Salience and Frontoparietal Network Patterns in Children with Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder

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Abstract

Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) have been difficult to differentiate in clinical settings, as these two disorders are phenotypically similar and both exhibit atypical attention and executive functioning. Mischaracterizations between these two disorders can lead to inappropriate medication regimes, significant delays in special services, and personal distress to families and caregivers. There is evidence that ASD and ADHD are biologically different for attentional and executive functioning mechanisms, as only half of individuals with co-occurring ASD and ADHD respond to stimulant medication. Further, neurobehavioral work has supported these biological differences for ASD and ADHD, with both shared and distinct functional connectivity. In specific, two brain networks have been implicated in these disorders: the salience network (SN) and frontoparietal network (FPN). The SN is a network anchored by bilateral anterior insula and the dorsal anterior cingulate cortex and has been implicated in "bottom-up" attentional processes for both internal and external events. The FPN is anchored by lateral prefrontal cortex areas and the parietal lobe and plays a roll in "top-down" executive processes. Functional connectivity subgroups differentiated ASD from ADHD with between SN-FPN connectivity patterns, but not by within-SN or within-FPN connectivity patterns. Further, subgroup differences in ASD+ADHD comorbidity vs. ASD only were found for within-FPN connectivity.

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General Abstract

Autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) have been difficult to differentiate in clinical settings, as these two disorders are similar and both exhibit attention and executive functioning difficulties. ASD and ADHD have shared and distinct functional brain network connectivity related to attention and executive functioning. Two brain networks have been implicated in these disorders: the salience network (SN) and frontoparietal network (FPN). The SN is a network that has been implicated in "bottom-up" attentional processes for both internal and external events. The FPN plays a roll in "top-down" executive processes. This study found that functional connectivity patterns between the SN and FPN differentiated ASD from ADHD. Further, connectivity patterns in children with co-occurring ASD and ADHD were characterized by within-FPN connectivity.

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Salience and Frontoparietal Network Patterns in Children with ASD and ADHD

Altered cognitive mechanisms, such as attention and executive function, are thought to have widespread effects on a social, emotional, and motoric behaviors for neurodevelopmental disorders (Dawson, Webb, & McPartland, 2005; Schultz, 2005; Philip Shaw, Stringaris, Nigg, & Leibenluft, 2014). Autism spectrum disorder (ASD) is a condition characterized by difficulties in reciprocal social interaction and restricted and repetitive behaviors. Attention deficit/hyperactivity disorder (ADHD) is characterized by difficulties with inattention (e.g., high distractibility, low concentration), hyperactivity (e.g., always on the run, fidgeting) and impulsivity. Both ASD and ADHD are highly comorbid (Matson, Rieske, & Williams, 2013; Stahlberg, Soderstrom, Rastam, & Gillberg, 2004) and display heterogeneous symptomology which has been demonstrated to be difficult to disentangle with standardized assessments and measures (Grzadzinski, Dick, Lord, & Bishop, 2016; Miodovnik, Harstad, Sideridis, & Huntington, 2015; Yerys et al., 2016). Challenges in differentiating these two disorders result from the number of similarities in phenotypic characteristics (e.g., hyperactive symptoms may seem like stereotypic motor behaviors and social impulsivity may seem like difficulties with reciprocal social interaction and vice versa). This overlap of phenotypic presentation complicates both assessment and diagnostic enterprises, resulting in frequent misattribution of ASD symptoms to ADHD (Miodovnik et al., 2015) and vice versa (Grzadzinski et al., 2016), which together may contribute to the high rates of co-occurring ADHD with ASD (Yerys et al., 2016). Phenotypic mischaracterizations result in a diverse set of unfavorable outcomes including inappropriate medication regimes, significant delays in special services, and personal distress to families and caregivers. One viable option for disentangling these two disorders is to better understand the biological mechanisms that underlie them. Specifically, ASD and ADHD seem to

have altering biological pathways for attention and executive function, as medications known to improve ADHD symptoms only work in about half of patients with ASD (Murray, 2010). The purpose of the current study is to determine whether patterns of resting-state brain connectivity can be used as a basis for differentiating ASD from ADHD.

As neurodevelopmental disorders such as ASD and ADHD have become increasingly accepted as conditions that stem from large-scale brain network disruptions (Di Martino, Zuo, et al., 2013), understanding the neural mechanisms that underlie and differentiate these two disorders may be vital in parsing their similarities and differences. Resting state fMRI has been successfully used to identify connectivity differences in several brain networks, which are frequently observed in both ADHD and ASD samples (Liddle et al., 2011; Uddin et al., 2008; Yerys et al., 2015). The salience (SN) and frontoparietal networks (FPN) are prominent networks thought to underlie attentional and executive functioning processes that have been implicated in both ASD and ADHD (Abbott et al., 2016; Posner et al., 2013; Seeley et al., 2007). The SN is responsible for the filtering and focusing of attention for both internal and external events (e.g., “bottom-up” attention). This network is anchored by bilateral anterior insula and the dorsal anterior cingulate cortex (dACC; Seeley et al., 2007). In contrast, the FPN is a “top-down” network involved in shifting and directing of attention. The FPN is represented by nodes in the prefrontal cortex (PFC) and lateral parietal areas, (Gordon et al., 2014), which are physically and functionally distinct from the SN (Seeley et al., 2007). Recent evidence has demonstrated that functional connectivity of key brain regions related to the SN and FPN have distinguished children with ASD, ADHD, and typically developing (TD) controls (Di Martino, Zuo, et al., 2013).

Theoretically, altered functioning within the SN may be related to the orienting deficits observed in ASD (Antezana, Mosner, Troiani, & Yerys, 2015; Elsabbagh et al., 2013; Keehn, Müller, & Townsend, 2013), which may be related to circumscribed interests and repetitive behaviors, and have cascading effects on social communication for this population. Further, the SN's physical connections with the FPN may be related to the cognitive inflexibility noted in ASD, as the saliency of an object may produce difficulties in shifting attention toward particularly important events in the environment. This pattern is opposite of what is typically observed in ADHD, in which individuals have difficulty inhibiting their attention toward events (e.g., high distractibility). This 'top-down' dysfunction implicates atypical FPN connectivity (Posner, Park, & Wang, 2014). These altering patterns have been noted both behaviorally and in the real world.

To date, the majority of studies that examine functional connectivity have used seed-based approaches or an independent components analysis (ICA). Seed-based approaches use *a priori* regions of interest (ROIs) to examine how signal fluctuations in the seed region correlate with other voxels in the brain. ICA is a data-driven approach, which separates signal from spatial and time components, from noise (e.g., motion). This approach yields several maps that represent networks, which reliably map onto established networks. Although approaches such as these have been used to evaluate the SN and FPN across a range of studies, the literature examining the specific alterations of these networks in these disorders is extensive and rapidly evolving.

The Salience Network (SN)

The SN has increasingly been studied in ASD with mixed findings noting both hypo- and hyperconnectivity across a variety of studies. Uddin and Menon (2009) were the first to propose that difficulties in ASD may be underscored by altered SN functional connectivity. In a meta-

analytic review, these authors found that individuals with ASD displayed hypoactivation of a main hub of this network-- the anterior insula (Uddin & Menon, 2009). The anterior insula has been linked to interoceptive, affective, and empathic processes, making it a key structure for the integration of external sensory stimuli with internal states through the SN and may be pivotal in understanding the cognitive and behavioral inflexibility that underlie key symptomology noted in ASD (e.g., insistence on sameness, "sticky attention", sensory seeking; (Uddin & Menon, 2009).

The theory of altered SN connectivity in ASD has been further supported by task-based fMRI analyses, including findings of greater activation of SN hubs (i.e., dACC and anterior insula) in children with ASD when viewing their circumscribed interests (Cascio et al., 2014). Additionally, children with ASD have demonstrated stronger within-SN connectivity, when presented with deviant faces in an oddball task, while TD control children demonstrated stronger cross-network interactions (Odriozola et al., 2015) suggesting altered processing of faces. Together, these findings demonstrate a vital role of the SN for attention and affective processing of stimuli for ASD. Findings from resting state functional connectivity have extended the understanding of how the SN interacts with other networks in ASD (i.e., "between-network" connectivity). When examining between-network connectivity in ASD, one study found that compared to controls, SN nodes in adult males with ASD demonstrated hypoconnectivity with amygdala and prefrontal regions (von dem Hagen, Stoyanova, Baron-Cohen, & Calder, 2013). Recent evidence has demonstrated predominant between-network hypoconnectivity of the SN with key nodes of the frontal and temporal sulcus nodes (Abbott et al., 2016). Consistent with these findings, decreases in connectivity of the SN with FPN nodes has also been noted in children with ASD (Elton, Di Martino, Hazlett, & Gao, 2015). These generally under-connected patterns of the SN have also been replicated with structural covariance fMRI (Zielinski et al.,

2012). Although between-network hypoconnectivity has been predominant in the literature, there is some evidence that the SN has demonstrated hyperconnectivity to sensory areas (Green, Hernandez, Bookheimer, & Dapretto, 2016). These atypical between-network patterns of the SN highlight the modulating role of the SN for processing information with other networks for ASD.

Between-network alterations may be rooted in how the SN interacts within itself (i.e., "within-SN" connectivity). Atypical within-SN connectivity has also defined difficulties in ASD. Uddin and colleagues (2013) found within-SN hyperconnectivity in children with ASD. Moreover, using a classification approach from an ICA, this hyperconnectivity of the SN distinguished children with ASD from TD control children with 83% accuracy, 67% sensitivity, and 100% specificity (Uddin et al., 2013). These increases in within-SN connectivity have been replicated in youth with ASD (Elton et al., 2015). Abnormalities of the SN, both within- and between-networks has been linked to different aspects of ASD. Altogether, between-network hypoconnectivity and within-SN hyperconnectivity has been supported as characteristic of ASD.

These alterations of the SN have been linked to core ASD symptomology. Specifically, weaker within-SN connectivity and greater social difficulties have been noted in children with ASD (Abbott et al., 2016). Further, weaker connections between the SN and precuneus connectivity have been linked to greater social difficulties in youth with ASD (Elton et al., 2015). This within-SN hyperconnectivity has been tied to restricted and repetitive behaviors and interests in ASD (Uddin et al., 2013). Further, stronger within-SN connectivity has been associated with greater sensory avoidance in ASD (Abbott et al., 2016). Additional research has supported the role of the SN in sensory difficulties with findings of strengthened hyperconnectivity of the SN with sensory processing areas in the context of mildly aversive auditory and tactile stimuli (Green et al., 2016). When comparing task-based to resting state

fMRI, findings have demonstrated a lesser degree of change in functional connectivity patterns (e.g., discriminability) of the SN and FPN in ASD compared to controls. This lack of change in connectivity patterns has been linked to severity of restricted and repetitive behaviors (Uddin et al., 2015). Additionally, although not core to the disorder, improvement of adaptive functioning has been predicted by within-SN connectivity in ASD (Plitt, Barnes, Wallace, Kenworthy, & Martin, 2015). Altogether, these findings link impairing aspects and core difficulties of ASD with alterations in SN connectivity.

Findings of alterations of the SN have been less prominent in ADHD. Between-network analyses have revealed SN hyperconnectivity with FPN areas in medication-naïve youth with ADHD (Choi, Jeong, Lee, & Go, 2013). This between SN-FPN hyperconnectivity has been replicated in children with ADHD who were off stimulants during scanning (Elton, Alcauter, & Gao, 2014). Moreover, adults with ADHD exhibit additional connections between the SN and FPN (Yu, 2013). Findings of hyperconnectivity of the SN with areas of the cerebellum in adults with ADHD have previously been demonstrated (Kucyi, Hove, Biederman, Van Dijk, & Valera, 2015). Additionally, one study found no differences in within-SN connectivity for adults with ADHD compared to controls, but found hypoconnectivity between the SN and dorsal attention network in the ADHD group. Despite these findings, altered connectivity of this network was not related to ADHD symptomology (Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2016). It should be noted that atypical between-network SN connectivity has not been replicated (Oldehinkel et al., 2016). Together, these results implicate a potential between-network hyperconnectivity of the SN for ADHD, with specific support for alterations with the FPN.

Core symptomology of ASD, and not ADHD, has been linked to within-SN hyperconnectivity and between SN-FPN hypoconnectivity. Conversely, between SN-FPN

hyperconnectivity seems to underlie ADHD symptomology. Understanding the between network dynamics for the FPN may be important for better understanding the attentional and executive deficits in ADHD.

The Frontoparietal Network (FPN)

Frontal lobe deficits have been consistently implicated in ADHD, as the PFC has been theorized to play a primary role in the attentional, hyperactive and impulsive symptoms noted in ADHD (Halperin & Schulz, 2006). Brain imaging research for ADHD has been motivated by pivotal findings of two- to five-year cortical maturational delays of the PFC in children with ADHD (Shaw et al., 2007). When using functional connectivity, the FPN has been a key candidate in understanding deficits in ADHD, as it is considered to be a top-down network important for executive functions and optimal decision-making (Castellanos & Aoki, 2016; Posner et al., 2014). Altered brain development for ADHD has been supported with resting-state functional connectivity analyses.

Atypical between-network connectivity has been demonstrated for the FPN in individuals with ADHD. One study explicitly examining connections of the FPN found that children with ADHD demonstrate hypoconnectivity of FPN hubs with striatal areas, compared to TD controls (Lin, Tseng, Lai, Matsuo, & Gau, 2015). Further, decreased connectivity of hubs of the FPN with striatal areas have been noted in children with ADHD (Posner et al., 2013). Conversely, hyperconnectivity between SN-FPN have been emphasized for ADHD (Choi et al., 2013; Elton et al., 2014; Yu, 2013). These hyperconnective patterns have also been found in adults with ADHD when examining between-network hyperconnectivity for areas of the FPN with default mode areas (Mattfeld et al., 2014). When examining between-network connectivity, individuals

with ADHD seem to exhibit hypoconnectivity with striatal areas, but hyperconnectivity for SN-FPN.

Within-FPN hypoconnectivity has been found for children with ADHD (Lin et al., 2015; Posner et al., 2013). These alteration have been supported for within-FPN, and not within-SN, for youth with ADHD versus TD controls (Park, Hong, Lee, & Park, 2016). It should be noted that directionality (e.g., hyper- or hypoconnectivity) of these differences were not stated, making it difficult to converge with findings from other studies. Further, connectivity of the FPN has been shown to be predictive of ADHD diagnosis. One study found higher predictive value of areas of the FPN for children with ADHD, with classification accuracies above 70% (dos Santos Siqueira, Biazoli Junior, Comfort, Rohde, & Sato, 2014). This is in line with findings from Gates and colleagues (2014), who examined the FPN in TD children and children with ADHD using a community detection technique and detected two subgroups were made up of predominantly ADHD participants and together predicted two-thirds of the ADHD group. Both subgroups were characterized by within-FPN hypoconnectivity (i.e., one demonstrated weaker connections between the left dorsolateral PFC and left intraparietal sulcus, while the other subgroup was characterized by weaker connections of the left to right frontal cortex; (Gates, Molenaar, Iyer, Nigg, & Fair, 2014). In line with these findings, within-FPN hyperconnectivity has been associated with symptom improvement in adults with ADHD (Francx et al., 2015). This finding of within-FPN hyperconnectivity in adults with ADHD has been recently replicated (Mostert et al., 2016). Overall, within-FPN hypoconnectivity may underlie deficits in children with ADHD, with improvements in ADHD symptomology over time strengthening these connections.

The role of FPN connectivity has been less studied for ASD. As noted above, there is some evidence that there is hypoconnectivity of the SN-FPN for children with ASD (Abbott et

al., 2016; Elton et al., 2015; von dem Hagen et al., 2013). Further, altered connectivity of the FPN with areas of the SN and default mode network have been found to predict ASD diagnosis (Plitt, Barnes, & Martin, 2014). Within-FPN alterations have not been found for adolescents with ASD compared to controls (Redcay et al., 2013). It should be noted that hypoconnectivity of areas of the FPN during a cognitive control task has been linked to ADHD symptomology in adolescents with ASD (Solomon et al., 2009). Together these findings implicate a potential SN-FPN hypoconnectivity for ASD, with connections relating to ADHD symptomology, rather than ASD symptomology.

Evidence of within-FPN hypoconnectivity has been supported for children with ADHD. Further, hyperconnectivity between SN-FPN seems to be implicated for ADHD. Conversely, children with ASD may demonstrate hypoconnectivity between SN-FPN nodes. Together, these brain alterations support specific network dynamics that ought to differentiate children with ASD from ADHD. The SN and FPN have been tied to specific attentional and executive functioning difficulties that have been hypothesized as core pathways that are affected in both ASD and ADHD (Gioia, Isquith, Kenworthy, & Barton, 2002; Johnson, Gliga, Jones, & Charman, 2014; Keehn et al., 2013; Visser, Rommelse, Greven, & Buitelaar, 2016; Willcutt et al., 2012). These findings suggest that functional connectivity may be a viable method for differentiating distinct neural connectivity for these two highly similar and heterogeneous disorders. Despite the promise of this approach, few studies have examined the functional properties co-occurring ASD+ADHD, as this group may demonstrate unique effects that are a combination of altered network connectivity of ASD and ADHD (Di Martino, Zuo, et al., 2013). It may be important to understand these connections for ASD+ADHD as this group may contribute additional heterogeneity that can be accounted for.

The Present Study

Whereas the majority of connectivity research in both ADHD and ASD has used seed-based functional connectivity and ICA, the purpose of the current study is to use a novel approach known as group iterative multiple model estimation (GIMME; Gates et al., 2014) to partition cases into subgroups based on case-wise patterns of brain connectivity. This method was originally derived from social network research in order to identify individuals with similar social communities, and has recently been extended for functional connectivity analyses in order to understand which individuals subgroup for certain "brain communities". This study aims to evaluate whether GIMME with community detection can be used to differentiate two phenotypically similar disorders using publically available neuroimaging datasets of resting state fMRI.

The working hypothesis for this study is that the connective properties of the SN and FPN can be used as a basis for clustering cases into communities, which share similar brain network properties. Using community detection with GIMME (GIMME+CSD) derived networks allows for graphical representations for evaluation of pathways differences amongst subgroups (Gates et al., 2014). These two techniques can determine whether individual-level patterns of brain connectivity are related to diagnostic status. The ultimate goal of this work is to improve the process of differential diagnosis for ASD and ADHD by better understanding the unique and combined effects of underlying neuroconnective processes.

Aims of the Current Study

The current study aims to (1) determine whether graph theory (i.e., GIMME) can robustly differentiate among ASD, ADHD, and TD based on the SN and FPN, and (2) determine whether

the status of co-occurring ASD+ADHD is merely an additive effect of both ASD and ADHD connectivity properties.

Hypotheses

Based on the functional connectivity literature in ASD and ADHD, and in line with the first aim of the study, I hypothesize that (1) community detection will identify subgroups based on within-SN, within-FPN, and between SN-FPN connectivity. Specifically, when using community detection for within-SN connectivity (1a) one subgroup will be characterized by hyperconnectivity of SN nodes, this subgroup will be primarily composed of individuals with ASD. Additionally, when using community detection for within-FPN connectivity, (1b) one subgroup will be characterized by hypoconnectivity of FPN nodes, this subgroup will be primarily composed of individuals with ADHD. Further, when using community detection for between SN-FPN connectivity, (1c) one subgroup will be characterized by SN-FPN hypoconnectivity and will be primarily composed of individuals with ASD and (1d) an additional subgroup will emerge that will be primarily composed of ADHD and characterized by hyperconnectivity of SN-FPN nodes. In line with the second aim of the study, I hypothesize (2) that individuals with co-occurring ASD+ADHD will be characterized by both within-SN hyperconnectivity and within-FPN hypoconnectivity.

Method

Participants

Cases were selected from publicly available data repositories. Specifically, the Autism Brain Imaging Data Exchange (ABIDE; http://fcon_1000.projects.nitrc.org/indi/abide) and the ADHD-200 (http://fcon_1000.projects.nitrc.org/indi/adhd200) databases were used. ABIDE-I, and its follow-up project ABIDE-II have collected functional and structural Magnetic Resonance

Imaging (MRI) data on 2,156 individual participants (ASD N=1,096; TD N=1,160) ranging from ages 5 to 64 years, from 23 international sites. The ADHD-200 has collected functional and structural MRI data on 776 participants (ADHD N=285; TD N=491) ranging from ages 7-21 years, across 8 international sites. Both ABIDE projects as well as ADHD-200 included scans from the New York University (NYU) Langone Medical Center. Due to differences across sites in scanner protocols, only cases from the NYU Langone Medical Center site were used in the current study. Scan protocols were matched on repetition time (TR), MRI acquisition, and length of functional MRI run. For ABIDE-I and II, the NYU site has contributed a total of 127 participants with ASD and 135 TD participants. Additionally, the NYU site has contributed 123 ADHD participants through the ADHD-200 database. Due to significant overlap in the TD sample across databases, the TD sample from the ADHD-200 sample was excluded (n=99).

In order to best match the datasets, specific exclusionary criteria were selected. First, since the ADHD-200 dataset only included youth (ages 7-17), participants from the ABIDE data set were excluded (ASD=21; TD=32) if they were ≥18 years at the time of the scan. Secondly, children from the ABIDE dataset that were <7 years old at time of scan were also excluded (ASD=11; TD=6). Third, the ABIDE sample included children that were both left- and right-handed, while the ADHD-200 sample only included children that were right-handed. For this reason, all left handed children (handedness scores of <-50) were excluded (ASD=5). Lastly, since all TD participants had an FIQ of ≥80, participants with an FIQ <80 (ASD=8; ADHD=3) or missing FIQ (ADHD=3) were excluded. Additionally, due to the potentially confounding factor of the neurological basis of tics and the potential for added motion, children with tics were excluded from analyses (ASD=4; ADHD=2). When excluding for reasons listed above, there

were a total of 115 children with ADHD, 78 children with ASD, and 97 TD children. Detailed information about the preliminary sample and final sample are listed below.

Data collection for the studies conducted at NYU and for all ABIDE/ADHD-200 sites were reviewed and approved by the local Institutional Review Board (IRB). Written informed consent and child assent were obtained from all participants. Additionally, it should be noted that in accordance with the Health Insurance Portability and Accountability (HIPAA) guidelines, the ABIDE Consortium and ADHD-200 Consortium ensured that all the datasets were fully anonymized, with no protected health information included. NYU Langone Medical Center site recruited participants from the New York City and surrounding areas through a variety of mechanisms including: Institutional Review Board (IRB) approved flyers, magazine and web advertisements, parent support groups, referrals from NYU Child Study Center clinical services, and by word of mouth.

ABIDE Dataset. After applying the preliminary exclusionary criteria, the preliminary sample from ABIDE included 78 individuals with ASD (range: 7.13-17.93 years; mean age: 10.78 years; FIQ mean = 108.90) and 97 TD (range: 7.11-17.70 years; mean age: 11.75 years; FIQ mean = 113.56). A total of 15 ASD participants were taking medications. Nine participants were on stimulants, 7 participants on SSRIs, and 3 participants on antihypertensives. It should be noted that 4 participants were on a combination of medications. Additional participant characteristics of the samples are described below (Table 1) and comorbidity rates are listed below (Table 2 and Table 5).

ADHD-200 Dataset. After applying the preliminary exclusionary criteria, the final sample from ADHD-200 included 115 individuals with ADHD (range: 7.24-17.61 years; 11.03 years; FIQ mean = 107.03). Specifics regarding medication status were not available

through the ADHD-200 database; 26 participants were listed as “not medication naïve”, 30 participants were listed as “medication naïve,” and many were missing medication status (n=59). Additional participant characteristics of the samples are described below (Table 1) and comorbidity rates are listed below (Table 2 and Table 5).

Procedures

For both ABIDE and ADHD-200 datasets, all participants completed an initial visit to complete diagnostic assessments (e.g., KSADS-PL, IQ; specifics listed below). Within three months of the assessment visit, participants completed a MRI scan. Prior to scanning, participants were shown pictures of the MRI scan and described the MRI procedures. All children completed at least one mock scan session preceding the MRI scanning session, and were given the chance to ask questions about the scanning procedures. Children taking stimulants were asked to withhold the medication at least 24 hours before the scan (reported taking stimulants: ASD=14; ADHD=29). Both ABIDE and ADHD-200 participants received a parent and child Schedule of Affective Disorders and Schizophrenia for Children-Present and Lifetime Version (KSADS-PL) to assess for psychopathology. Comorbidities determined were listed for ASD and ADHD groups (Table 2 and Table 5). Additionally, all participants completed a Wechsler Abbreviated Scale of Intelligence (WASI). Both ABIDE and ADHD-200 provided Full IQ (FIQ), Verbal IQ (VIQ), and Performance IQ (PIQ).

ABIDE Dataset – Assessment Procedures. ASD diagnosis was determined by review of available records, an Autism Diagnostic Observation Schedule, review of the participant's history, and when possible, an Autism Diagnostic Interview-Revised. For the ASD participants, ABIDE provided available ADOS domain scores (e.g., reciprocal social communication, communication, stereotyped behavior, and total scores), as well as ADOS-2 domain scores (i.e.,

social affect, restricted and repetitive behaviors, total scores) and severity scores. Available ADI-R scores were also provided (e.g., social score, verbal score, restricted and repetitive behavior score, and onset score). TD participants were included in the study if they did not meet DSM-IV criteria for any Axis I disorders as assessed by the KSADS-PL child and parent.

ADHD-200 Dataset – Assessment Procedures. ADHD participants completed a WASI and parent and child KSADS-PL. ADHD was determined by parent and child responses on KSADS-PL, and clinically significant T-scores ($\geq$ 65) on at least one ADHD index from the Conners' Parent Rating Scale-Revised, Long Version (CPRS-LV). All participants were right handed. T-score indices for ADHD total, ADHD inattentive, and ADHD hyperactive/impulsive form the CPRS-LV were provided.

MRI Data Acquisition. All imaging data were collected on a Siemens 3 Tesla Allegra MRI scanner at the NYU Langone Medical Center. A 6-min resting state functional scan comprising of 180 contiguous whole brain functional volumes was acquired for each participant using a multi-echo echo-planar imaging sequence (TR=2000ms; flip angle=90°; 33 slices; TE=15ms, FOV=240×192mm; voxel size=3×3×4mm). Participants were instructed to lie still, relax, and think of nothing in particular while a cross hair was presented on the screen. The majority of participants were instructed to rest with eyes open, while a subset was instructed to rest with eyes closed. Individual data regarding eyes open/closed was not available through the ABIDE or ADHD-200, therefore this variable could not be controlled for. Prior research using the NYU datasets from ADHD-200 and ABIDE, have found no group differences in acquisition of eyes open or closed (Chabernaud et al., 2012). A T1-weighted anatomical image was also acquired using a magnetization prepared gradient echo sequence (TR=2530ms; TE=3. .25ms; TI=1100ms; flip angle=7°; 128 slices; FOV=256mm; voxel size=1.3×1×1.3mm).

Data Pre-Processing. Raw imaging data were pre-processed (bandpass filter, motion corrected, smooth) using NiPype (Gorgolewski et al., 2011), a python-based framework designed for highly pipelined processing of fMRI data from several neuroimaging packages (http://nipy.org/nipype). Head motion can create artifacts in functional connectivity data (Power et al., 2014; Satterthwaite et al., 2013; Van Dijk, Sabuncu, & Buckner, 2012), for this reason a scrubbing method was used to censor time points in which the signal was affected by motion. As temporal scrubbing of imaging data introduces computational challenges due to the deletion of time points making granger causality estimates unstable, frame-to-frame displacement (FD) between volumes were examined. If the FD was greater than 0.2 mm (Di Martino, Yan, et al., 2013), then the parameter estimate for the frame was deleted and each temporal discontinuity was replaced by a dummy variable based on the Dirac unit impulse function (Chen et al., 2011). We separately evaluated the impact of a relatively more stringent threshold (0.2 mm) as well as a more lenient threshold that is still within acceptable limits for data scrubbing (0.8 mm).

Data Analysis Plan

Matching Samples. In addition to the preliminary exclusion, participants were discarded (62 discarded; ASD=18; ADHD=34; TD=10) from analyses if their mean relative displacement (MRD) is > 0.55mm after scrubbing (Satterthwaite et al., 2013). Direct one-to-one matches were completed for the female participants, since the ASD group contained few females (n=4), and a total of 27 (ADHD=12; TD=15) participants were discarded when matching TD girls and girls with ADHD to the 4 remaining girls in the ASD. At this step, diagnostic groups did not significantly differ on age (p = .37), but continued to differ for FIQ, $F(2,193) = 4.37, p < .05$, and motion, $F(2,193) = 3.28, p < .05$. With regard to FIQ, post-hoc analyses revealed the TD group demonstrated a significantly greater FIQ than the ADHD group (FIQ: ASD = 105.95; TD

= 113.14, $p < .05$), but not ASD (FIQ: ASD = 107.62; $p = .08$). With regard to motion, post-hoc analyses revealed the TD group demonstrated significantly less motion than the ASD group (MRD: ASD = .029mm; TD = .024mm, $p < .05$), but not ADHD (MRD: ADHD = .027mm; $p = .58$).

As differences still remained in FIQ, the remaining participants were matched on FIQ across three groups. As a first attempt to match samples, a hybrid matching approach was used, in which z-scores were calculated for age and FIQ in the ASD group. These means and standard deviations from the ASD group were used to calculate z-scores for the ADHD and TD control groups. The z-scores for age and FIQ were multiplied against one another for every group. The individuals in the ADHD and TD groups that exhibit the most deviation for this variable were excluded. As this proposed matching approach failed and instead widened the gap in FIQ and age scores for ADHD vs TD, an alternative matching approach was completed for matching TD participants with the ASD and ADHD participants.

All TD subjects with >1.5 SD in FIQ from the ASD and ADHD mean were discarded (TD = 7). The final sample consisted of 60 ASD, 64 ADHD, and 65 TD participants (Table 4). The diagnostic groups did not differ on age, FIQ, or sex (all *p*s > .15). It should be noted that motion continued to be significantly different between groups, $F(2,186) = 3.60$, $p < .05$. Post-hoc analyses revealed the ASD group demonstrated significantly more motion than the TD group ($p < .05$), but not the ADHD group ($p = .58$, MRD: TD = .023 mm; ADHD = .027 mm; ASD = .029 mm).

Regions of Interest. Regions of interest were chosen for the SN and FPN on the basis of automated meta-analysis available through neurosynth software (http://neurosynth.org). Neurosynth is a platform for large-scale automatic synthesis of fMRI data. Neurosynth generated

a single 3D image of each network, based on results from 60 studies for "Salience Network," and an image based on results from 79 studies for the "Frontoparietal Network." Cluster tables were extracted from the images provided by Neurosynth (Figure 1), and regions of interest were chosen for the top clusters that overlapped with areas identified by brain network parcellations (Gordon et al., 2014). Specifically, important nodes for the salience network include bilateral insula and the ACC. Important nodes for the frontoparietal network include bilateral frontal areas and parietal areas. The final coordinates for the ROIs are listed in Table 3. All ROIs were derived from the peak activation of the cluster within a 5mm (diameter) spherical extraction. Time series from each ROI was extracted with the Configurable Pipeline for the Analysis of Connectomes (C-PAC; https://fcp-indi.github.io/), which is tool, which builds upon pre-existing fMRI analysis software packages to create data analytic pipelines. C-PAC contains a time series extraction tool, which extracts the mean of each ROI across all time points. This extracted data was used as an input for GIMME, in order to establish the spatial and temporal pathways between ROIs present in each network.

Group Iterative Multiple Model Estimation (GIMME). Resting state fMRI analyses aim to gain a better understanding of brain connectivity. Although many brain connectivity approaches have been developed to aggregate data across several individuals, research has demonstrated that sample heterogeneity consistently contributes to failure of the represented group models in describing individual members. GIMME (http://www.nitrc.org/projects/gimme/) is a novel approach that addresses the issue of heterogeneity by utilizing between-subjects heterogeneity as useful information, which can in turn be used as a basis for subtyping on the basis of brain connectivity mapping. GIMME is an adaptation of unified structural equation modeling (uSEM), that takes into account temporally lagged predictive modeling (aka Granger

"causality" which is a test determining whether one time series can predict the next). By modeling both the structural and temporal processes of a network basis set, GIMME can identify brain connections that exist in subsets of cases, and therefore cluster cases together on the basis of relatively more homogenous connectivity profiles. First, GIMME selects signal from noise by capitalizing on shared pathways amongst individuals to create a group-model. Then, GIMME identifies reliable paths at the individual level using the group-level paths as a starting point. This process improves the precision of the model for each iteration. To date, GIMME has outperformed all other methods (e.g., individual uSEM, dynamic causal modeling), in the reliable recovery of directed connections in brain connectivity maps (Gates & Molenaar, 2012; Smith et al., 2011).

Community Detection. Community structure detection (CSD; (Newman, 2006) is a clustering method for subgrouping individuals based on structure commonalities and was first used in social network research. Extending this method to brain imaging allows for detection of "brain communities" that include certain individuals whose brain network properties are more similar to each other than to members of another community. After estimating pathways for individual cases, subgroups are synthesized based on case-wise beta matrices. Individual–level maps are then fed into the CSD algorithm from the Brain Connectivity Toolbox (http://www.brain-connectivity-toolbox.net). Subgroups are formed on the basis of the robustness, spatial and temporal properties of networks, by using an algorithm that groups cases with similar beta estimates for the same path together. Community detection has previously been used with fMRI data to identify topologies of brain regions that work together by looking at the strength of connections among regions of interest (ROIs).

Data Analytic Plan for Assessing Diagnostic Specificity of Subgroups. One-way analysis of variance (ANOVA) or independent t-tests were conducted on diagnostic groups and GIMME+CSD-derived subgroups for each model using age, FIQ, and motion. Chi-square tests (X^2) were used to examine proportion of sex between diagnostic groups and subgroups. For significant one-way ANOVAs, Tukey's post-hoc tests were completed.

In order to determine whether GIMME+CSD could differentiate diagnostic groups, chi-square tests (X^2) were used with diagnostic group and GIMME+CSD-derived subgroup membership to identify significant differences in the proportion of diagnostic groups in each subgroup. Significant effects will be followed by post hoc chi-square tests (TD vs. ADHD; TD vs. ASD; ASD vs. ADHD) with a Bonferroni correction of (p =. 05)/3 = p < .017. Chi-squares tests were used within the solely ASD group in order to examine differences in subgroup membership for co-occurring ASD+ADHD vs. ASD only.

Results

Scrubbing Results

GIMME successfully ran on both the unscrubbed and scrubbed data for a relatively more lenient motion threshold (FD = 0.8 mm) with no errors. However the application of the more stringent scrubbing at FD = 0.2 mm resulted in insufficient time series data (>50% time series data loss in 53 participants; TD = 12; ADHD = 23; ASD = 18) and unstable parameter estimates causing the GIMME model to fail. Therefore, only analyses for unscrubbed and scrubbed data at FD = 0.8 mm are presented below.

Within-SN Connectivity

Unscrubbed Results. At the group level, GIMME identified autocorrelations at all ROIs, which indicated that each ROI was significantly predictive of its own future values. No additional paths were common to *all* participants. Six subgroups were detected; though three subgroups only contained one subject (ADHD = 1; TD = 2). These one-subject subgroups were discarded and the three remaining subgroups were characterized as follows. Subgroup A (n = 63) was characterized by two strong positive paths for R Insula→L Insula and L Insula→ACC (blue paths in Figure 2a). Subgroup B (n = 62) was characterized by two weak positive paths for R Insula→L Insula and L Insula→ACC (blue paths in Figure 2b). Subgroup C (n = 61) had no additional connectivity paths from the group-level (Figure 2c). Subgroups were significantly different on age, $F(2,183) = 3.86$, $p < .05$, and motion, $F(2,183) = 11.60$, $p < .001$, but not sex or FIQ (all *p*s > .21). Post-hoc analyses revealed Subgroup A demonstrated significantly more motion than Subgroup C (MRD: A = .031 mm; C = .021 mm, $p < .001$). Further, Subgroup A was younger than Subgroup C (Mean age: A = 10.60 years; C = 11.95 years, $p < .05$). In order to test hypothesis (1a) that ASD would be characterized by within-SN hyperconnectivity a chi-square test was performed on subgroup membership and diagnostic group. No relationship was found between diagnostic group (ASD, ADHD, TD) and the frequency of subgroup membership, X^2 (1, N = 186) = 6.57, p =.16 (Figure 2d).

Additionally, in order to test the hypothesis (2) that ASD+ADHD would be primarily characterized by within-SN hyperconnectivity a chi-square test was performed. No relationship was found between status of ADHD comorbidity and the frequency of subgroup membership, X^2 (1, N = 60) = 3.10, p =.21 (Figure 2e).

Scrubbed Results. At the group level, GIMME identified that autocorrelations indicated that all ROIs were significantly predictive of their own future values. As before, no additional

paths were common to all participants. Four subgroups were detected; though two subgroups only contained one subject (ADHD = 1; TD = 1). These one-subject subgroups were discarded and the two remaining subgroups were characterized as follows. Subgroup A (n = 100) had no additional connectivity paths from the group-level (Figure 3a). Subgroup B (n = 87) was characterized by two positive paths for R Insula→L Insula and L Insula→ACC (blue paths in Figure 3b). Subgroups did not differ on sex, age, motion, or FIQ (all *p*s > .08). In order to test hypothesis (1a) that ASD would be characterized by within-SN hyperconnectivity a chi-square test was performed. No relationship was found between diagnostic group (ASD, ADHD, TD) and the frequency of subgroup membership, X^2 (1, N = 187) = 3.84, p = .14 (Figure 3c).

In order to test hypothesis (2) that ASD+ADHD would be primarily characterized by within-SN hyperconnectivity, a chi-square test was performed. No relationship was found between status of ADHD comorbidity and the frequency of subgroup membership, X^2 (1, N = 60) = 2.91, p = .09 (Figure 3d).

Within-FPN Connectivity

Unscrubbed Results. At the group level, GIMME identified two positive paths for R IFG/MFG→ACC, ACC→L Parietal (white paths in Figure 4a and 4b), and that autocorrelations for all ROIs were significantly predictive of their own future values. Two subgroups were detected. Subgroup A (n = 84) had five positive paths for L Parietal→R MFG/SFG, R MFG/SFG→R Parietal, R Parietal→R IFG/MFG, R IFG/MFG→L MFG/IFG, and R IFG/MFG→L SFG (blue paths in Figure 4a). Subgroup B (n = 105) had no additional connectivity paths from the group-level (Figure 4b). Subgroups were significantly different on motion, $t(187) = 2.42$, $p < .001$, with Subgroup A demonstrating more motion than Subgroup B (MRD: A = .030 mm; B = .023 mm). No subgroup differences were found for sex, age or FIQ

(all *p*s > .09). In order to test the hypothesis (1b) that ADHD would be characterized by within-FPN hypoconnectivity a chi-square test was performed. No relationship was found between diagnostic group (ASD, ADHD, TD) and the frequency of subgroup membership, X^2 (1, N = 189) = 2.81, p = .25 (Figure 4c).

In order to test the hypothesis (2) that ASD+ADHD would be primarily characterized by within-FPN hypoconnectivity a chi-square test was performed. A relationship was found between the status of ADHD comorbidity and the frequency of subgroup membership, X^2 (1, N = 60) = 4.41, p < .05 (Figure 4d). Consistent with hypothesis 2 that the ASD+ADHD group would within-FPN hypoconnectivity that have previously been linked to ADHD, 72.7% of participants with ASD+ADHD were in Subgroup B, while only 44.7% of ASD only participants were in Subgroup B. Within the ASD group, there were no subgroup differences in age and FIQ (all *p*s > .25). Similar to the whole sample, subgroups were significantly different on motion, t(58) = 2.17, p < .001, with Subgroup A demonstrating more motion than Subgroup B (MRD: A = .032 mm; B = .026 mm).

Scrubbed Results. At the group level, GIMME identified a positive path for R IFG/MFG→L Parietal (white paths in Figure 5a and 5b),, and that autocorrelations for all ROIs were significantly predictive of their own future values. At the subgroup level, two subgroups were detected. Subgroup A (n = 89) had positive five paths for R Parietal→R IFG/MFG, R IFG/MFG→L SFG, R IFG/MFG→L MFG/IFG, L Parietal→R MFG/SFG, and L Parietal→ACC (blue paths in Figure 5a). Subgroup B (n = 100) had no additional connectivity paths from the group-level (Figure 5b). Subgroups were significantly different on motion, t(187) = 2.45, p < .05, with Subgroup A demonstrating more motion than Subgroup B (MRD: A = .028 mm; B = .024 mm). No subgroup differences were found for sex, age or FIQ (all *p*s > .39). In order to the test

hypothesis (1b) that ADHD would be characterized by within-FPN hypoconnectivity a chi-square test was performed and no relationship was found between diagnostic group (ASD, ADHD, TD) and the frequency of subgroup membership, X^2 (1, N = 189) = 2.24, p = .33 (Figure 5c).

In order to test the hypothesis (2) that ASD+ADHD would be primarily characterized by within-FPN hypoconnectivity a chi-square test was performed. No relationship was found between status of ADHD comorbidity and the frequency of subgroup membership, X^2 (1, N = 60) = 1.88, p = .17 (Figure 5d).

Between SN-FPN Connectivity

Unscrubbed Results. At the group level, GIMME identified positive paths for L SFG→R MFG/SFG, FPN-ACC→R Insula, R Insula→L Insula (white paths in Figure 6a and 6b), and that autocorrelations for all ROIs were significantly predictive of their own future values. At the subgroup level, two subgroups were detected. Subgroup A (n = 152) had three positive paths for L SFG→L Parietal, L Insula→SN-ACC, and R MFG/SFG→R Parietal (blue paths in Figure 6a). Subgroup B (n = 37) had eight positive paths for R Insula→R IFG/MFG, R IFG/MFG→L MFG/IFG, R IFG/MFG→L SFG, L MFG/IFG→L SFG, L SFG→R Parietal, R Parietal→L Parietal, R MFG/SFG→FPN-ACC, and FPN-ACC→SN-ACC (blue paths in Figure 6b). Subgroups were significantly different on age, $t(187) = 2.19$, $p < .05$, with younger ages in Subgroup B than in Subgroup A (Mean age: A = 11.61 years; B = 10.48 years). Subgroups were significantly different on motion, $t(187) = -5.80$, $p < .001$, with Subgroup B demonstrating more motion than Subgroup A (MRD: A = .024 mm; B = .036 mm). No subgroup difference was found for sex or FIQ (all ps > .06). In order to test the hypotheses that (1c) ASD would be characterized by between SN-FPN hypoconnectivity and (1d) ADHD would be characterized by

between SN-FPN hyperconnectivity a chi-square test was performed. A relationship was found between diagnostic group (ASD, ADHD, TD) and the frequency of subgroup membership, X^2 (1, N = 189) = 10.01, $p < .01$ (Figure 6c). Of note, 90.8% of the TD group was in subgroup A, while the ASD and ADHD groups had 81.7% and 68.8% in subgroup A, respectively. Bonferroni-corrected ($p < .017$) post hoc chi-square analyses revealed a significant difference in frequency of ADHD vs. TD groups with subgroup membership, X^2 (1, N = 129) = 9.72, $p = .002$, but not for ASD vs. TD ($p > .13$), or ASD vs. ADHD ($p > .09$).

In order to explore between SN-FPN connectivity in ASD+ADHD a chi-square test was performed to determine whether ASD+ADHD was more prominent in one of the subgroups. No relationship was found between status of ADHD comorbidity and the frequency of subgroup membership, X^2 (1, N = 60) = .001, $p = .98$ (Figure 6d).

Scrubbed Results. At the group level, GIMME identified three positive paths for L SFG→R MFG/SFG, R MFG/SFG→R Parietal, FPN-ACC→R Insula (white paths in Figure 7a and 7b), and that autocorrelations for all ROIs were significantly predictive of their own future values. At the subgroup level, two subgroups were detected. Subgroup A (n = 70) had seven positive paths for R MFG/SFG→FPN-ACC, FPN-ACC→SN-ACC, FPN-ACC→R IFG/MFG, FPN-ACC→L Insula, R IFG/MFG→L SFG, L SFG→L MFG/IFG, and L SFG→L Parietal (blue paths in Figure 7a). Subgroup B (n = 119) had one positive path for R Insula→L Insula (blue paths in Figure 7b). Subgroups were significantly different on motion $t(187) = 2.86$, $p < .01$, with Subgroup B demonstrating more motion than Subgroup A (MRD: A = .029 mm; B = .024 mm). No subgroup differences were found for sex, age, motion or FIQ (all *p*s > .22). In order to test the hypotheses that (1c) ASD would be characterized by between SN-FPN hypoconnectivity and (1d) ADHD would be characterized by between SN-FPN hyperconnectivity a chi-square test was

performed. A relationship was found between diagnostic group (ASD, ADHD, TD) and the frequency of subgroup membership, X^2 (1, N = 189) = 7.18, $p < .05$ (Figure 7c). Of note, 71.7% of the ASD group and 67.7% of the TD group was in subgroup B, while the ADHD group demonstrated more heterogeneity with and 50% in subgroup B. Bonferroni-corrected ($p < .017$) post hoc chi-square analyses revealed a significant difference in frequency of ASD vs. ADHD groups with subgroup membership, X^2 (1, N = 124) = 6.08, $p = .014$, but not for ADHD vs. TD ($p > .04$), or ASD vs. TD ($p > .62$).

In order to explore between SN-FPN connectivity in ASD+ADHD a chi-square test was performed to determine whether ASD+ADHD was more prominent in one of the subgroups. No relationship was found between status of ADHD comorbidity and the frequency of subgroup membership, X^2 (1, N = 60) = 3.66, $p = .055$ (Figure 7d). Although observed only at the level of a trend the frequencies of subgroup membership indicated that 86.4% of ASD+ADHD subjects were in Subgroup B, while only 63.2% of ASD only subjects were in Subgroup B. Within the ASD group, there were no subgroup differences in age, sex, FIQ, and motion (all *p*s > .09).

Overall Summary of Results

Results for within-SN connectivity using both unscrubbed and scrubbed data did not support hypothesis 1a that GIMME+CSD-derived subgroups would characterize ASD based on hyperconnectivity of within-SN nodes. Results for within-FPN connectivity using unscrubbed and scrubbed data did not support hypothesis 1b that GIMME+CSD-derived subgroups would characterize ADHD based on hypoconnectivity of within-FPN nodes. Results for between SN-FPN connectivity using both unscrubbed and scrubbed data supported hypothesis 1c that GIMME+CSD-derived subgroups would characterize ASD based on hypoconnectivity of between SN-FPN nodes, with the ASD group demonstrating the highest proportion of between

SN-FPN hypoconnectivity (72.7%), though this result was only significant when compared to ADHD (50%) and not TD (67.7%) groups for scrubbed data. Results for between SN-FPN connectivity using unscrubbed and scrubbed data partially supported hypothesis 1d that GIMME+CSD-derived subgroups would characterize ADHD based on hyperconnectivity of between SN-FPN nodes, with the ADHD group demonstrated the highest proportion of between SN-FPN hyperconnectivity (50%), though this result was only significant when compared to ASD and not TD groups.

Results related to within-SN connectivity for ASD+ADHD comorbidity did not support hypothesis 2 that ASD+ADHD would demonstrate within-SN hyperconnectivity, similar to previous ASD patterns. Consistent with previous findings of within-FPN hypoconnectivity patterns in ADHD, hypothesis 2 was partially supported in that the ASD+ADHD comorbidity demonstrated a greater proportion (72.7%) of subgroup membership in within-FPN hypoconnectivity versus the ASD only group (44.7%) for unscrubbed data. Though it should be noted that this result did not hold for scrubbed data, nor was this hypoconnectivity of within-FPN for the ADHD group replicated in this sample. Exploratory analyses with between SN-FPN connectivity for ASD+ADHD were completed, with a trend in scrubbed data toward ASD+ADHD (86.4) demonstrating a greater proportion with hypoconnectivity than ASD only (63.2%).

Discussion

The present study determined that GIMME+CSD was able to robustly differentiate ASD, ADHD, and TD groups based on between network (SN-FPN) connectivity patterns, but not within-SN or within-FPN connectivity patterns. Although subgroups were identifiable for within-SN and within-FPN connectivity patterns, diagnostic groups were not significantly

different in these newly formed groups. Findings were similar for both scrubbed and unscrubbed data. In line with the between SN-FPN hypothesis (1c), a greater proportion of ASD participants were characterized by between SN-FPN hypoconnectivity when using scrubbed data, but not with unscrubbed data. Moreover, consistent with between SN-FPN hypothesis (1d), half of the ADHD group was characterized by between SN-FPN hyperconnectivity for scrubbed, but not unscrubbed data. The present study further determined that GIMME+CSD may be able to differentiate ASD+ADHD and ASD only based on within-FPN connectivity patterns, but not within-SN. Of note, this differentiation based on within-FPN connectivity patterns for ASD+ADHD did not hold with the scrubbed data. When exploring between SN-FPN connectivity for ASD+ADHD vs. ASD only, there was a trend in subgroup membership for scrubbed data. Altogether, there is evidence for support of GIMME+CSD to differentiate ASD and ADHD groups, and further to better understand heterogeneity in co-occurring ASD+ADHD.

In line with the first aim of the study, GIMME+CSD-derived subgroups were able to characterize ASD and ADHD patterns based on between SN-FPN differences, though neither the ASD nor the ADHD group were significantly different in frequency of group membership from the TD group for scrubbed data. A greater proportion of the ASD group demonstrated between SN-FPN hypoconnectivity with 71.7% of the sample characterized by the hypoconnectivity pattern, which was significantly different from the 50% of ADHD participants characterized by this subgroup. The TD group demonstrated a similar pattern to the ASD group with 68.7% of TD participants falling into the between SN-FPN hypoconnectivity group. Previous connectivity studies have found hypoconnectivity for between SN-FPN paths in ASD compared to TD controls (Abbott et al., 2016; von dem Hagen et al., 2013). For example, hypoconnectivity between the right anterior insula of the SN and left inferior parietal lobule of the FPN has been

found in children with ASD compared to TD controls (Abbott et al., 2016). Similarly, von dem Hagen and colleagues (2013) also found hypoconnectivity between insular nodes and PFC nodes in adults with ASD compared to controls. These ASD vs. TD group differences in individual hypoconnected paths were not replicated in this study. This discrepancy in ASD vs. TD result may be due to the fact that GIMME+CSD's sensitivity to heterogeneity using a data-driven approach which parses group-level followed by subgroup-level paths may have masked individual differences in favor of wholistic network connectivity patterns. Further, it should be noted that no current studies to date have used graph theory and community detection to examine connectivity patterns in ASD and ADHD groups. These two neurodevelopmental groups are phenotypically similar, as they have overlapping social, motor, and executive functioning difficulties that make it difficult to parse these two disorders apart using diagnostic measures alone (Grzadzinski et al., 2016; Miodovnik et al., 2015; Yerys et al., 2016).

Interestingly, despite these phenotypic similarities, GIMME+CSD found a significant difference in frequency of between SN-FPN subgroup membership for ASD vs. ADHD. ADHD had the highest proportion (50%) of between SN-FPN hyperconnectivity, demonstrating more heterogeneity in connectivity alterations that can characterize ADHD. This between SN-FPN hyperconnectivity finding is consistent with previous studies of between SN-FPN hyperconnectivity in ADHD compared to TD controls. For example, when compared to TD youth, medication-naïve youth with ADHD demonstrated hyperconnectivity between SN and FPN nodes (Choi et al., 2013). Further, children with ADHD who were off stimulants during scanning have also demonstrated between SN-FPN hyperconnectivity (Elton et al., 2014), and it is possible that this neural alteration continues into adulthood (Yu, 2013). As previous findings have highlighted the role of medication status with hyperconnectivity in ADHD, it may be

important to examine the role of medication status and responsivity to subgroup findings. This between SN-FPN hyperconnectivity for children with ADHD has not been previously been detected in comparison to ASD.

Although previous studies have found shared and distinct connectivity for ASD vs. ADHD (Di Martino, Zuo, et al., 2013; Ray et al., 2014), no studies have explicitly examined between SN-FPN connectivity using graph theory and community detection. Between SN-FPN connectivity plays an important role in attention and executive functioning difficulties (Seeley et al., 2007), which are mechanisms that have both been linked to ASD and ADHD. More specifically, SN and FPN connections have been linked to cognitive flexibility (Menon & Uddin, 2010). Further, there has been an increase in evidence indicating that the SN has an important role in modulating FPN and default mode network signals for ASD (Abbott et al., 2016; Plitt et al., 2015; Yerys et al., 2015) and ADHD (Choi et al., 2013; Mattfeld et al., 2014). Thus, these between SN-FPN findings for ASD and ADHD may be related to saliency processing. Specifically, exogenous and endogenous attention are processed through the anterior insula of the SN, sending signals to regulate behavior through the SN's ACC hub, which then streams to differential posterior cingulate cortex hubs for the default mode network and FPN (Bressler & Menon, 2010; Menon, 2011). Dysfunction of this triple network (SN, FPN, default mode network) dynamic has been implicated in facets of cognitions such as rumination, goal-directed behavior, and decision making across disorders (Menon, 2011). Altogether, differences in between SN-FPN subgroup membership for ASD vs. ADHD may reveal alterations in cognitive processing that may underlie these disorders.

In line with the second aim of the study 72.7% of the ASD+ADHD group were characterized by within-FPN hypoconnectivity, while only 44.4% of the ASD only group was

characterized by the within-FPN hypoconnectivity. This result was not significant when using the scrubbed data, though demonstrated a similar pattern. Within-SN connectivity did not characterize ASD+ADHD for scrubbed or unscrubbed data. There was a trend for significance for between SN-FPN for ASD+ADHD vs. ASD only, with the ASD+ADHD group demonstrating a greater proportion of hypoconnectivity, similar to previous ASD findings. Only one paper has examined connectivity in ASD+ADHD, with findings of added connections for the basal ganglia for comorbid ASD+ADHD. As the basal ganglia is a source of sensory and limbic input to the anterior insula (Menon, 2011) and FPN (Langen, Durston, Kas, van Engeland, & Staal, 2011), future work should examine how these connections are altered for ASD+ADHD. Altogether, the FPN and potentially between SN-FPN connectivity may be a useful network to examine comorbid ASD+ADHD. It is important to examine how these connectivity differences may be related to other dimensional facets of behavior, rather than categorical diagnostic comorbidity.

This study was limited in several ways. First, these results are primarily based off of male participants. Due to 4 remaining girls in the ASD group, several girls were dropped from the TD and ADHD groups. There has been an increase in appreciation for the presentation of ASD (Supekar & Menon, 2015) and ADHD (Nussbaum, 2012; O'Brien, Dowell, Mostofsky, Denckla, & Mahone, 2010) in girls. For example, increased repetitive behaviors have been found for girls with ASD, and altering difficulties in executive function (e.g., planning) have been found for girls with ADHD. Thus, the heterogeneity girls may add to the model was not captured by this study. It will be important to examine whether these patterns are stable with a greater representation of girls. Secondly, the ASD and ADHD groups were well matched FIQ, while the TD group had significantly higher FIQ scores. In order for groups to match on FIQ, TD

participants with a > 1.5 SD FIQ from the ASD and ADHD mean were discarded. As the FIQ scores for the TD group were fenced, these results are only representative of TD children with FIQ scores up to 129. Further, despite attempting to control for motion through several variables (e.g., discarding individuals with > 0.55 mm MRD, scrubbing data at FD = 0.2 mm and 0.8 mm), motion continued to be significantly different between diagnostic groups and was frequently different across GIMME+CSD-derived subgroups. Though it should be noted that this study's findings of similar connectivity results between unscrubbed and scrubbed data is consistent with previous research using scrubbing at FD = .02 (Di Martino, Yan, et al., 2013). Of note, subgroups that demonstrated hyperconnectivity always had higher motion. Therefore, future studies with findings of hyperconnectivity should examine the role of motion on connectivity.

Another limitation of the present study is that GIMME works best with 5-15 ROIs (Price et al., 2017), therefore the few number of ROIs chosen for the SN (ROIs = 3) may have limited variability in pathways that could differentiate groups. This limitation is captured by the within-SN subgroups that were solely characterized by auto recursive paths for each ROI, without additional paths for other ROIs. These subgroups are likely representative of very heterogeneous connectivity patterns for several participants. Finally, the participants in the current study did not have behavioral data (e.g., symptom severity, executive functioning difficulties, adaptive functioning) on all participants. Thus, subgroups that emerged may be representative of other dimensional facets of behavior, which could not be captured by this study and may be separate from diagnostic classifications.

Consistent with previous literature, between network hypoconnectivity for SN-FPN may characterize ASD vs. ADHD youth. Altogether, the use of graph theory and community detection techniques with resting state connectivity may aid in parsing similarities and

differences between ASD, ADHD and TD youth. Further, within-FPN and between SN-FPN connectivity may be important in understanding additive ASD+ADHD effect. Future work should examine dimensional facets of behavior that may predict subgroup membership, as this can aid in identifying specific brain-behavior relationships that may be relevant to assessment at treatment.

References

Abbott, A. E., Nair, A., Keown, C. L., Datko, M., Jahedi, A., Fishman, I., & Müller, R.-A. (2016). Patterns of Atypical Functional Connectivity and Behavioral Links in Autism Differ Between Default, Salience, and Executive Networks. *Cerebral Cortex (New York, N.Y.: 1991)*, *26*(10), 4034–4045. https://doi.org/10.1093/cercor/bhv191

Antezana, L., Mosner, M. G., Troiani, V., & Yerys, B. E. (2015). Social-Emotional Inhibition of Return in Children with Autism Spectrum Disorder Versus Typical Development. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-015-2661-9

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. *Trends in Cognitive Sciences*, *14*(6), 277–290. https://doi.org/10.1016/j.tics.2010.04.004

Cascio, C. J., Foss-Feig, J. H., Heacock, J., Schauder, K. B., Loring, W. A., Rogers, B. P., … Bolton, S. (2014). Affective neural response to restricted interests in autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *55*(2), 162–171. https://doi.org/10.1111/jcpp.12147

Castellanos, F. X., & Aoki, Y. (2016). Intrinsic Functional Connectivity in Attention-Deficit/Hyperactivity Disorder: A Science in Development. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *1*(3), 253–261. https://doi.org/10.1016/j.bpsc.2016.03.004

Chabernaud, C., Mennes, M., Kelly, C., Nooner, K., Di Martino, A., Castellanos, F. X., & Milham, M. P. (2012). Dimensional brain-behavior relationships in children with

attention-deficit/hyperactivity disorder. *Biological Psychiatry*, *71*(5), 434–442. https://doi.org/10.1016/j.biopsych.2011.08.013

Chen, G., Glen, D. R., Saad, Z. S., Paul Hamilton, J., Thomason, M. E., Gotlib, I. H., & Cox, R. W. (2011). Vector autoregression, structural equation modeling, and their synthesis in neuroimaging data analysis. *Computers in Biology and Medicine*, *41*(12), 1142–1155. https://doi.org/10.1016/j.compbiomed.2011.09.004

Choi, J., Jeong, B., Lee, S. W., & Go, H.-J. (2013). Aberrant Development of Functional Connectivity among Resting State-Related Functional Networks in Medication-Naïve ADHD Children. *PLoS ONE*, *8*(12), e83516. https://doi.org/10.1371/journal.pone.0083516

Dawson, G., Webb, S. J., & McPartland, J. (2005). Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. *Developmental Neuropsychology*, *27*(3), 403–424. https://doi.org/10.1207/s15326942dn2703_6

Di Martino, A., Yan, C.-G., Li, Q., Denio, E., Castellanos, F. X., Alaerts, K., … Milham, M. P. (2013). The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Molecular Psychiatry*. https://doi.org/10.1038/mp.2013.78

Di Martino, A., Zuo, X.-N., Kelly, C., Grzadzinski, R., Mennes, M., Schvarcz, A., … Milham, M. P. (2013). Shared and Distinct Intrinsic Functional Network Centrality in Autism and Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, *74*(8), 623–632. https://doi.org/10.1016/j.biopsych.2013.02.011

dos Santos Siqueira, A., Biazoli Junior, C. E., Comfort, W. E., Rohde, L. A., & Sato, J. R. (2014). Abnormal Functional Resting-State Networks in ADHD: Graph Theory and Pattern Recognition Analysis of fMRI Data. *BioMed Research International*, *2014*. https://doi.org/10.1155/2014/380531

Elsabbagh, M., Fernandes, J., Jane Webb, S., Dawson, G., Charman, T., & Johnson, M. H. (2013). Disengagement of Visual Attention in Infancy Is Associated with Emerging Autism in Toddlerhood. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2012.11.030

Elton, A., Alcauter, S., & Gao, W. (2014). Network connectivity abnormality profile supports a categorical-dimensional hybrid model of ADHD: Categorical-Dimensional Hybrid Model of ADHD. *Human Brain Mapping*, *35*(9), 4531–4543. https://doi.org/10.1002/hbm.22492

Elton, A., Di Martino, A., Hazlett, H. C., & Gao, W. (2015). Neural Connectivity Evidence for a Categorical-Dimensional Hybrid Model of Autism Spectrum Disorder. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2015.10.020

Francx, W., Oldehinkel, M., Oosterlaan, J., Heslenfeld, D., Hartman, C. A., Hoekstra, P. J., … Mennes, M. (2015). The executive control network and symptomatic improvement in attention-deficit/hyperactivity disorder. *Cortex*, *73*, 62–72. https://doi.org/10.1016/j.cortex.2015.08.012

Gates, K. M., & Molenaar, P. C. M. (2012). Group search algorithm recovers effective connectivity maps for individuals in homogeneous and heterogeneous samples. *NeuroImage*, *63*(1), 310–319. https://doi.org/10.1016/j.neuroimage.2012.06.026

Gates, K. M., Molenaar, P. C. M., Iyer, S. P., Nigg, J. T., & Fair, D. A. (2014). Organizing heterogeneous samples using community detection of GIMME-derived resting state

functional networks. *PloS One*, *9*(3), e91322. https://doi.org/10.1371/journal.pone.0091322

Gioia, G. A., Isquith, P. K., Kenworthy, L., & Barton, R. M. (2002). Profiles of everyday executive function in acquired and developmental disorders. *Child Neuropsychology*, *8*(2), 121–137.

Gordon, E. M., Laumann, T. O., Adeyemo, B., Huckins, J. F., Kelley, W. M., & Petersen, S. E. (2014). Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. *Cerebral Cortex*. https://doi.org/10.1093/cercor/bhu239

Gorgolewski, K., Burns, C. D., Madison, C., Clark, D., Halchenko, Y. O., Waskom, M. L., & Ghosh, S. S. (2011). Nipype: a flexible, lightweight and extensible neuroimaging data processing framework in python. *Frontiers in Neuroinformatics*, *5*, 13. https://doi.org/10.3389/fninf.2011.00013

Green, S. A., Hernandez, L., Bookheimer, S. Y., & Dapretto, M. (2016). Salience Network Connectivity in Autism Is Related to Brain and Behavioral Markers of Sensory Overresponsivity. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(7), 618-626.e1. https://doi.org/10.1016/j.jaac.2016.04.013

Grzadzinski, R., Dick, C., Lord, C., & Bishop, S. (2016). Parent-reported and clinician-observed autism spectrum disorder (ASD) symptoms in children with attention deficit/hyperactivity disorder (ADHD): implications for practice under DSM-5. *Molecular Autism*, *7*, 7. https://doi.org/10.1186/s13229-016-0072-1

Halperin, J. M., & Schulz, K. P. (2006). Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. *Psychological Bulletin*, *132*(4), 560–581. https://doi.org/10.1037/0033-2909.132.4.560

Johnson, M. H., Gliga, T., Jones, E., & Charman, T. (2014). Annual Research Review: Infant development, autism, and ADHD - early pathways to emerging disorders. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. https://doi.org/10.1111/jcpp.12328

Keehn, B., Müller, R.-A., & Townsend, J. (2013). Atypical Attentional Networks and the Emergence of Autism. *Neuroscience and Biobehavioral Reviews*, *37*(2), 164–183. https://doi.org/10.1016/j.neubiorev.2012.11.014

Kucyi, A., Hove, M. J., Biederman, J., Van Dijk, K. R. A., & Valera, E. M. (2015). Disrupted functional connectivity of cerebellar default network areas in attention-deficit/hyperactivity disorder. *Human Brain Mapping*, *36*(9), 3373–3386. https://doi.org/10.1002/hbm.22850

Langen, M., Durston, S., Kas, M. J. H., van Engeland, H., & Staal, W. G. (2011). The neurobiology of repetitive behavior: …and men. *Neuroscience and Biobehavioral Reviews*, *35*(3), 356–365. https://doi.org/10.1016/j.neubiorev.2010.02.005

Liddle, E. B., Hollis, C., Batty, M. J., Groom, M. J., Totman, J. J., Liotti, M., … Liddle, P. F. (2011). Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *52*(7), 761–771. https://doi.org/10.1111/j.1469-7610.2010.02333.x

Lin, H.-Y., Tseng, W.-Y. I., Lai, M.-C., Matsuo, K., & Gau, S. S.-F. (2015). Altered Resting-State Frontoparietal Control Network in Children with Attention-Deficit/Hyperactivity Disorder. *Journal of the International Neuropsychological Society*, *21*(04), 271–284. https://doi.org/10.1017/S135561771500020X

Matson, J. L., Rieske, R. D., & Williams, L. W. (2013). The relationship between autism spectrum disorders and attention-deficit/hyperactivity disorder: An overview. *Research in Developmental Disabilities*, *34*(9), 2475–2484. https://doi.org/10.1016/j.ridd.2013.05.021

Mattfeld, A. T., Gabrieli, J. D. E., Biederman, J., Spencer, T., Brown, A., Kotte, A., … Whitfield-Gabrieli, S. (2014). Brain differences between persistent and remitted attention deficit hyperactivity disorder. *Brain*, *137*(9), 2423–2428. https://doi.org/10.1093/brain/awu137

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences*, *15*(10), 483–506. https://doi.org/10.1016/j.tics.2011.08.003

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure & Function*, *214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Miodovnik, A., Harstad, E., Sideridis, G., & Huntington, N. (2015). Timing of the Diagnosis of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder. *Pediatrics*, *136*(4), e830-837. https://doi.org/10.1542/peds.2015-1502

Mostert, J. C., Shumskaya, E., Mennes, M., Onnink, A. M. H., Hoogman, M., Kan, C. C., … Norris, D. G. (2016). Characterising resting-state functional connectivity in a large sample of adults with ADHD. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *67*, 82–91. https://doi.org/10.1016/j.pnpbp.2016.01.011

Murray, M. J. (2010). Attention-deficit/Hyperactivity Disorder in the Context of Autism Spectrum Disorders. *Current Psychiatry Reports*. https://doi.org/10.1007/s11920-010-0145-3

Newman, M. E. J. (2006). Modularity and community structure in networks. *Proceedings of the National Academy of Sciences*, *103*(23), 8577–8582. https://doi.org/10.1073/pnas.0601602103

Nussbaum, N. L. (2012). ADHD and Female Specific Concerns: A Review of the Literature and Clinical Implications. *Journal of Attention Disorders*, *16*(2), 87–100. https://doi.org/10.1177/1087054711416909

O'Brien, J. W., Dowell, L. R., Mostofsky, S. H., Denckla, M. B., & Mahone, E. M. (2010). Neuropsychological Profile of Executive Function in Girls with Attention-Deficit/Hyperactivity Disorder. *Archives of Clinical Neuropsychology*, *25*(7), 656–670. https://doi.org/10.1093/arclin/acq050

Odriozola, P., Uddin, L. Q., Lynch, C. J., Kochalka, J., Chen, T., & Menon, V. (2015). Insula response and connectivity during social and non-social attention in children with autism. *Social Cognitive and Affective Neuroscience*. https://doi.org/10.1093/scan/nsv126

Oldehinkel, M., Beckmann, C. F., Franke, B., Hartman, C. A., Hoekstra, P. J., Oosterlaan, J., … Mennes, M. (2016). Functional connectivity in cortico-subcortical brain networks underlying reward processing in attention-deficit/hyperactivity disorder. *NeuroImage. Clinical*, *12*, 796–805. https://doi.org/10.1016/j.nicl.2016.10.006

Park, B.-Y., Hong, J., Lee, S.-H., & Park, H. (2016). Functional Connectivity of Child and Adolescent Attention Deficit Hyperactivity Disorder Patients: Correlation with IQ. *Frontiers in Human Neuroscience*, *10*, 565. https://doi.org/10.3389/fnhum.2016.00565

Plitt, M., Barnes, K. A., & Martin, A. (2014). Functional connectivity classification of autism identifies highly predictive brain features but falls short of biomarker standards. *NeuroImage : Clinical*, *7*, 359–366. https://doi.org/10.1016/j.nicl.2014.12.013

Plitt, M., Barnes, K. A., Wallace, G. L., Kenworthy, L., & Martin, A. (2015). Resting-state functional connectivity predicts longitudinal change in autistic traits and adaptive functioning in autism. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(48), E6699-6706. https://doi.org/10.1073/pnas.1510098112

Posner, J., Park, C., & Wang, Z. (2014). Connecting the dots: A review of resting connectivity MRI studies in Attention-Deficit/Hyperactivity Disorder. *Neuropsychology Review*, *24*(1), 3–15. https://doi.org/10.1007/s11065-014-9251-z

Posner, J., Rauh, V., Gruber, A., Gat, I., Wang, Z., & Peterson, B. S. (2013). Dissociable attentional and affective circuits in medication-naïve children with attention-deficit/hyperactivity disorder. *Psychiatry Research*, *213*(1), 24–30. https://doi.org/10.1016/j.pscychresns.2013.01.004

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048

Price, R. B., Lane, S., Gates, K., Kraynak, T. E., Horner, M. S., Thase, M. E., & Siegle, G. J. (2017). Parsing Heterogeneity in the Brain Connectivity of Depressed and Healthy Adults During Positive Mood. *Biological Psychiatry*, *81*(4), 347–357. https://doi.org/10.1016/j.biopsych.2016.06.023

Ray, S., Miller, M., Karalunas, S., Robertson, C., Grayson, D. S., Cary, R. P., … Fair, D. A. (2014). Structural and functional connectivity of the human brain in autism spectrum disorders and attention-deficit/hyperactivity disorder: A rich club-organization study. *Human Brain Mapping*. https://doi.org/10.1002/hbm.22603

Redcay, E., Moran, J. M., Mavros, P. L., Tager-Flusberg, H., Gabrieli, J. D. E., & Whitfield-Gabrieli, S. (2013). Intrinsic functional network organization in high-functioning adolescents with autism spectrum disorder. *Frontiers in Human Neuroscience*, *7*, 573. https://doi.org/10.3389/fnhum.2013.00573

Satterthwaite, T. D., Elliott, M. A., Gerraty, R. T., Ruparel, K., Loughead, J., Calkins, M. E., … Wolf, D. H. (2013). An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *NeuroImage*, *64*, 240–256. https://doi.org/10.1016/j.neuroimage.2012.08.052

Schultz, R. T. (2005). Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience*, *23*(2–3), 125–141. https://doi.org/10.1016/j.ijdevneu.2004.12.012

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. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Shaw, P, Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D., … Rapoport, J. L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(49), 19649–19654. https://doi.org/10.1073/pnas.0707741104

Shaw, Philip, Stringaris, A., Nigg, J., & Leibenluft, E. (2014). Emotion Dysregulation in Attention Deficit Hyperactivity Disorder. *American Journal of Psychiatry*, *171*(3), 276–293. https://doi.org/10.1176/appi.ajp.2013.13070966

Sidlauskaite, J., Sonuga-Barke, E., Roeyers, H., & Wiersema, J. R. (2016). Altered intrinsic organisation of brain networks implicated in attentional processes in adult attention-deficit/hyperactivity disorder: a resting-state study of attention, default mode and salience network connectivity. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(4), 349–357. https://doi.org/10.1007/s00406-015-0630-0

Smith, S. M., Miller, K. L., Salimi-Khorshidi, G., Webster, M., Beckmann, C. F., Nichols, T. E., … Woolrich, M. W. (2011). Network modelling methods for FMRI. *NeuroImage*, *54*(2), 875–891. https://doi.org/10.1016/j.neuroimage.2010.08.063

Solomon, M., Ozonoff, S., Ursu, S., Ravizza, S., Cummings, N., Ly, S., & Carter, C. S. (2009). The neural substrates of cognitive control deficits in autism spectrum disorders. *Neuropsychologia*, *47*(12), 2515–2526. https://doi.org/10.1016/j.neuropsychologia.2009.04.019

Stahlberg, O., Soderstrom, H., Rastam, M., & Gillberg, C. (2004). Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. *Journal of Neural Transmission*, *111*(7), 891–902. https://doi.org/10.1007/s00702-004-0115-1

Supekar, K., & Menon, V. (2015). Sex differences in structural organization of motor systems and their dissociable links with repetitive/restricted behaviors in children with autism. *Molecular Autism*, *6*, 50. https://doi.org/10.1186/s13229-015-0042-z

Uddin, L. Q., Kelly, A. M. C., Biswal, B. B., Margulies, D. S., Shehzad, Z., Shaw, D., … Milham, M. P. (2008). Network homogeneity reveals decreased integrity of default-mode network in ADHD. *Journal of Neuroscience Methods*, *169*(1), 249–254. https://doi.org/10.1016/j.jneumeth.2007.11.031

Uddin, L. Q., & Menon, V. (2009). The anterior insula in autism: under-connected and under-examined. *Neuroscience and Biobehavioral Reviews*, *33*(8), 1198–1203. https://doi.org/10.1016/j.neubiorev.2009.06.002

Uddin, L. Q., Supekar, K., Lynch, C. J., Cheng, K. M., Odriozola, P., Barth, M. E., … Menon, V. (2015). Brain State Differentiation and Behavioral Inflexibility in Autism. *Cerebral Cortex (New York, N.Y.: 1991)*, *25*(12), 4740–4747. https://doi.org/10.1093/cercor/bhu161

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*, 1–11. https://doi.org/10.1001/jamapsychiatry.2013.104

Van Dijk, K. R. A., Sabuncu, M. R., & Buckner, R. L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *NeuroImage*, *59*(1), 431–438. https://doi.org/10.1016/j.neuroimage.2011.07.044

Visser, J. C., Rommelse, N. N. J., Greven, C. U., & Buitelaar, J. K. (2016). Autism spectrum disorder and attention-deficit/hyperactivity disorder in early childhood: A review of unique and shared characteristics and developmental antecedents. *Neuroscience and Biobehavioral Reviews*, *65*, 229–263. https://doi.org/10.1016/j.neubiorev.2016.03.019

von dem Hagen, E. A. H., Stoyanova, R. S., Baron-Cohen, S., & Calder, A. J. (2013). Reduced functional connectivity within and between “social” resting state networks in autism spectrum conditions. *Social Cognitive and Affective Neuroscience*, *8*(6), 694–701. https://doi.org/10.1093/scan/nss053

Willcutt, E. G., Nigg, J. T., Pennington, B. F., Solanto, M. V., Rohde, L. A., Tannock, R., … Lahey, B. B. (2012). Validity of DSM-IV attention–deficit/hyperactivity disorder symptom dimensions and subtypes. *Journal of Abnormal Psychology*, *121*(4), 991–1010. https://doi.org/10.1037/a0027347

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. https://doi.org/10.1016/j.nicl.2015.07.018

Yerys, B. E., Nissley-Tsiopinis, J., Marchena, A. de, Watkins, M. W., Antezana, L., Power, T. J., & Schultz, R. T. (2016). Evaluation of the ADHD Rating Scale in Youth with Autism. *Journal of Autism and Developmental Disorders*, 1–11. https://doi.org/10.1007/s10803-016-2933-z

Yu, D. (2013). Additional Brain Functional Network in Adults with Attention-Deficit/Hyperactivity Disorder: A Phase Synchrony Analysis. *PLoS ONE*, *8*(1), 1–10. https://doi.org/10.1371/journal.pone.0054516

Zielinski, B. A., Anderson, J. S., Froehlich, A. L., Prigge, M. B. D., Nielsen, J. A., Cooperrider, J. R., … Lainhart, J. E. (2012). scMRI Reveals Large-Scale Brain Network Abnormalities in Autism. *PLoS ONE*, *7*(11), e49172. https://doi.org/10.1371/journal.pone.0049172

Table 1. Preliminary Dataset: Participant characteristics by diagnostic group.

	TD n=97	ADHD n=115	ASD n=78	*p*-value
Age (years) *M*(SD)	11.75 (2.89)	11.03 (2.67)	10.78 (2.81)	0.051*
Range	7.11-17.70	7.24-17.61	7.13-17.93	
FIQ (SS) *M*(SD)	113.56 (14.54)	107.03 (13.69)	108.90 (15.88)	0.005*
Range	80-144	80-134	80-148	
Sex (M:F)	78:19	92:23	73:5	0.022*
CPRS Inattentive T-score *M*(SD)	47.25 (6.87)	70.33 (9.44)	65.72 (9.53)	<0.001*
Range	40-61	51-90	40-84	
CPRS H/I T-Score *M*(SD)	49.42 (6.24)	68.46 (11.46)	62.80 (11.41)	<0.001*
Range	41-65	43-90	44-83	
CPRS Total T	48.13 (6.01)	71.11 (8.47)	65.60 (9.60)	<.001*
Range	40-60	55-90	41-86	
ADOS-2 Social Affect	--	--	8.96 (3.95)	--
Range			2-20	
ADOS-2 RRB	--	--	3.23 (1.57)	--
Range			0-7	
ADOS-2 Total	--	--	12.17 (4.83)	--
Range			4-26	
ADOS-2 CCS	--	--	6.92 (2.06)	--
Range			2-10	

CCS=Calibrated Comparison Score
CPRS= Conners' Parent Rating Scale-Revised, Long Version
H/I=Hyperactive/Impulsive
GCA=Global Composite Ability
RRB=Restricted and Repetitive Behaviors
FIQ=Full Scale IQ (*M*=100; SD=15)

*Note: ADOS-2 scores were only available for 71 participants with ASD. CPRS scores were only available for 25 participants with ASD, 24 TD participants, and 114 participants with ADHD.

Table 2. Preliminary Dataset: Number (%) of participants in ADHD or ASD groups with co-occurring diagnoses, as determined by the KSADS-PL

	ADHD	ASD	*p*-value
	n=115	n=78	
ADHD	--	34 (43.60%)	--
ADHD-Inattentive	--	11 (14.10%)	--
ADHD-Combined	--	10 (12.82%)	--
ADHD-Hyperactive/Impulsive	--	1 (1.28%)	--
ADHD-NOS	--	3 (3.85%)	--
ODD/Disruptive Disorder NOS	5 (4.35%)	4 (5.13%)	0.36
Anxiety	8 (6.96%)	14 (17.95%)	0.02*
GAD	--	5 (6.41%)	
SAD	1 (0.87%)	2 (1.56%)	0.66
Specific Phobia	5 (4.35%)	5 (6.41%)	0.53
Anxiety NOS	2 (1.73%)	2 (1.56%)	0.93
Depression NOS/Mood NOS/Adjustment	4 (3.51%)	6 (7.69%)	0.20
Enuresis/Encropresis	1 (0.87%)	2 (1.56%)	0.66
Learning Disorder	2 (1.74%)	--	--
Dyslexia/Dycalculia	3 (2.61%)	--	--

Table 3. MNI Coordinates for Salience and Frontoparietal Network ROIs

ROI	Peak MNI Coordinate		
	X	**Y**	**Z**
Salience Network			
R Insula	-38	-18	+2
ACC	-6	-26	+28
L Insula	+38	–14	-6
Frontoparietal Network			
R Parietal	-20	+58	+56
L Parietal	+14	+66	+52
ACC	-4	-18	+48
R MFG/SFG	-26	0	+52
L MFG/IFG	+44	-6	+32
R IFG/MFG	-50	-10	+28
L SFG	+28	+4	+54

Figure 1. Neurosynth maps for the (1a) SN and (1b) FPN.

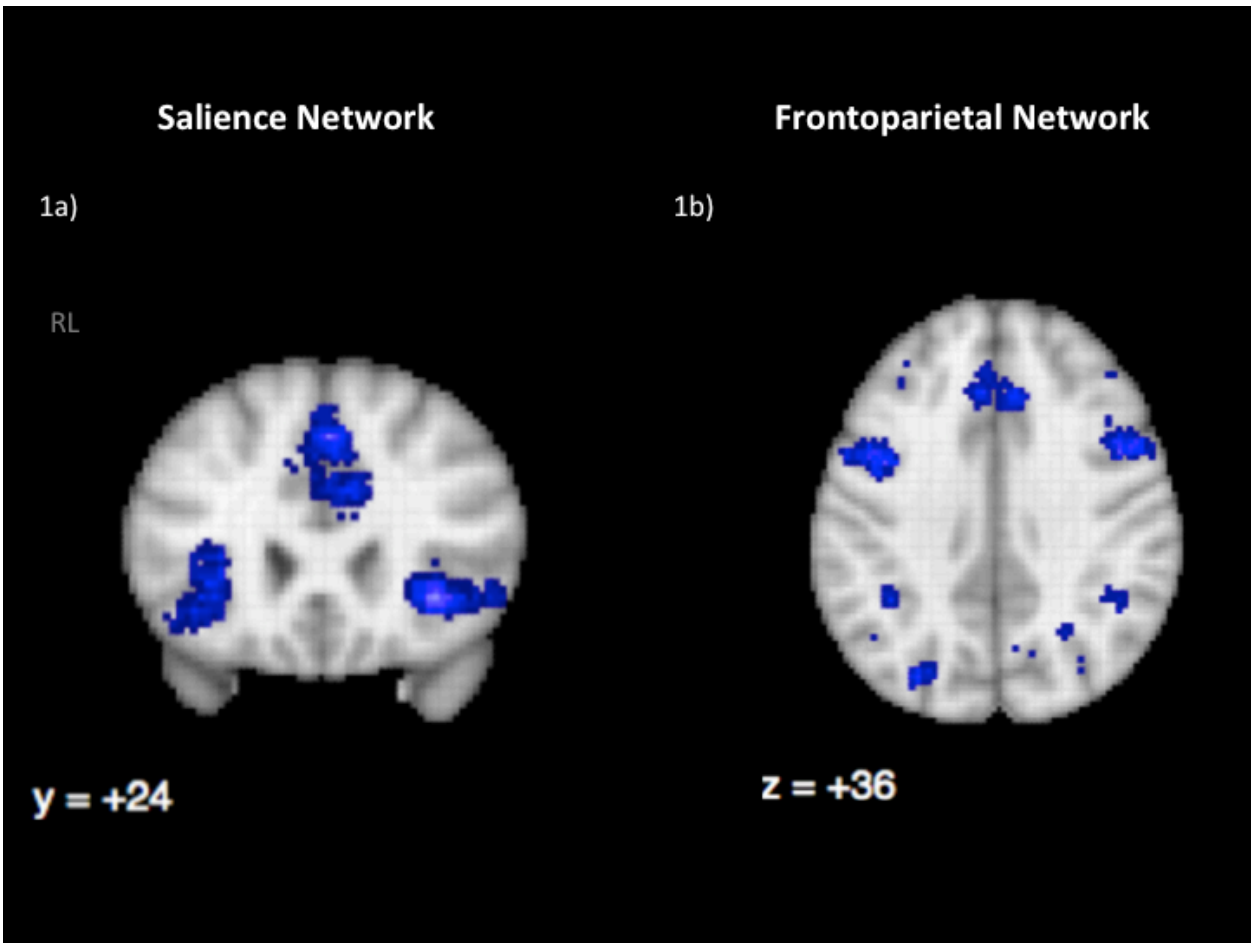

Table 4. Final Dataset: Participant characteristics by diagnostic group.

	TD n=65	ADHD n=64	ASD n=60	*p*-value
Age (years) *M*(SD)	11.79 (2.93)	11.39 (2.75)	10.96 (2.83)	0.27
Range	7.11-17.70	7.25-17.61	7.13-17.93	
FIQ (SS) *M*(SD)	110.85 (12.79)	105.95 (14.71)	107.62 (15.88)	0.15
Range	80-129	80-134	80-148	
MRD (mm) *M*(SD)	0.023 (0.01)	0.027 (0.01)	0.029 (0.01)	0.03*
Range	0.009-0.55	0.007-0.53	0.009-0.55	
Sex (M:F)	61:4	60:4	56:4	0.99
CPRS Inattentive T-score *M*(SD)	45.88 (6.41)	69.20 (8.81)	67.17 (8.70)	<0.001*
Range	40-55	51-90	45-84	
CPRS H/I T-Score *M*(SD)	48.69 (6.16)	67.61 (11.01)	60.94 (10.83)	<0.001*
Range	40-55	51-90	46-83	
CPRS Total T	46.94 (5.81)	69.61 (7.65)	65.67 (9.37)	<0.001*
Range	40-60	55-90	45-86	
ADOS-2 Social Affect	--	--	8.78 (3.80)	--
Range			3-20	
ADOS-2 RRB	--	--	3.00 (1.44)	--
Range			0-7	
ADOS-2 Total	--	--	11.76 (4.54)	--
Range			6-26	
ADOS-2 CCS	--	--	6.76 (1.96)	--
Range			3-10	

CCS=Calibrated Comparison Score
CPRS= Conners' Parent Rating Scale-Revised, Long Version
H/I=Hyperactive/Impulsive
GCA=Global Composite Ability
RRB=Restricted and Repetitive Behaviors
FIQ=Full Scale IQ (*M*=100; SD=15)
*Note: ADOS-2 scores were only available for 54 participants with ASD. CPRS scores were only available 16 TD participants, 64 participants with ADHD, for 18 participants with ASD.

Table 5. Final Dataset: Number (%) of participants in ADHD or ASD groups with co-occurring diagnoses, as determined by the KSADS-PL

	ADHD	ASD	*p*-value
	n=64	n=60	
ADHD	--	22 (36.66%)	--
ADHD-Inattentive	--	10 (16.66%)	--
ADHD-Combined	--	8 (13.33%)	--
ADHD-Hyperactive/Impulsive	--	1 (1.66%)	--
ADHD-NOS	--	3 (5.00%)	--
ODD/Disruptive Disorder NOS	5 (7.81%)	5 (8.33%)	0.92
Anxiety	4 (6.25%)	10 (16.66%)	0.07
GAD	--	3 (5.00%)	--
SAD	1 (1.56%)	1 (1.66%)	0.96
Specific Phobia	3 (4.69%)	5 (8.33%)	0.41
Anxiety NOS	--	1 (1.66%)	--
Depression NOS/Mood NOS/Adjustment	1 (1.56%)	3 (5.00%)	0.28
Enuresis/Encropresis	--	2 (3.33%)	--
Learning Disorder	2 (3.13%)	--	--
Dyslexia/Dycalculia	3 (4.69%)	--	--

Figure 2. GIMME+CSD-derived subgroups for within-SN using unscrubbed data. Auto recursive paths for each ROI (not shown here) were present for all participants. Blue arrows represent subgroup specific paths. Three subgroups emerged: (2a) subgroup A, characterized by strong hyperconnectivity, (2b) subgroup B, characterized by weak hyperconnectivity, and (2c) subgroup C, characterized by hypoconnectivity. Proportions of diagnostic groups that were characterized by each subgroup (2d) were not significant (p = .16). Proportions of ASD+ADHD comorbidity that were characterized by subgroup (2e) were not significant (p = .21).

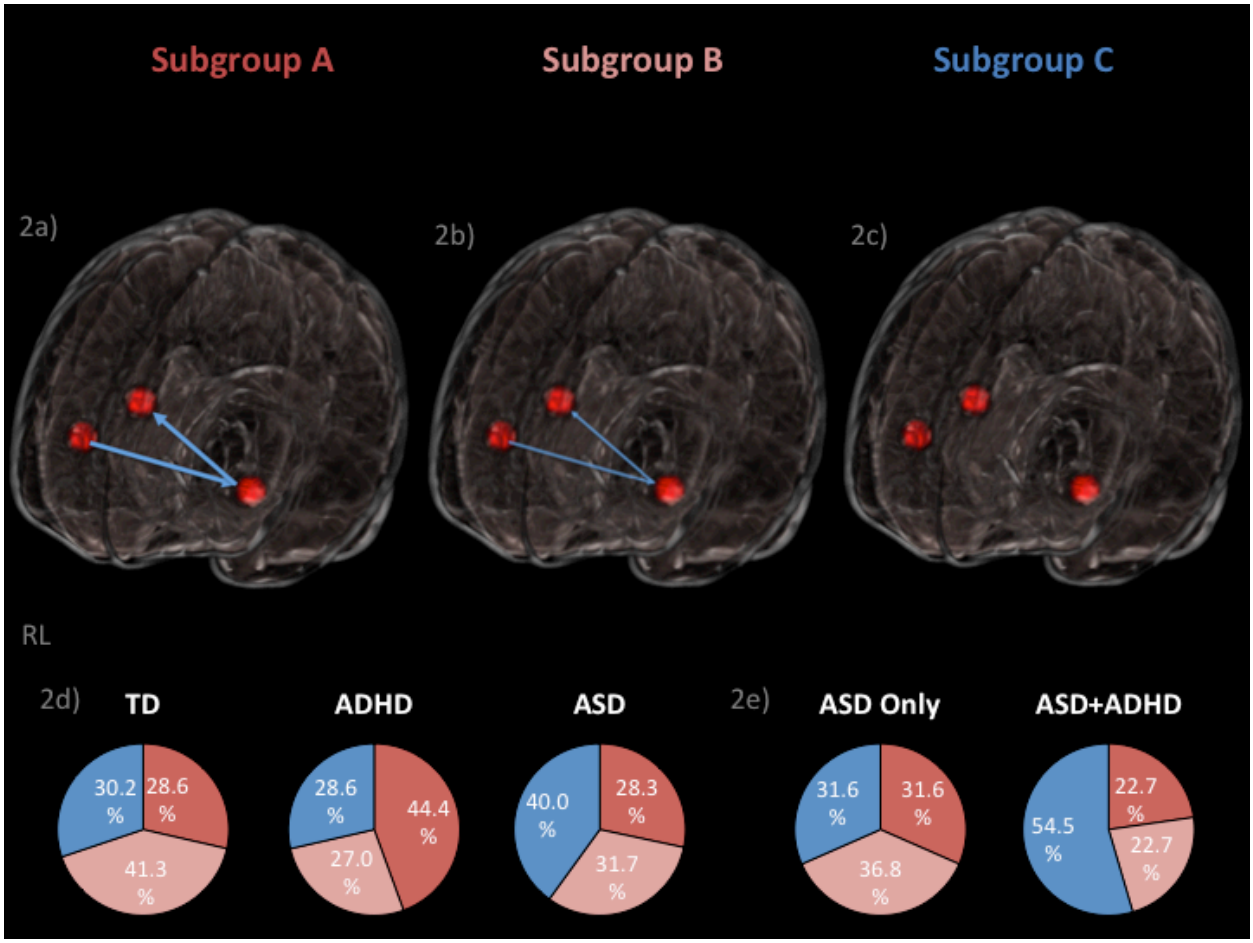

Figure 3. GIMME+CSD-derived subgroups for within-SN using scrubbed data at FD = 0.8mm. Auto recursive paths for each ROI (not shown here) were present for all participants. Blue arrows represent subgroup specific paths. Two subgroups emerged: (3a) subgroup A, characterized by hypoconnectivity, and (3b) subgroup B, characterized by hyperconnectivity. Proportions of diagnostic groups that were characterized by each subgroup (3c) were not significant (p = .14). Proportions of ASD+ADHD comorbidity that were characterized by subgroup (3d) were not significant (p = .09).

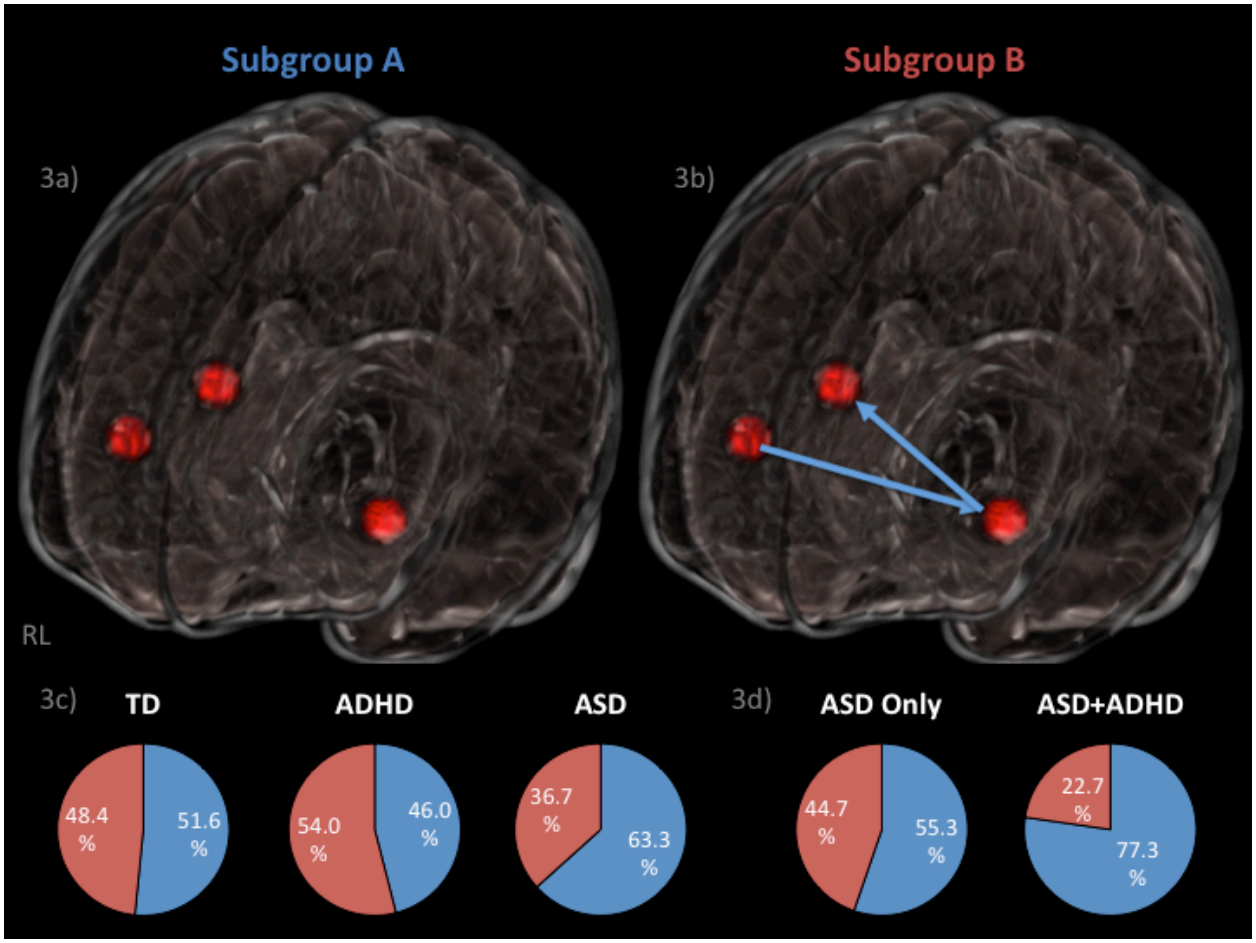

Figure 4. GIMME+CSD-derived subgroups for within-FPN using unscrubbed data. The white arrows represent paths that were present for all participants, in addition to the auto recursive paths for each ROI (not shown here). Blue arrows represent subgroup specific paths. Two subgroups emerged: (4a) subgroup A, characterized by hyperconnectivity, and (4b) subgroup B characterized by hypoconnectivity. Proportions of diagnostic groups that were characterized by each subgroup (4c) were not significant (p = .25). Proportions of ASD+ADHD comorbidity that were characterized by subgroup (4d) were significant (p < .05), with a greater proportion (72.7%) of the comorbid ASD+ADHD group being characterized by hypoconnectivity of within-FPN.

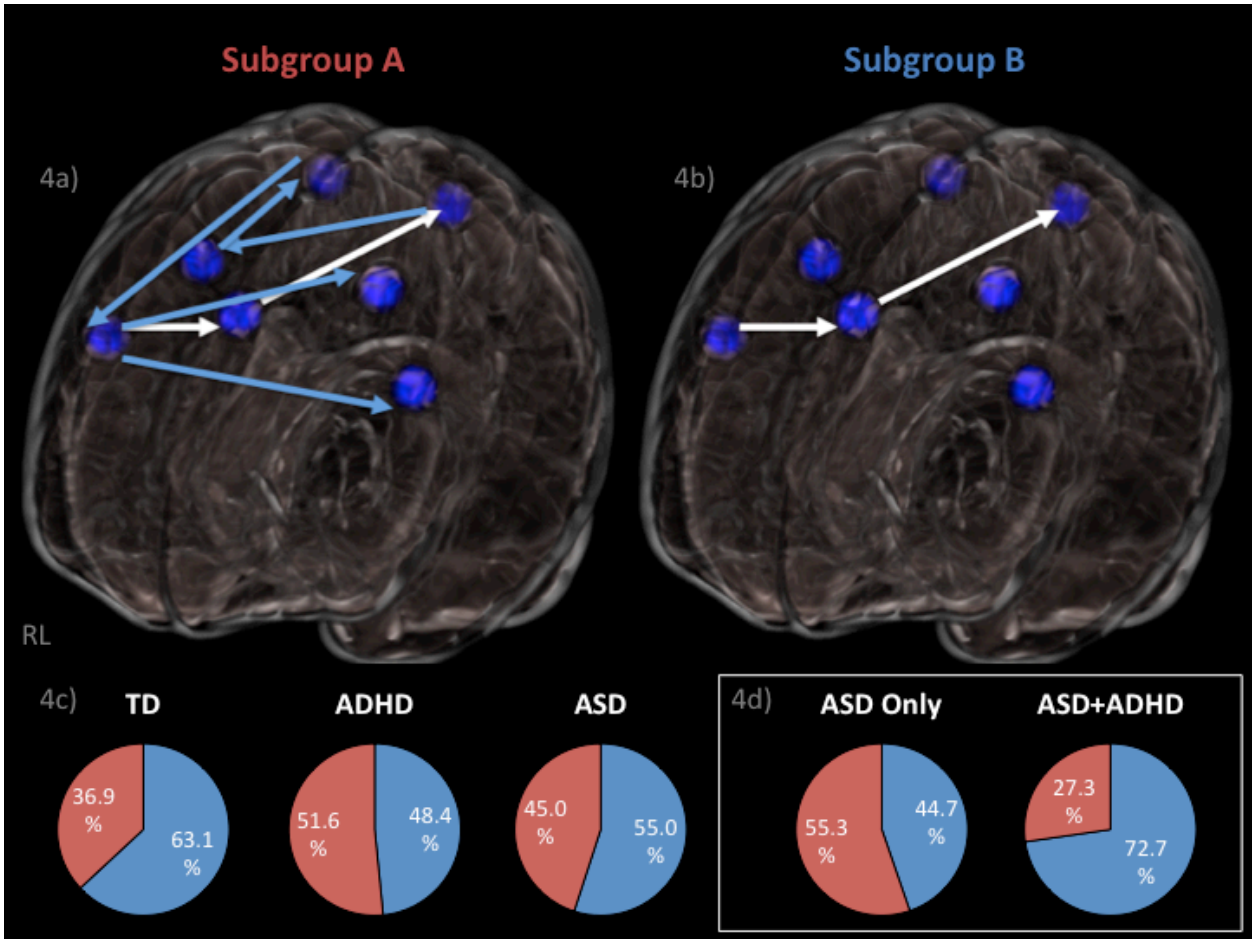

Figure 5. GIMME+CSD-derived subgroups for within-FPN using scrubbed data at FD = 0.8mm. The white arrows represent paths that were present for all participants, in addition to the auto recursive paths for each ROI (not shown here). Blue arrows represent subgroup specific paths. Two subgroups emerged: (5a) subgroup A, characterized by hyperconnectivity, and (5b) subgroup B, characterized by hypoconnectivity. Proportions of diagnostic groups that were characterized by each subgroup (5c) were not significant (p = .33). Proportions of ASD+ADHD comorbidity that were characterized by subgroup (5d) were not significant (p = .17).

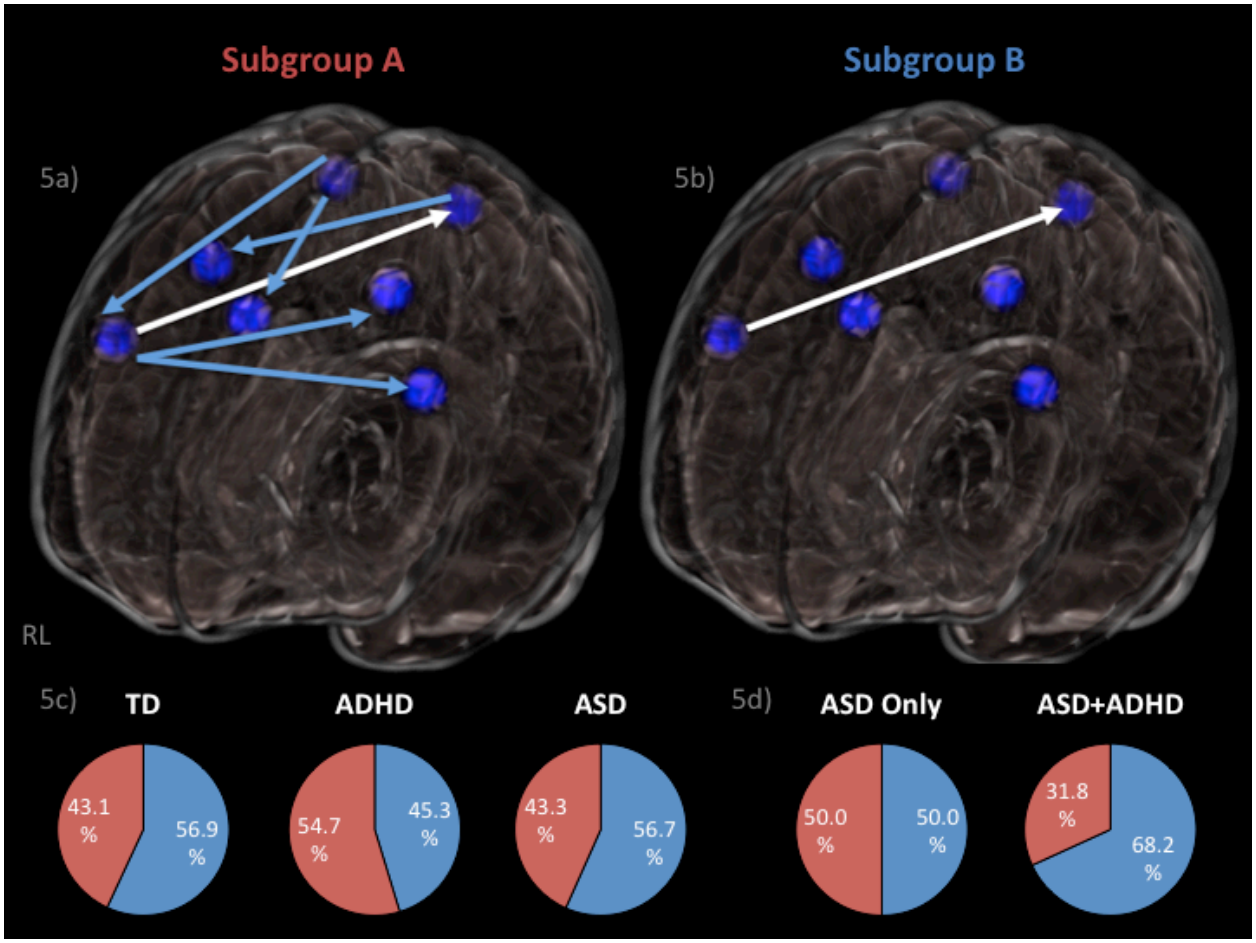

Figure 6. GIMME+CSD-derived subgroups for between SN-FPN using unscrubbed data. SN ROIs are depicted in red and FPN ROIs are depicted in blue. The white arrows represent paths that were present for all participants, in addition to the auto recursive paths for each ROI (not shown here). Blue arrows represent subgroup specific paths. Two subgroups emerged: (6a) subgroup A, characterized by hypoconnectivity, and (6b) subgroup B, characterized by hyperconnectivity. Proportions of diagnostic groups that were characterized by each subgroup (6c) were significantly different ($p < .01$). Proportions of ASD+ADHD comorbidity that were characterized by subgroup (6d) were not significant ($p = .98$).

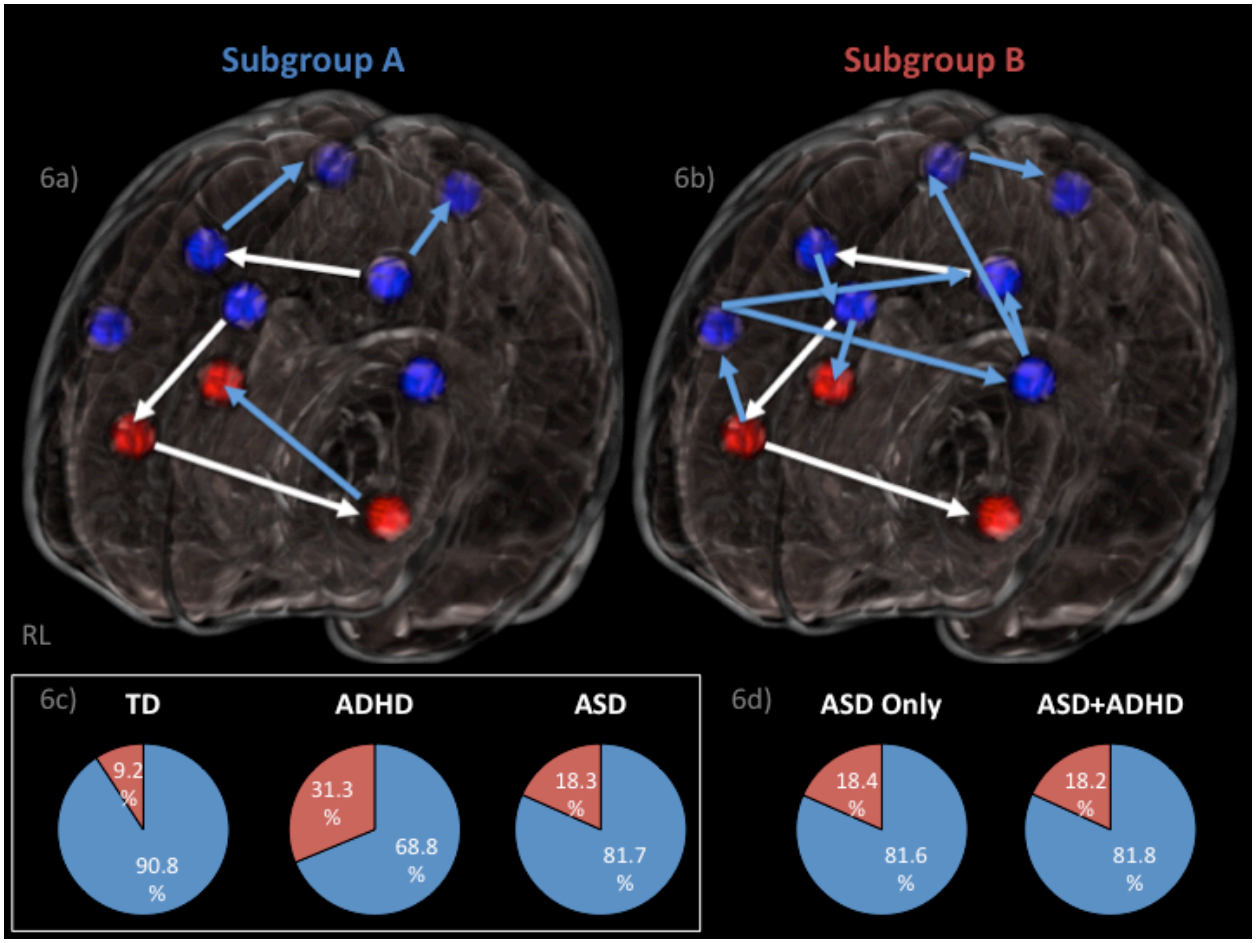

Figure 7. GIMME+CSD-derived subgroups for between SN-FPN using scrubbed data at FD = 0.8mm. SN ROIs are depicted in red and FPN ROIs are depicted in blue. The white arrows represent paths that were present for all participants, in addition to the auto recursive paths for each ROI (not shown here). Blue arrows represent subgroup specific paths. Two subgroups emerged: (7a) subgroup A, characterized by hyperconnectivity, and (7b) subgroup B, characterized by hypoconnectivity. Proportions of diagnostic groups that were characterized by each subgroup (7c) were significantly different ($p < .05$). Proportions of ASD+ADHD comorbidity that were characterized by subgroup (7d) were not significant ($p = .055$).