *Autism Research, 5*(5), 289-313.

Uddin, L. Q., Supekar, K., Amin, H., Rykhlevskaia, E., Nguyen, D. A., Greicius, M. D., & Menon, V. (2010). Dissociable connectivity within human angular gyrus and intraparietal sulcus: evidence from functional and structural connectivity. *Cerebral cortex, 20*(11), 2636-2646.

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 in cognitive sciences, 11*(4), 153-157.

Uddin, L. Q., Menon, V., Young, C. B., Ryali, S., Chen, T., Khouzam, A., ... & Hardan, A. Y. (2011). Multivariate searchlight classification of structural magnetic resonance imaging in children and adolescents with autism. *Biological psychiatry, 70*(9), 833-841.

- Uddin, L. Q., Supekar, K., Lynch, C. J., Khouzam, A., Phillips, J., Feinstein, C., ... & Menon, V. (2013). Salience Network-Based Classification and Prediction of Symptom Severity in Children With Autism. *JAMA psychiatry*, 70(8), 869-879.
- van den Heuvel, M. P., Stam, C. J., Kahn, R. S., & Pol, H. E. H. (2009). Efficiency of functional brain networks and intellectual performance. *The Journal of Neuroscience*, 29(23), 7619-7624.
- Washington, S. D., Gordon, E. M., Brar, J., Warburton, S., Sawyer, A. T., Wolfe, A., ... & VanMeter, J. W. (2013). Dysmaturation of the default mode network in autism. *Human brain mapping*.
- White, S. W., Bray, B. C., & Ollendick, T. H. (2012). Examining shared and unique aspects of social anxiety disorder and autism spectrum disorder using factor analysis. *Journal of autism and developmental disorders*, 42(5), 874-884.
- Wedeen, V. J., Wang, R. P., Schmahmann, J. D., Benner, T., Tseng, W. Y. I., Dai, G., ... & de Crespigny, A. J. (2008). Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers. *Neuroimage*, 41(4), 1267-1277.
- Wechsler, D. (1999). *Wechsler abbreviated scale of intelligence*. Psychological Corporation.
- Yerys, B. E., Gordon, E. M., Abrams, D. N., Satterthwaite, T. D., Weinblatt, R., Jankowski, K. F., ... & Vaidya, C. J. (2015). Default mode network segregation and social deficits in autism spectrum disorder: Evidence from non-medicated children. *NeuroImage: Clinical*, 9, 223-232.

Tables and figures**Table 1.**

	Age	Social CSR	IQ	LSAS Fear
	Mean (<i>SD</i>)			
ASD	23.64 (1.76)	4.28 (0.47)	118.78 (3.69)	32.38 (3.65)
SAD	26.53 (2.25)	5.6 (0.21)	115.4 (2.85)	38.00 (2.14)
Controls	22.14 (0.60)	1.07 (0.32)	116.64 (2.04)	1.16 (3.04)

Table 1. Demographic and characterization information, with means by group, and standard deviations (in italics)

Table 2.

Cluster	MNI coordinates		
	X	Y	Z
382	2	-22	44

Table 2. Activation table for ASD+SAD > TD contrast

Table 3.

Connections	ASD	SAD	Controls	All
	Mean (<i>SD</i>)			
Left Parietal Region <--> Posterior Cingulate Cortex	0.111 (0.058)	0.302 (0.048)	0.339 (0.067)	0.249 (0.036)
Left Parietal Region <--> Anterior Cingulate Cortex	0 (0)	0 (0)	0 (0)	0 (0)
Left Parietal Region <--> Right Parietal Region	0 (0)	0 (0)	0 (0)	0 (0)
Posterior Cingulate Cortex <--> Anterior Cingulate Cortex	0.044 (0.044)	0 (0)	0 (0)	0.0147 (0.147)
Right Parietal Region <--> Posterior Cingulate Cortex	0.202 (0.071)	0.202 (0.063)	0.313 (0.061)	0.232 (0.038)
Right Parietal Region <--> Anterior Cingulate Cortex	0.152 (0.064)	0 (0)	0 (0)	0.051 (0.024)

Table 3. This table shows FA values by group and across groups for FA values between regions of interest. This table includes mean values and standard deviations in parentheses.

Figure 1.

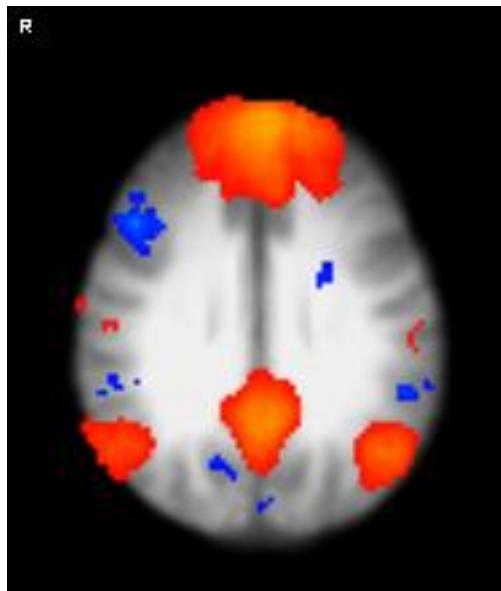


Figure 1. This image depicts the output of MELODIC component 4, the component chosen to represent the DMN in the dual regression analyses.

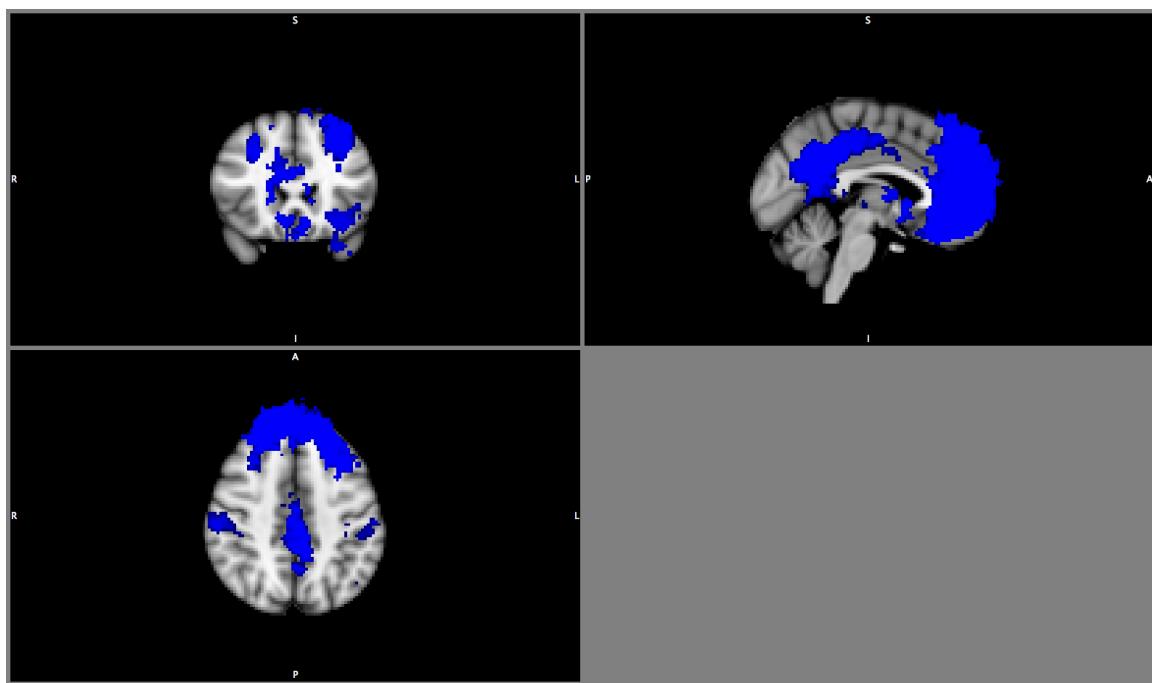
Figure 2.**Figure 2.** This image depicts the dual regression results for the ASD group.

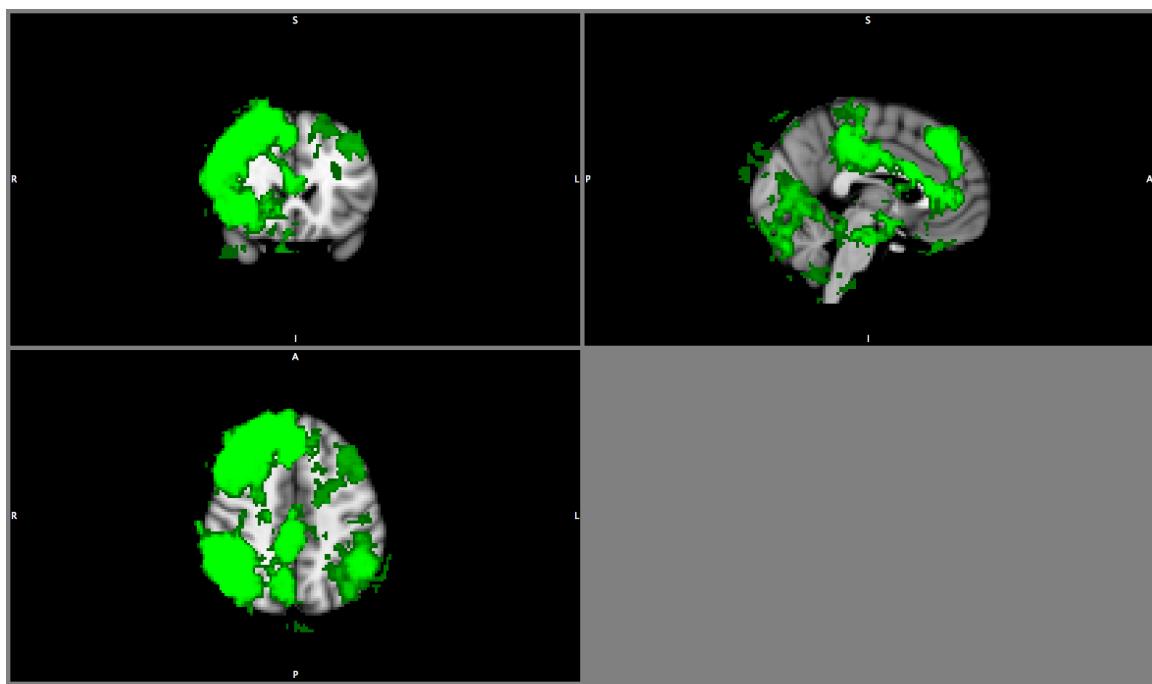
Figure 3.

Figure 3. This image depicts the results of the dual regression for the TD group.

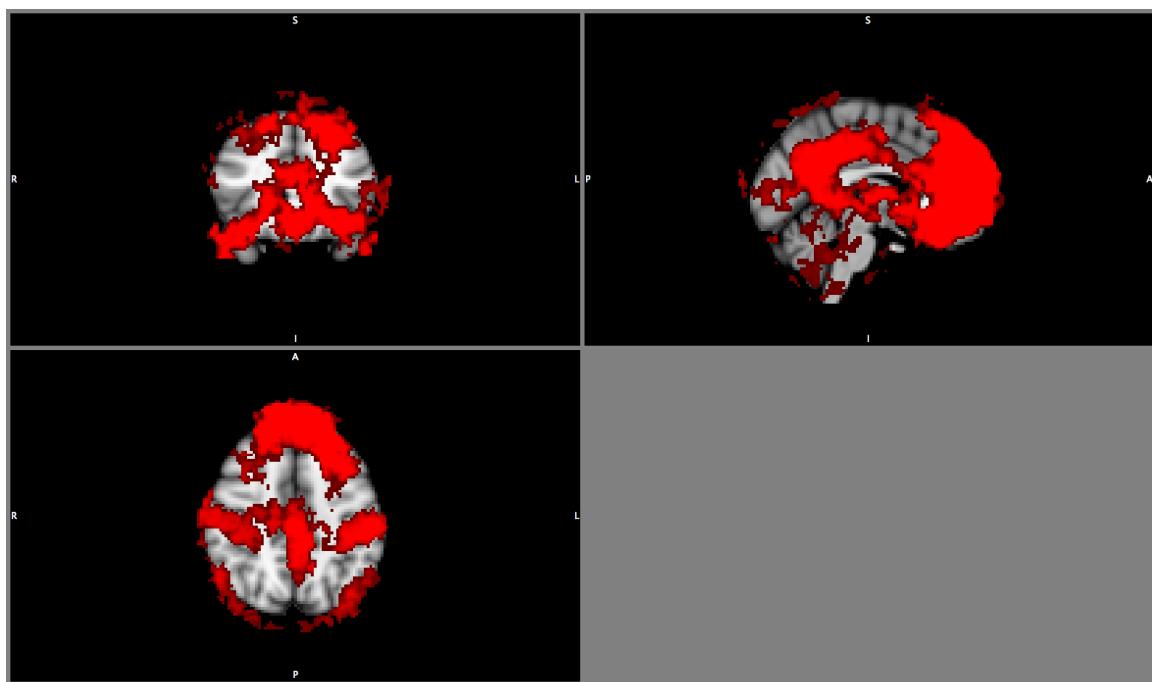
Figure 4.**Figure 4.** This image depicts the results of the dual regression

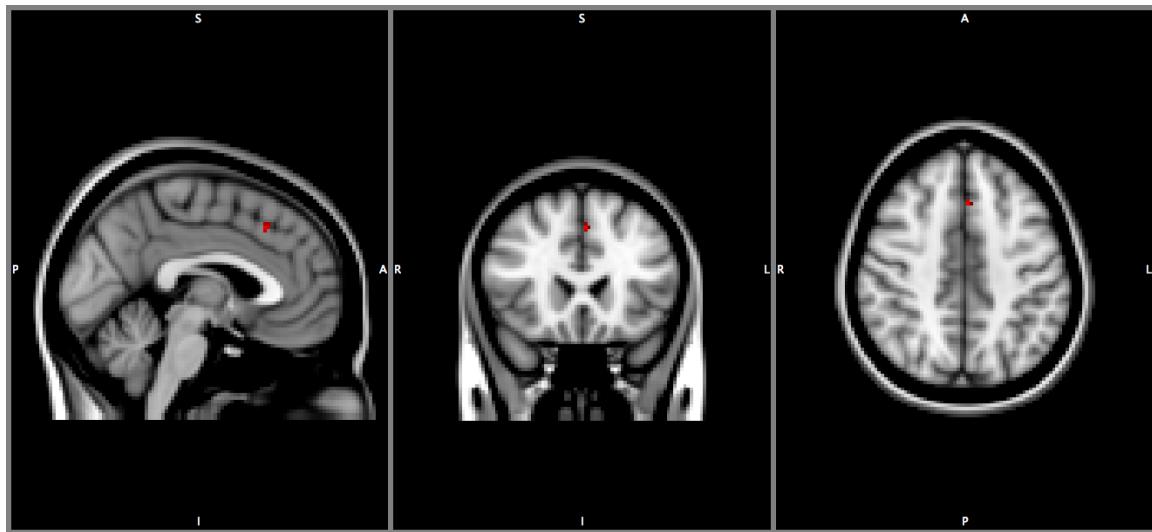
Figure 5.

Figure 5. This image depicts activation in the dmPFC for the Clinical > TD contrast at corrected $p < .05$.

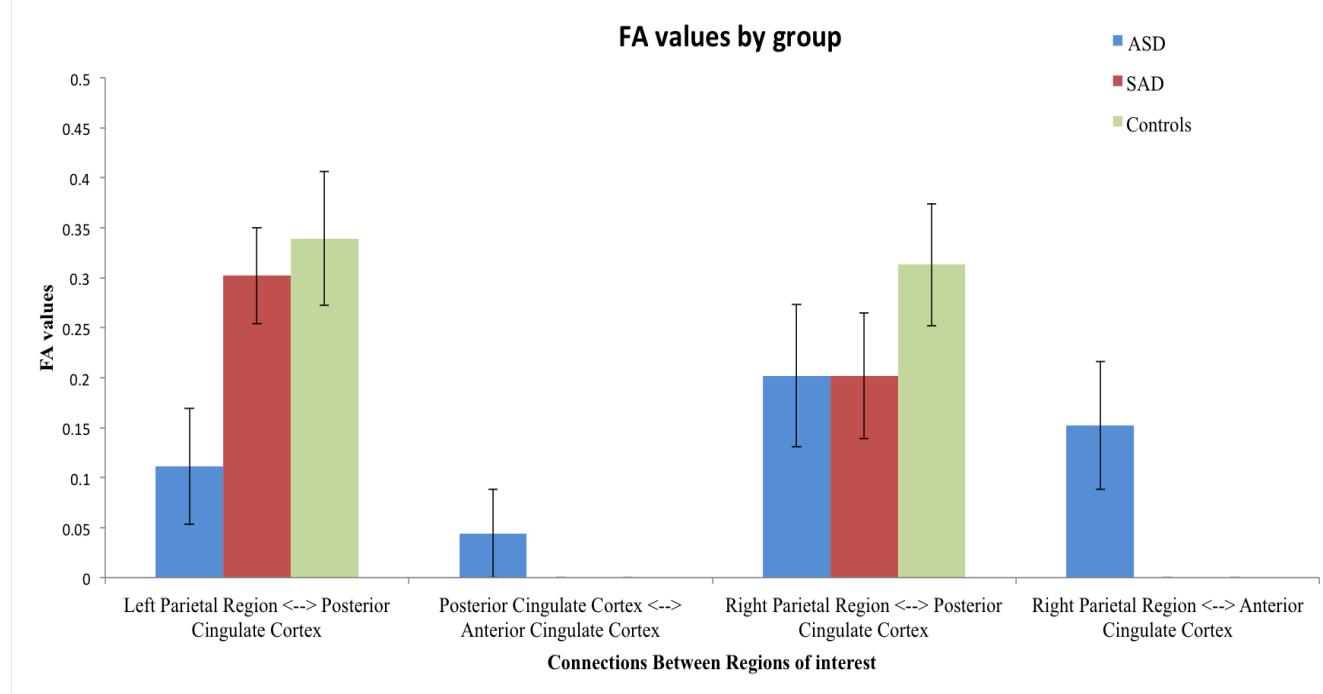
Figure 6.

Figure 6. This figure depicts the mean connectivity between regions by group. Participants in the ASD group evidenced significant differences between the Left Parietal Region and Posterior Cingulate Cortex compared to both the SAD and TD group. Participants in the ASD group also evidenced a significant difference in the Right Parietal Region and Anterior Cingulate Cortex compared to controls.

Appendix A

Missing Data	Age	Diagnosis	Gender	Social CSR	Data missing	Reason missing
1	30	ASD	F		2	DTI, LSAS generated DT data, no grid file; participated prior to this portion of study
2	21	ASD	M		5	DTI generated DT data, no grid file
3	18	ASD	M		4	DTI does not generate DT data
4	26	SAD	M		5	DTI unable to parse diffusion.nii
5	28	SAD	F		5	DTI generated DT data, no grid file
6	22	Control	M		0	DTI unable to parse diffusion.nii
7	22	Control	F		1	DTI does not generate DT data
8	22	Control	F		0	DTI generated DT data, no grid file
9	20	Control	M		0	DTI does not generate DT data
10	22	Control	M		0	DTI does not generate DT data
11	20	ASD	F		6	LSAS participated prior to this portion of study
12	21	ASD	M		6	LSAS participated prior to this portion of study
13	22	ASD	M		5	LSAS participated prior to this portion of study
14	23	ASD	M		5	LSAS participated prior to this portion of study
15	18	ASD	F		6	LSAS participated prior to this portion of study

Appendix A. This table depicts the characteristics of participants who are missing data from the DTI analyses.