The Functional Connectivity of the Resting Brain in Children With Attention Deficit Hyperactivity Disorder

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a prevalent and detrimental psychiatric disorder that is recently being examined with a distributed network perspective using functional magnetic resonance imaging (fMRI). Specific disruptions in the connections within and in between intrinsic connectivity networks during a resting state have been considered as a way to characterize various psychiatric disorders including ADHD. Disruptions in the within-network connectivity of the default mode network (DMN) as well as in the regulation of the salience network (SAL) have been implicated in the pathophysiology of ADHD. The current study examined these disruptions by performing independent component analyses on the resting state fMRI scans of 13 children with ADHD and 13 age and gender matched neurotypical children. SAL activations were compared between groups to determine whether the SAL was being adequately attenuated in children with ADHD. Our results indicate that the left prefrontal cortical region of the SAL was improperly attenuated, while the left posterior parietal region was overly attenuated during a resting state in children with ADHD compared to controls. Intrinsic connectivity of the DMN was examined using group correlation matrices. Results from this analysis show that some of the connectivities within the DMN exhibited previously determined developmentally delayed trends that highlighted a failure for circuitry to integrate. However, several other connectivities found to be disrupted in the current study in children with ADHD were not connectivities that had been identified by previous literature to be developmentally dynamic. Therefore, these findings provide mixed results that do not unanimously support the maturational delay hypothesis of ADHD. Overall, this study's findings provide preliminary evidence that state-inappropriate SAL activations and specific connectivity disruptions within the DMN are present during the resting state in children with ADHD.

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Introduction

A Brief Overview of Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent psychiatric disorders of childhood affecting 5-8% of children worldwide (Sripada et al., 2014). ADHD also frequently persists into adulthood with 30-50% of cases continuing past childhood (Posner et al., 2014). ADHD is characterized by age-inappropriate inattention, impulsivity, and hyperactivity (Sripada et al., 2014). Additionally, other non diagnostic symptoms include poor frustration tolerance, emotional lability, and defiant behaviors that can often times be just as intrusive on daily functioning as the usual diagnostic symptoms (Posner et al., 2014). Furthermore, the disorder has been correlated with poor academic and economic outcomes as well as psychosocial impairments that have been known to lead to incarceration, underemployment, and substance abuse (Sripada et al., 2014). Clearly, the many deficits observed with ADHD can be extremely detrimental not only to those with the disorder, but also to their families and to society as a whole.

Many of the behaviors associated with the psychopathology of ADHD have already been associated with specific brain regions. Attention deficits are involved with disruptions in frontal areas such as the dorsolateral prefrontal cortex and the anterior cingulate, as well as striatal areas of the basal ganglia (Bonelli & Cummings, 2007). Impulsivity has also been found to be involved with disruptions in similar frontal-subcortical, or fronto-striate, circuits that involve the caudate nucleus and the putamen (Monchi et al., 2006). Disruptions in the orbitofrontal cortex have especially been implicated in behavioral disinhibition, inattention, and distractability. Fronto-parietal circuitry involving the dorsolateral and medial portions of the frontal lobes, the posterior parietal lobe, parts of the striatum, and the cingulate gyrus is known to be involved in

mediating related processes such as attention and motivation (Bonelli & Cummings, 2007; Stefanatos &Wasserstein, 2006).

More recent studies also focusing on ADHD's neurobiological mechanisms have shifted their attention from the examination of distinct brain regions to a distributed network perspective. Network-level organization is now being considered as a key component in the pathophysiology of psychiatric disorders along with its associations with cognition and symptom severity. Connectivity within specific networks is being examined and network contingency analysis is being used to look at the interrelationships between brain networks (Sripada et al., 2014). Moreover, there has been a growing interest in resting state connectivity instead of the connectivity during attention tasks that is more typically examined in studies on ADHD (Konrad & Eikhoff, 2010). Functional MRI has consistently been used in the field, allowing for the quantification of the functional connectivity and dynamic fluctuations of these networks (Konrad & Eikhoff, 2010). Although the field is growing, there is still a need for more research focusing on the functional connectivity of brain networks and how they relate to ADHD pathophysiology. Further research using the network perspective could aid in the better characterization of dysfunctional distributed network organization and the developmental and symptom severity implications of those neural network disruptions.

The Distributed Network Approach

The network perspective involves looking at intrinsic connectivity networks (ICNs) that are characterized by functional connectivity, or strongly temporally correlated fMRI blood-oxygen-level dependent (BOLD) signals across different brain regions. Therefore, ICNs describe large-scale functionally connected brain networks that are present in both resting state and task-based neuroimaging data (Laird et al., 2011). Different ICNs can be involved in everything from

visual, attention, internal cognitive, somatomotor, and executive functioning. Within the network perspective, there has also been a shift from studying static networks to the examination of more dynamic fluctuations in ICNs and their interactions with each other due to technical advances that allow for the measurement of these dynamic changes in high resolution (Cohen, 2017).

Disruptions in specific ICNs have been implicated in many other neuropsychiatric disorders such as schizophrenia and autism, which is a main reason why an ICN approach is being considered for ADHD as well (Konrad & Eikhoff, 2010). Current ongoing genetic research on schizophrenia has even provided data suggesting that altered brain connectivity could emerge as an intrinsic neuro-genetic architecture of psychiatric illness (Konrad & Eikhoff, 2010). Following this trend, several studies have come to focus on the interconnectivity of brain regions and its implications on various psychiatric illnesses including, not only schizophrenia, autism and ADHD, but also bipolar spectrum disorders, anxiety disorders, and disruptive behavior disorders (Bebko et al., 2015). For example, Bebko et al. (2015) did a study on the functional uncoupling of neural regions involved in emotional processing and regulation for all of those aforementioned psychiatric illnesses. They found that functional connectivity between the amygdala and posterior insula decreased during a resting state with increased severity of behavioral and emotional dysregulation and depression (Bebko et al., 2015). Therefore, considering the roles that ICNs have in the pathophysiology of ADHD could lead to a new understanding of the disorder that has not been considered until the past couple decades.

A Focus on Resting State Connectivity

Even more specific to the network perspective as a whole is the focus on resting state connectivity. A resting state allows for the collection of information on ICNs that is independent of specific cognitive tasks that may not necessarily be reflective of every day occurrences.

Notably, the introspective thinking and mind wandering that occur during a resting state are common daily occurrences, especially in children (Bebko et al., 2015). This approach differs from many prior studies on ADHD that have largely focused on the neural regions involved in task-related analyses during an attentive state, such as the amygdala, striatum, prefrontal cortex, anterior cingulate cortex, and insula-centered neural networks that support salience, interoception and emotion processing (Bebko et al., 2015). More recently, resting-state functional connectivity MRI (rs-fcMRI) has been an emerging method in studying ADHD since it was first described by Biswal et al. (1995). One of the main benefits of examining the resting state is its ability to illuminate potential stable traits in individuals that would not be possible with the complex manipulations involved in task-centered studies.

Resting state networks are defined by correlated BOLD signals across multiple brain regions just like any other ICN. Despite the existence of these resting state ICNs, it is still debated as to what exactly the purpose of the resting state activity is. One explanation is that the resting state activity is an endogenous mechanism of the brain to self-organize, since the spontaneous neural activity aids in the strengthening of ICN synaptic connectivities (Posner et al., 2014). Further investigation on the nature of this form of brain activity that centers on internally focused cognitions is still needed.

The Default Mode Network and The Salience Network

A major focus of many rs-fcMRI studies is the default mode network (DMN) that has been associated with task irrelevant mental processes and mind wandering that occur during a resting state (Posner et al., 2014). As mentioned before, prior ADHD research has tended to center on fronto-striatal circuitry; however, abnormalities in many other brain areas including parietal, occipital, temporal, and the DMN are now being considered (Choi et al., 2013). The

brain areas in the DMN demonstrate strongly correlated neural activity during rest and include the precuneus/ posterior cingulate cortex, medial prefrontal cortex, and medial, lateral and inferior parietal cortex (Fox et al., 2005). The DMN shows increased functional connectivity during resting states and gets attenuated when switching to externally driven tasks, with increasing deactivation as the difficulty of the task increases (Konrad & Eikhoff, 2010). The unsuccessful attenuation of the DMN when switching from rest-to-task states causes momentary lapses in attention characterized by longer reaction times. Therefore, the DMN is considered to be a task-negative network (Konrad & Eikhoff, 2010).

The interaction of the DMN with the cognitive control network, also known as the salience network (SAL), involves antagonistic processes that appear to mirror each other in function. The SAL encompasses the dorsal anterior cingulate cortex, dorsolateral prefrontal cortex, inferior frontal junction, anterior insular cortex and the posterior parietal cortex (Elton et al., 2014; Choi et al., 2013; Posner et al., 2014). This network is involved in high-level cognitive processes that include inhibitory control, set shifting, and working memory. The SAL is considered to be a task-positive network that works in opposition to the DMN. As attentional demands increase, the SAL gets increasingly activated, while the DMN gets increasingly deactivated. When transitioning back into a resting state, the SAL typically gets attenuated while the DMN becomes more activated (Posner et al., 2014). Overall, the SAL is thought to be responsible for the regulation of shifts between internally directed and externally focused mentation; and therefore mediates the interactions between the DMN and other attentional networks as well (Sripada et al., 2014).

DMN and SAL Activity Regulation Studies

The relationships between the DMN and the networks and connections that seem to modulate its activity have been a major point of focus for many rs-fcMRI studies. For example, several studies have shown that these anti-correlations between the SAL and the DMN are either reduced or absent in children, adolescents, and adults with ADHD. A resulting effect includes DMN-mediated mind wandering and introspective thinking impeding sustained attention as DMN activity disrupts, or interferes with, the normal functioning of the SAL (Posner et al., 2014). The idea of aberrant interactions between task-negative and task-positive attentional networks being involved in the pathophysiology of ADHD is termed the 'DMN interference hypothesis' and was first mentioned by Castellanos et al. (2008).

Several studies have attempted to characterize the aberrant connections that may mediate the disrupted anti-correlations between the SAL and the DMN underlying the DMN interference hypothesis. Both Sun et al. (2012) and Choi et al. (2013) found aberrant functional connections between the DMN and the dorsal anterior cingulate cortex of the SAL. Sripada et al. (2014) found increased interconnectivity between the posterior cingulate cortex in the DMN and three regions of the SAL in ADHD. These results all provide support for SAL interconnectivity with the DMN being a key locus of dysfunction in ADHD, and suggest that a distributed dysconnectivity between large-scale networks is indeed present. The resulting effect appears to be a failure of the DMN to be attenuated in the transition from rest-to-task states (Konrad & Eikhoff, 2010).

In addition, Hoekzema et al. (2014) provided evidence that not only is the DMN poorly attenuated when transitioning to an attentive state, but the SAL also gets poorly attenuated when switching to a resting state in ADHD. Hoekzema et al. (2014) found that the dorsolateral

prefrontal cortex (dlPFC) seed of the SAL in particular had a reduced anti-correlational relationship with the DMN. Their findings of insufficient suppression of dlPFC signaling in relation to DMN activity during a resting state indicates that the typical anti-correlational relationship between these two networks is reduced in both directions (Hoekzema et al., 2014). Therefore, the disrupted functional connectivities between the DMN and SAL observed in the aforementioned studies may also be contributing to SAL intrusion during a resting state. Overall, the dysfunctions observed suggest an abnormal balance or interaction between attentional and intrinsic thought in those with ADHD (Choi et al., 2013).

Altered Connectivity Within the DMN and the Maturational Delay Hypothesis

Along with studies that have examined the interconnectivity and relationships between the DMN and other ICNs, several studies have attempted to determine differences in DMN connectivity within the network itself. Despite the mixed results, it still seems possible that distributed connectivity dysfunction both between and within these large ICNs plays a major role in the neurobiological mechanisms of ADHD. Various studies have considered ADHD as a disorder involving either the hyperconnectivity or the hypoconnectivity of the DMN (Tian et al., 2006; Castellanos et al., 2008; Helps et al., 2008). Regardless, the misconfiguration of the DMN does seem to be involved in ADHD, but most likely in a more complicated manner than simply an overall connectivity dysfunction in a single direction (Konrad & Eikhoff, 2010). For example, the maturation of the DMN being delayed or disrupted in ADHD children aged 7 to 16 has been termed the maturational delay hypothesis of ADHD, since its conception by El-Sayed et al. (2003). Studies examining maturational differences in children with ADHD have shown that ADHD is closely associated with impairments in functional network segregation, where the typical developmental trend of local connections weakening with age is not observed in ADHD.

In addition, ADHD is associated with impairments in functional network integration, where distant connections that typically strengthen with age are weaker in ADHD (Bos et al., 2017; Fair et al., 2010; Hoekzema et al., 2013; Sripada et al., 2014). Therefore, depending on the specific connection, patterns of both increases and decreases in functional network connectivity should be seen in children with ADHD (Bos et al., 2017).

This notion of a disrupted developmental trajectory involving the functional connectivity of resting state ICNs has been the subject of several recent studies that have generally supported the maturational delay hypothesis (Bos et al., 2017; Choi et al., 2013; Fair et al., 2010; Hoekzema et al., 2013; Posner et al., 2014). However, the results are still mixed with some studies not finding any aberrant within-network DMN connections, and there has not been enough support on the specifics of which connections are aberrant within the DMN (Konrad & Eikhoff, 2010). Notably, Fair et al. (2008) identified fourteen connections within the DMN that were developmentally dynamic. Out of the fourteen connections, eleven were found to be aberrant in children with ADHD (Fair et al., 2010). Furthermore, Choi et al. (2013) found that medication-naïve children with ADHD failed to show an age-related increase in connectivity between the posterior and anterior DMN (pDMN and aDMN, respectively). Decreased aDMN-pDMN connectivity has also been reported in adults with ADHD and the cingulum bundle has been identified as a possible anatomical connection between the aDMN and the pDMN that develops into adulthood. Several studies have reported aberrant connectivity in this bundle in patients with ADHD (Choi et al., 2013). These findings are significant because they suggest that dysfunctional DMN connectivity patterns parallel structural MRI findings that are also consistent with neuromaturation delays being implicated in ADHD (Posner et al., 2014).

A more recent study did not find any disrupted between-network connectivities, but did find several aberrant within-network connectivities in the DMN (Bos et al., 2017). Bos et al. (2017) found that those with ADHD had increased connectivity in the right inferior frontal gyrus, increased connectivity in the aDMN network's right medial prefrontal cortex, and decreased connectivity in the right posterior cingulate gyrus all in the DMN. These findings further underline the uncertainties about whether a between-network disruption is present developmentally and support that dysfunction within the DMN is indeed characteristic of ADHD.

Hypotheses for Current Study

Because the research on resting state functional connectivity patterns in ADHD has been mixed and relatively sparse, this study will attempt to provide insight on what patterns are observed in our set of data and whether those patterns align with existing findings. Therefore, my first hypothesis is that I will also find evidence of SAL intrusion during a resting state indicative of disrupted functional connectivities between the SAL and the DMN. More specifically, I hypothesize that during the resting state, children with ADHD will exhibit increased activity of the dlPFC region of the SAL compared to neurotypical children, consistent with Hoekzema at al.'s findings (2014). Second, I hypothesize that our ADHD data will support the DMN maturational delay hypothesis by exhibiting aberrant functional connectivity in the areas that have been known to be developmentally dynamic. The specific trends I expect to find include the several atypical developmental patterns observed in Fair et al.'s (2010) study, a reduced connectivity of the aDMN and the pDMN as described by Choi et al. (2013), and the aberrant connections observed by Bos et al. (2017).

Methods

Participants

Functional MRI data was used from the Cognition and Neuroimaging in Teens (CogNIT) study from the Neurocognition and Imaging Research Lab (NIRL) at the University of North Carolina at Chapel Hill (UNC-CH). The resting state scans of every CogNIT-recruited participant with an ADHD diagnosis was examined in the current study. A parent initially reported the ADHD diagnosis and was then asked to sign a HIPAA waiver in order to allow the lab access to the participant's medical records. An Electronic Privacy Information Center (EPIC) search was then used to confirm the ADHD diagnosis for each participant. Initially, there were 17 scans identified, but one scan was acquired with a different resting state sequence and would not have been comparable to the other scans. Another scan only had 27 out of 107 time points due to the participant leaving the scanner during the scan. Two other scans were marked as un-useable due to excessive motion. The remaining 13 resting state scans of participants with ADHD were analyzed in this study.

The finalized sample included 13 children with a current ADHD diagnosis in the ADHD group, and 13 age and gender matched neurotypical children in the control group (N=26; M=11.73 years, SD=1.95). Participants ranged from 9 to 15 years old. More detailed demographic information on each group is shown in Table 1. The parents of all 26 participants were asked to indicate their child's racial/ ethnic background (Interracial/Indicated multiple races=7.7%, Caucasian/White/ European= 76.9%, African American= 11.5%, Hispanic/ Latinx= 3.8%). Out of the 13 participants with an ADHD diagnosis, 6 were taking ADHD medication and 7 were not. Informed consent was obtained from each participant prior to scanning in accordance with the UNC-CH and Duke University Internal Review Boards.

Data Collection

Procedure.

At the Duke Children's Hospital, participants and their parents were first taken to a mock scanner room to fill out some questionnaires. These questionnaires asked a variety of questions important for the CogNIT study, but the only information from the questionnaires that is relevant for the current study is the demographic and clinical information that was mentioned in the participant's section. Some physiological samples were also taken for CogNIT, but were not used in the current study. Afterwards, the participant was placed in the mock scanner for practice hearing scanner sounds and getting accustomed to being in the scanner core. Participants also practiced tasks for CogNIT that would be performed later during the fMRI scan, but those tasks are not important for the current study. After being in the mock scanner, participants were taken to the real fMRI scanner room, some saliva samples were taken for CogNIT, and participants were told to lie down on the scanner bed. Once on the scanner bed, participants were given earplugs, headphones, a blanket, a button box, and a pulse oximeter that was placed on their left index finger. Participants were then wheeled into the scanner core and given instructions through their headphones. The first scan that was performed was an anatomical scan, which was followed by a resting state scan. During both scans, participants were instructed to look at a cross on a screen and to try not to fall asleep. Participants were monitored with an eye camera to ensure they did not fall asleep during each scan.

fMRI Acquisitions.

Both anatomical and resting state scans were taken on a GE MR750 3.0T scanner (GE Healthcare, Waukesha, WI, USA) with an eight-channel head coil at the Duke Children's Hospital. A 7-minute anatomical scan was taken first. The anatomical images were acquired with

a T1-weighted Spoiled Gradient Recalled Echo (SPGR) pulse sequence in the axial plane with a flip angle (FA) of 12° and a 1 mm slice thickness. The anatomical scan was acquired using the following additional parameters: repetition time (TR)=8.2ms; echo time (TE)=3.2ms; inversion time (TI)= 450ms; field of view (FOV) of 24 cm; 256 × 256 acquisition matrix.

The anatomical scan was followed by a 6-minute resting state scan consisting of 107 time points. Resting state MRI (rsMRI) data were acquired using a two-band and two-shot interleaved EPI pulse sequence on the GE MR750 3.0T scanner (Chang et al., 2014). The multi-band sequence was acquired with the following parameters: TR=2800ms; TE=25ms; FA=90°; FOV= 230 x 230 mm^2; matrix size 128 x 128; 1.8 mm slice thickness; 80 slices without gaps. After the anatomical and resting state scans, participants remained in the scanner and performed a variety of tasks important for the larger CogNIT study. However, the current study focuses only on the first 13 minutes of the scan that include the anatomical and resting state fMRI data.

Analysis

Preprocessing of fMRI Data

The rsMRI data was run through a preprocessing pipeline that used a combination of toolboxes (AFNI, FSL, SPM, and GIFT). First, we used the FSL tool "slicetimer" to correct for timing differences in slice acquisition. Then, the slice-time corrected data was run through SPM12's realignment procedure to calculate motion parameters and to correct for any head-motion related artifacts (Friston et al., 1995). Next, the rsMRI data were despiked using AFNI's "3dDespike" program to help lessen the effects of outliers. The rsMRI was subsequently warped to a Montreal Neurological Institute (MNI) EPI template by applying the warped deformation fields calculated by running SPM's non-linear registration procedure (Ashburner and Friston, 2005). The output of the preceding step resulted in rsMRI data in standard MNI space and

resampling to $2mm^3$ isotropic voxels. Next, all non-brain areas including the eyes and skull were removed using the FSL Brain Extraction Tool (BET2). We then smoothed the data to 8mm full width at half maximum (FWHM) using the AFNI tool "BlurToFWHM", which smoothes using a more conservative finite difference approximation to the diffusion equation. Finally, we used the GIFT software to run variance normalization for each voxel time series. This helps to better decompose subcortical sources and cortical networks in the subsequent ICA steps (Damaraju et al., 2014).

Group Independent Component Analysis (ICA)

After preprocessing, the resting state data from both control and ADHD groups were also analyzed using Vince Calhoun's Group ICA of fMRI toolbox (GIFT) on MATLAB (Calhoun et al., 2001). MATLAB, or Matrix Laboratory, is a technical computing software that integrates computation, visualization, and programming in one environment. All of the data were analyzed using the spatial group ICA (GICA) framework as implemented in the GIFT software. For more information on the GIFT analysis technique, see Calhoun et al.'s (2001) paper on the method. Overall, ICA is a data-driven blind source separation technique that decomposes high-dimensionality data into maximally spatiotemporal components, and is used frequently to extract the DMN and SAL components from the fMRI data (Hoekzema et al., 2014).

The GICA was conducted according to the GICA methods section of Damaraju et al.'s (2014) paper. Subject data were concatenated across time and a group data principal component analysis (PCA) step reduced the matrix into 40 components along directions of maximal group variability. Forty independent components were obtained from the group PCA reduced matrix using the Infomax algorithm (Bell & Sejnowski, 1995). The ICA algorithm was repeated 20 times in ICASSO to ensure stability of estimation. Aggregate spatial maps were estimated as the

modes of component clusters. Subject specific spatial maps and time courses were obtained using GIFT's spatiotemporal regression back reconstruction approach (Calhoun at al., 2001).

The SAL component was selected using a spatial correlation analysis that finds the components that best fit GIFT's anterior SAL (aSAL) and posterior SAL (pSAL) templates for the averaged resting state signal for each group (control and ADHD). The best match components for both the aSAL (control: r=0.098; ADHD: r=0.185) and pSAL (control: r=0.191; ADHD: r=-0.0834) were selected and combined to represent the SAL as a whole. Two-sample t-tests were then performed to compare the combined SAL components between the control and ADHD groups.

The DMN component was selected using the same spatial correlation analysis on GIFT that finds the components that best fit GIFT's DMN template, but for each individual subject rather than the average for each group ($M \pm SD$; control: $r=0.204 \pm 0.043$; minimum:0.146; maximum:0.310; ADHD: $r=0.185 \pm 0.054$; minimum:0.103; maximum:0.286). The main structures that make up the template include the precuneus, posterior part of the superior parietal cortex, the temporoparietal junction, the frontal pole, and the posterior cingulate cortex. All of the aforementioned regions have been repeatedly implicated in the DMN according to prior research such as Fox et al.'s (2005) study. The best match component to the DMN template was then selected and two-sample t-tests were performed to compare the DMN component between groups.

DMN Intrinsic Connectivity Preprocessing, Computation of Group Mean Matrices, and Direct Comparisons Between Groups

Before the intrinsic connectivity analysis, the preprocessed data was put through additional preprocessing steps to remove variance not associated with neuronal activity. The

additional steps included an automated tissue segmentation (FSL-FAST) to produce white matter (WM) and cerebrospinal fluid (CSF) masks (Zhang, Brady, & Smith, 2001), regression of the average signal from those WM and CSF masks, and a temporal band-pass filter (0.001 Hz < f < 0.08 Hz). We then extracted an average resting state signal from 13 previously defined regions (12mm diameter spheres) of the DMN (Fox et al., 2005), as shown in Figure 1, and computed region-by-region correlation values. This produced a 13x13 matrix of correlation coefficients (*r*) for the DMN of each subject (see Figure 5). Mean regression values for all potential connections represented in the 13×13 matrices were calculated for each group, and compared using a two sample two-tailed *t*-test. Fisher *z* transformation was then applied.

Results

SAL Activations

In general, our analysis on the SAL activations between groups showed that several brain areas of the SAL were significantly more active in the ADHD group compared to controls, and that one region of the SAL was significantly more active in the control group compared to the ADHD group ($p<0.021$). Figures 2, 3, and 4 show the comparison of SAL activations between ADHD and control groups. In all of these figures, panels A through C show the averaged SAL activity for the ADHD group, while panels D through F show the averaged SAL activity for the control group. Furthermore, panels G through I show the areas of the SAL that are more activated in the control group compared to the ADHD group, while panels J through L show the areas of the SAL that were more activated in the ADHD group compared to the control group. As shown in Figure 2 panels G through I, there were significantly higher activations in the left angular and supramarginal gyri of the parietal lobe SAL region in the control group compared to the ADHD group ($p<0.021$). Figure 2 panels J through L show that the left frontal pole and some

of the anterior cingulate gyrus had significantly higher activations in the ADHD group compared to the control group (p<0.021).

Figure 3 panels J through L highlight the higher activation of the SAL in the left putamen of the basal ganglia in the ADHD group compared to the control group. Figure 4 panels J through L highlight the higher activation of the left insular cortex in the ADHD group compared to the control group (p<0.021). In panels G through I for both Figures 3 and 4 there were unremarkable activations that were higher in the control group compared to the ADHD group apart from the higher activations shown in the parietal region in Figure 4 panel G that was already shown in Figure 2.

Altered Connectivity Within the DMN

The DMN intrinsic connectivity analysis revealed that several DMN connections were stronger in the control group compared to the ADHD group, while only one DMN connection was stronger in the ADHD group compared to controls. The first column in Table 2 summarizes every DMN connection that differed between the ADHD and control groups according to Figure's 5 and 6 (p<0.089). Figure 5 shows the results from the calculation of the mean regression values for each group that were then used to make the matrices in Figure 6. On the left, Figure 6 shows the 13 × 13 matrix that reveals the one connection that was more active in the ADHD group compared to the control group (p=0.089): between the left inferior temporal and the left lateral parietal cortices. On the right, Figure 6 shows all of the connections that were more active in the control group compared to the ADHD group (p<0.089). The one connection that most significantly differed between groups was between the anterior medial prefrontal cortex (mPFC) and the right lateral parietal cortex (p<0.003). The connection was found to be stronger in the control group compared to the ADHD group.

The analysis comparing the DMN activations between groups revealed that parts of the DMN were significantly more activated in the control group compared to the ADHD group (p<0.021). Figure 7 shows the comparisons between the DMN activations of the ADHD and control groups in four different brain slices. Panels A through D show the averaged DMN activity for the ADHD group, while panels E through H show the averaged DMN activity for the control group. Figure 7 panels I through L reveal that the control group had some significantly stronger DMN activations compared to the ADHD group (p<0.021). As shown in panels I and J, significantly stronger DMN activation in the control group compared to the ADHD group was exhibited primarily in ventral mPFC and posterior cingulate areas, respectively (p<0.021). Panels M through P show that there were not any notable DMN activations that were higher in the ADHD group compared to the control group.

Discussion

The current study provided evidence of aberrant SAL activation, decreased DMN activation, and several aberrant DMN connectivities during the resting state in children with ADHD. The first hypothesis was partially supported since some PFC regions of the SAL were more active in the ADHD group compared to the control group, indicating a disruption in the typical attenuation of the SAL during a resting state. Interestingly, parietal regions of the SAL were found to be less active in the ADHD group compared to controls. The second hypothesis was also partially supported with some of the aberrant connectivities found in the study matching the broader maturational delay hypothesis of ADHD. However, several other connectivities did not support the maturational delay hypothesis, creating mixed results.

State-inappropriate SAL Activity in ADHD

Although some of the SAL activation differences between ADHD and control groups were unexpected, our findings still suggest aberrant regulation of the SAL during a resting state in children with ADHD. Hoekzema et al.'s (2014) study focused on the dlPFC SAL seed in their analyses and found that, in ADHD, there is a reduced anti-correlational relationship between the connectivity of the dlPFC seed with the DMN during a resting state that was characterized by insufficient suppression of dlPFC signaling. In the current study, the SAL appears to be more activated in similar PFC regions also in the resting state of children with ADHD (see Figure 2). These results support Hoekzema et al.'s (2014) findings that state-inappropriate neural activity in ADHD is not confined to DMN intrusion during an attentive state, since there appears to be SAL intrusion during the resting state as well.

The current study's findings also suggest that aberrant SAL activity in children with ADHD includes decreases in SAL activation, particularly in the left parietal cortex (see Figure 2). This specific relationship was not mentioned in Hoekzema et al.'s (2014) study, and indicates that potential over-attenuation of particular regions of the SAL occurs along with inadequate attenuation in other regions such as the PFC. Overall, there appears to be both inappropriate SAL activation and SAL deactivation during a resting state involved in ADHD pathophysiology during childhood. These dysfunctions during a resting state suggest that this attentional network may be more difficult to regulate in those with ADHD. This implication is important since it highlights a potential mechanism underlying ADHD symptomatology during an attentive state that could involve an increased amount of effort and energy expenditure required to regulate attentional networks.

Evaluation of Developmentally Dynamic DMN Connections

Comparison to Fair et al.'s (2010) Findings. In order to determine whether our data exhibited similar trends in DMN connectivity compared to the Fair et al. (2010) study, we examined 14 *a priori* connections of interest that had been identified as developmentally dynamic (Fair et al., 2008). As described by Fair et al. (2010), connections that usually get weaker with age tended to be stronger in children with ADHD due to an inability of the circuits to segregate properly. Furthermore, connections that usually get stronger with age were weaker in children with ADHD due to an inability of the circuits to integrate as well. Fair et al. (2010) found that 11 out of the 14 developmentally dynamic connections followed those trends.

As shown in the second column of Table 2, 3 out of the 17 connections found in the current study that were different between ADHD and control groups ($p<0.089$) matched the trends found in Fair et al.'s study (2010). The connectivities were between the anterior mPFC and posterior cingulate cortex, the ventral mPFC and posterior cingulate cortex, and the anterior mPFC and left lateral parietal cortex. These connections were all stronger in the control group compared to the ADHD group ($p<0.089$) and support the maturational delay hypothesis because they suggest that DMN circuitry is not integrating normally in ADHD. No evidence was found that the DMN was not segregating normally since the only connection found to be stronger in the ADHD group compared to controls ($p=0.089$) had not been established as developmentally dynamic by prior literature (Fair et al., 2008).

Furthermore, the Fair et al. (2010) study did not examine the relationship of the cerebellar tonsil DMN locus to the other DMN loci. As shown in the first column of Table 2, the current study did examine this relationship and found two additional connectivities that were stronger in the control group compared to the ADHD group ($p<0.089$): between the cerebellar tonsils and

left lateral parietal cortex, and between the cerebellar tonsils and right superior frontal cortex. These connectivities had not been previously identified to be developmentally dynamic, so these findings still do not support the maturational delay hypothesis of ADHD. However, these findings do provide evidence that other previously undetermined trends in DMN connectivity dysfunction may be playing an important role in ADHD pathophysiology.

Comparison to Choi et al.'s (2013) Findings. The connectivities displayed in the first column of Table 2 were also compared to Choi et al.'s (2013) study. Choi et al.'s (2013) main finding within the DMN was a reduced connection between the aDMN and the pDMN in children with ADHD compared to typically developing children (Choi et al., 2013). In their study, Choi et al. (2013) defined the aDMN as consisting of primarily the ventral mPFC (vmPFC) and anterior mPFC (amPFC) DMN loci, while the pDMN/ precuneus network constituted the rest of the DMN. In the present study, the third column in Table 2 lists the connectivities that included either the vmPFC or the amPFC that were weaker in the ADHD group compared to the control group. Therefore, a total of 6 out of the 17 total connectivities found to differ between groups were consistent with Choi et al.'s (2013) study. This finding suggests that a reduced connection between the aDMN and the pDMN is present in children with ADHD, and supports the maturational delay hypothesis. However, the other 11 connectivities found to be different between ADHD and control groups do not follow the developmental trends posed by the maturational delay hypothesis.

Comparison to Bos et al.'s (2017) Findings. In order to compare the current study's findings with the Bos et al. (2017) paper, the relative activities of the DMN were compared between groups as shown in Figure 7. In Figure 8, the three specific areas found by Bos et al. (2017) to be significantly different in children with ADHD compared to controls were compared

to the current study's DMN activation findings. None of the trends found in the three coordinates by the Bos et al. (2017) study were observed in the current study according to the lack of activation differences in those areas as shown in Figure 8. This finding does not provide support for the maturational delay hypothesis of ADHD.

DMN Connectivity Summary. Overall, the analysis examining previously determined developmentally dynamic DMN connectivities yielded mixed results. Although some of the connectivities did correspond to previous findings, many connectivities did not (Fair et al., 2010; Choi et al., 2013; Bos et al., 2017). These mixed findings suggest that maturational deficits along with other specific dysconnectivity trends are involved in ADHD pathophysiology. Notably, the majority of the connectivities that supported previous findings and the maturational delay hypothesis of ADHD involved mPFC areas. This finding suggests that dysfunctional connectivity involving the aDMN specifically could be a key locus of dysfunction in ADHD that can be observed even in small sample sizes, as was used in the current study (N=26). It is also important to note that no connectivities appeared to be stronger in the ADHD group compared to the control group until the significance threshold was lowered to a *p*-value of 0.089. Even then, as shown in Figure 6, only a single connectivity was found. In contrast, there were several connectivities that were stronger in the control group compared to the ADHD group, suggesting some DMN hypoconnectivity in children with ADHD that supports some previous findings (Sripada et al., 2014; Castellanos et al., 2008).

Attenuated DMN Activation in ADHD. The DMN activity comparisons between ADHD and control groups shown in Figure 7 indicated decreases in DMN activation in children with ADHD. This finding, that the DMN may not be as activated in certain areas as it normally is, supports previous findings that implicate aberrant DMN regulation in ADHD pathophysiology

(Sun et al., 2012; Choi et al., 2013; Sripada et al., 2014). In ADHD, the DMN may be getting mildly attenuated during the resting state due to improper regulation, since it typically should be getting more activated. These results mirror the SAL findings in the current study and indicate that aberrations in resting state network activity are a persistent feature of ADHD (Hoekzema et al., 2014).

Conclusions and Future Directions

The findings in the present study provide preliminary evidence that implicates SAL and DMN activity dysregulation as well as developmentally related dysfunction and additional dysconnectivity within the DMN in children with ADHD during a resting state. However, the significance of the findings is limited by the study's small sample size, hindering the applicability of the findings to broader contexts. There were also some confounding variables within the ADHD group that included medication status and comorbidity with other psychiatric disorders that could have impacted the results. Furthermore, weak matches of the SAL and DMN components from the resting state signal was another limitation to the study that may explain some of the inconsistencies with previous studies that were able to achieve stronger component matches. Attempts to increase the signal-to-noise ratio of our data could potentially provide better SAL and DMN matches for future study.

Overall, future directions for the current study will focus on attaining a larger sample size in order to examine the resting state functional activity and connectivity on more dimensions. Once a more adequate sample size is obtained, dimensional analyses could examine differences in resting state ICNs attributed to variables such as gender, age, medication status, comorbidity, genetic risk for psychiatric disorders such as schizophrenia, and executive functioning skills such as reward processing. Finding specific associations between SAL and DMN dysfunctions during

a resting state and various cognitive abilities could lead to the development of more specific and precise diagnostic tools for ADHD. The aberrant SAL and DMN activations and DMN connectivity trends found in the current study could even be considered as potential therapeutic targets for ADHD in the future.

References

Ashburner, J. & Friston, K.J. (2005). Unified segmentation. *NeuroImage,* 26, 839–851.

Bebko, G., Bertocci, M., Chase, H., Dwojak, A., Bonar, L., Almeida, J., … Phillips, M. L. (2015). Decreased amygdala-insula resting state connectivity in behaviorally and emotionally dysregulated youth. *Psychiatry Research*, 231, 77-86.

Bell, A.J. & Sejnowski, T.J. (1995) An information-maximization approach to blind separation and blind deconvolution. Neural Computation, 7, 1129-1159.

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, 34, 537–541. doi:10.1002/mrm.1910340409.

Bonelli, R. M., & Cummings, J. L. (2007). Frontal-subcortical circuitry and behavior. *Dialogues in Clinical Neuroscience*, *9*(2), 141–151.

Bos, D. J., Oranje, B., Achterberg, M., Vlaskamp, C., Ambrosino, S., de Reus, M. A., … Durston, S. (2017). Structural and functional connectivity in children and adolescents with and without attention deficit/hyperactivity disorder. *J Child Psychol Psychiatr*, 58, 810–818. doi:10.1111/jcpp.12712

Calhoun, V. D., Adali, T., Pearlson, G. D., Pekar, J. J. (2001). A method for making group inferences from functional MRI data using independent component analysis. *Human Brain Mapping*, 14, 140-151.

Castellanos, F. X., Margulies, D. S., Kelly, C., Uddin, L. Q., Ghaffari, M., & Kirsch, A. (2008). Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 63, 332–337.

Chang, H-C., Gaur, P., Chou, Y-H., Chu, M-L., Chen, N-K. (2014). Interleaved EPI based fMRI improved by multiplexed sensitivity encoding (MUSE) and simultaneous multi-band imaging. *PloS One,* 9, Retrieved from http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0116378.

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, Retrieved from https://doi.org/10.1371/journal.pone.0083516.

Cohen, J.R. (2017). The behavioral and cognitive relevance of time-varying, dynamic changes in functional connectivity. *Neuroimage*, *epub ahead of print*.

Damaraju, E., Allen, E. A., Belger, A., Ford, J. M., McEwen, S., Mathalon, D. H., … Calhoun, V. D. (2014). Dynamic Functional Connectivity Analysis Reveals Transient States of Dysconnectivity in Schizophrenia. *Neuroimage: Clinical*, 5, 298-308. https://doi.org/10.1016/j.nicl.2014.07.003.

El-Sayed, E., Larsson, J.-O., Persson, H., Santosh, P. & Rydelius, P.-A. (2003), "Maturational lag" hypothesis of attention deficit hyperactivity disorder: an update. Acta Pædiatrica, 92: 776–784. doi:10.1111/j.1651-2227.2003.tb02531.x.

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

Fair, D., Cohen, A., Dosenbach, N., Church, J., Miezin, F., Barch, D., . . . Schlaggar, B. (2008). The Maturing Architecture of the Brain's Default Network. *Proceedings of the National*

Academy of Sciences of the United States of America, 105(10), 4028-4032. Retrieved from http://www.jstor.org/stable/25461360.

Fair, D.A., Posner, J., Nagel, B.J., Bathula, D., Dias, T.G.C., Mills, K.L., … & Nigg, J.T. (2010). Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 68, 1084–1091.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678. http://doi.org/10.1073/pnas.0504136102.

Friston, K.J., Frith, C., Frackowiak, R.S.J, & Turner, R. (1995) Characterizing dynamic brain responses with fMRI: A multivariate approach. *NeuroImage*, 2, 166–172.

Helps, S., James, C., Debener, S., Karl, A., & Sonuga-Barke, E. J. (2008) Very low frequency EEG oscillations and the resting brain in young adults: A preliminary study of localisation, stability and association with symptoms of inattention. *J Neural Transm,* 115, 279–285.

Hoekzema, E., Carmona, S., Ramos-Quiroga, J. A., Richarte Fernández, V., Bosch, R., Soliva, J. C., … Vilarroya, O. (2014). An independent components and functional connectivity analysis of resting state fMRI data points to neural network dysregulation in adult ADHD. *Human Brain Mapping*, 35, 1261–1272. doi:10.1002/hbm.22250.

Konrad, K. & Eikhoff, S. B. (2010). Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. *Human Brain Mapping*, 31, 904-916.

Laird, A. R., Fox, P. M., Eickhoff, S. B., Turner, J. A., Ray, K. L., McKay, D. R., … Fox, P. T. (2011). Behavioral Interpretations of Intrinsic Connectivity Networks. *Journal of Cognitive Neuroscience*, *23*(12), 4022–4037. http://doi.org/10.1162/jocn_a_00077.

Monchi O., Petrides M., Strafella AP., Worsley KJ., Doyon J. (2006) Functional role of the basal ganglia in the planning and execution of actions. *Ann Neurol,* 59, 257–264.

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, 3-15.

Sripada, C., Kessler, D., Fang, Y., Welsh, R. C., Kumar, K. P., & Angstadt, M. (2014). Disrupted network architecture of the resting brain in attention-deficit/ hyperactivity disorder. *Human Brain Mapping*, 35, 4693-4705.

Stefanatos, G. A. & Wasserstein, J. (2006) Attention Deficit/ Hyperactivity Disorder as a Right Hemisphere Syndrome. *Annals of the New York Academy of Sciences*, 931(1), 172-195.

Sun, L., Cao, Q., Long, X., Sui, M., Cao, X., & Zhu, C. (2012). Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder. *Psychiatry Research: Neuroimaging*, 201, 120–127.

Tian, L., Jiang, T., Wang, Y., Zang, Y., He, Y., Liang, M., Sui, M., Cao, Q., Hu, S., Peng, M., & Zhuo, Y. (2006) Altered resting-state functional connectivity patterns of anterior cingulate cortex in adolescents with attention deficit hyperactivity disorder. *Neurosci Lett,* 400, 39–43.

Zhang, Y., Brady, M., & Smith, S. (2001) Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imag*, 20(1), 45-57.

Table 1

Sample Demographics

Variable	ADHD Group	Control Group	*t*	*p*
Age, M ± SD (range)	11.77 ± 1.80 (9-15)	11.85 ± 2.15 (9-15)	0.77	.449
Gender (F/M)	4/9	4/9		
n	13	13		

Note. ADHD=attention deficit hyperactivity disorder; M=mean; SD=standard deviation.

Table 2

Altered DMN Connectivities Between ADHD and Control Groups

All Connectivities That Differed Between Groups (p<0.089)	Connectivities Consistent with Fair et al. (2010)[a]	Connectivities Consistent with Choi et al. (2013)[b]
amPFC – R lat.parietal	amPFC – Post.cingulate	amPFC – R lat.parietal
amPFC – Post.cingulate	vmPFC – Post.cingulate	amPFC – Post.cingulate
R lat.parietal – Post.cingulate	amPFC – L lat.parietal	vmPFC – Post.cingulate
vmPFC – Post.cingulate		amPFC – L lat.parietal
amPFC – L lat.parietal		R inf.temporal - vmPFC
L sup.frontal - Retrosplenial		R parahippocampus - vmPFC
L parahippocampus - Retrosplenial		
Cerebellar.tonsils – L lat.parietal[c]		
L lat.parietal - Retrosplenial		
R inf.temporal - vmPFC		
R parahippocampus – Post.cingulate		
R parahippocampus – L lat.parietal		
R parahippocampus - vmPFC		
R parahippocampus – R sup.frontal		
Cerebellar.tonsils – R sup.frontal[d]		
Retrosplenial – Post.cingulate		
L inf.temporal – L lat.parietal[e]		

Note. All connectivities were stronger in the control group compared to the ADHD group unless otherwise noted (p<0.089).

[a]Connectivities were compared to the findings in "Atypical default network connectivity in youth with attention-deficit/hyperactivity disorder," by D. A. Fair, J. Posner, B. J. Nagel, D. Bathula, T. G. C. Dias, K. L. Mills, M. S. Blythe, A. Giwa, C. S. Schmitt, and J. T. Nigg, 2010, *Biological Psychiatry*, 68, p. 1084–1091. [b]Connectivities were compared to the findings in "Aberrant Development of Functional Connectivity among Resting State-Related Functional Networks in Medication-Naïve ADHD Children," by J. Choi, B. Jeong, S. W. Lee, and H-J. Go, 2013, PLoS ONE, 8. [c, d]These connectivities had not been examined in the Fair et al. (2010) paper. [e]This connectivity was stronger in the ADHD group compared to the control group, p=0.089.

Figure Captions

Figure 1. Default mode network regions used in the computation of group mean matrices. The Montreal Neurological Institute brain template was used and Talairach coordinates are displayed in the upper right corner of each panel. S=superior; P=posterior; A=anterior; I=inferior; R=right; L=left. The thirteen regions were adapted from "The human brain is intrinsically organized into dynamic, anticorrelated functional networks," by M. D. Fox, A. Z. Snyder, J. L. Vincent, M. Corbett, D. C. Van Essen, and M. E. Raichle, 2005, *Proceedings of the National Academy of Sciences of the United States of America*, *102,* p.9673-9678.

Figure 2. Salience network activations in frontal and parietal cortical areas compared between ADHD and control group averages. Brighter colored areas represent higher activities. An activation threshold of p=0.021 was used. The Montreal Neurological Institute brain template was used and Talairach coordinates are displayed at the top of each column. Control>ADHD=activations that were significantly higher in the control group compared to the ADHD group; ADHD>Control=activations that were significantly higher in the ADHD group compared to the control group; S=superior; P=posterior; A=anterior; I=inferior; R=right; L=left.

Figure 3. Salience network activations in the basal ganglia compared between ADHD and control group averages. Brighter colored areas represent higher activities. An activation threshold of p=0.021 was used. The Montreal Neurological Institute brain template was used and Talairach coordinates are displayed at the top of each column. Control>ADHD=activations that were significantly higher in the control group compared to the ADHD group; ADHD>Control=activations that were significantly higher in the ADHD group compared to the control group; S=superior; P=posterior; A=anterior; I=inferior; R=right; L=left.

Figure 4. Salience network activations in the insular cortex compared between ADHD and control group averages. Brighter colored areas represent higher activities. An activation threshold of p=0.021 was used. The Montreal Neurological Institute brain template was used and Talairach coordinates are displayed at the top of each column. Control>ADHD=activations that were significantly higher in the control group compared to the ADHD group; ADHD>Control=activations that were significantly higher in the ADHD group compared to the control group; S=superior; P=posterior; A=anterior; I=inferior; R=right; L=left.

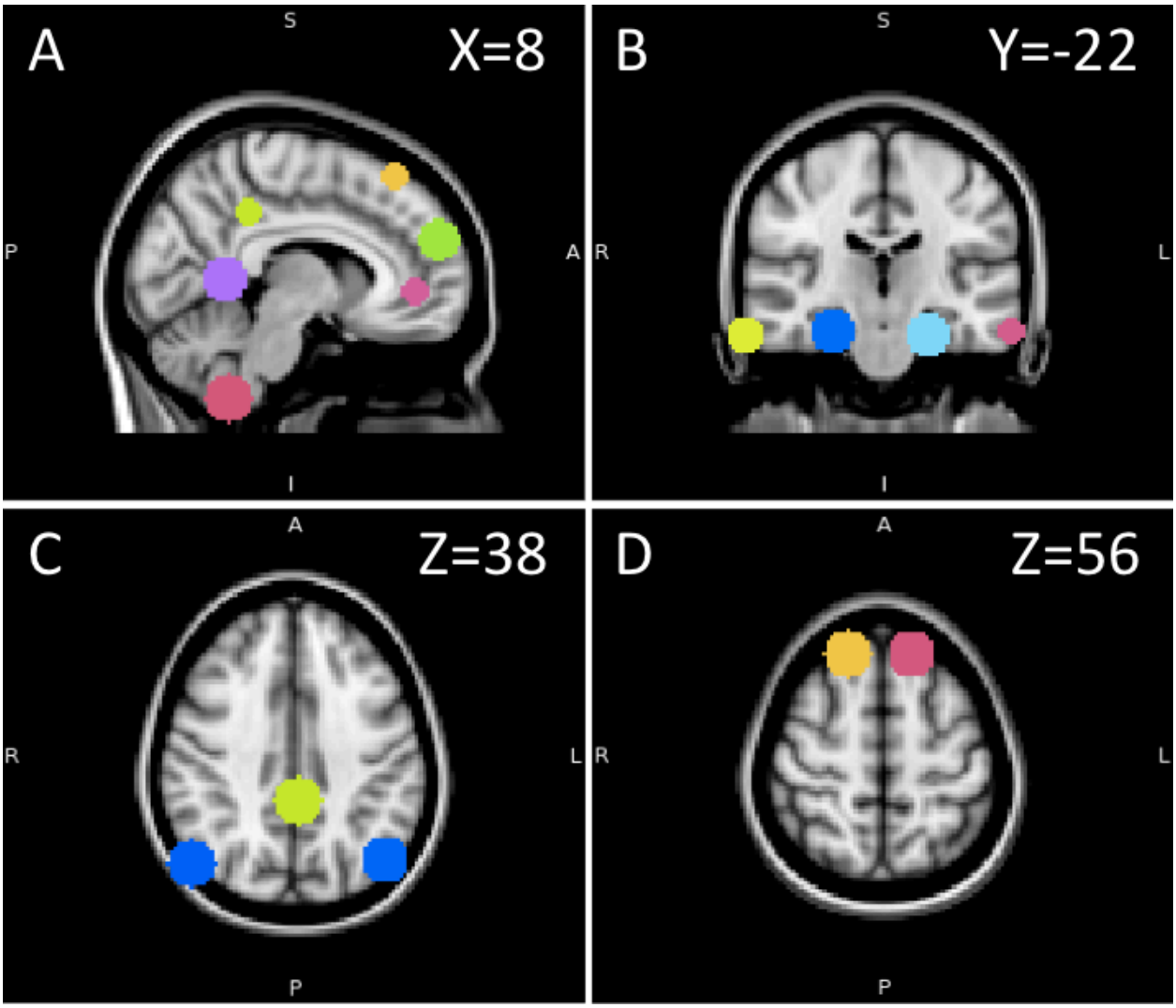
Figure 5. Default mode network group mean correlation matrices for ADHD and control groups. Abbreviations were adapted from "The Maturing Architecture From the Brain's Default Network," by D. A. Fair, A. L. Cohen, N. U. F. Dosenbach, J. A. Church, F. N. Miezin, D. M. Barch, M. E. Rachle, S. E. Peterson, and B. L. Schlaggar, 2008, *Proceedings of the National Academy of Sciences of the United States of America, 105,* p. 4028-4032.

Figure 6. Default mode network connectivity matrices comparing ADHD and control groups. On the left is the matrix showing the connectivities that were stronger in the ADHD group compared to the control group (p<0.089). On the right is the matrix showing the connectivities that were stronger in the control group compared to the ADHD group (p<0.089). Abbreviations were adapted from "The Maturing Architecture From the Brain's Default Network," by D. A. Fair, A. L. Cohen, N. U. F. Dosenbach, J. A. Church, F. N. Miezin, D. M. Barch, M. E. Rachle, S. E.

Peterson, and B. L. Schlaggar, 2008, *Proceedings of the National Academy of Sciences of the United States of America, 105,* p. 4028-4032.

Figure 7. Default mode network activations compared between ADHD and control group averages. Brighter colored areas represent higher activities. An activation threshold of p=0.021 was used. The Montreal Neurological Institute brain template was used and Talairach coordinates are displayed at the top of each column. Control>ADHD=activations that were significantly higher in the control group compared to the ADHD group; ADHD>Control=activations that were significantly higher in the ADHD group compared to the control group; S=superior; P=posterior; A=anterior; I=inferior; R=right; L=left.

Figure 8. Default mode network coordinates from prior literature overlaid on current study's default mode network activation comparisons between ADHD and control groups. Crosshairs indicate the DMN loci of interest. Brighter colored areas represent higher activities. Top two rows show current study DMN activations that were higher in the ADHD group compared to the control group. Bottom row shows current study DMN activations that were higher in the control group compared to the ADHD group. The Montreal Neurological Institute brain template was used and Talairach coordinates are displayed at the upper right corner of each panel. 1=Coordinate (X,Y,Z) (35,23,-4.5); 2=(-9,32,-18.5); 3=(-6,-31,41); S=superior; P=posterior; A=anterior; I=inferior; R=right; L=left. The three coordinates being displayed with the crosshairs are from "Structural and functional connectivity in children and adolescents with and without attention deficit/hyperactivity disorder," by D. J. Bos, B. Oranje, M. Achterberg, C. Vlaskamp, S. Ambrosino, M. A. de Reus, M. P. van den Heuvel, S. A. Rombouts, and S. Durston, 2017, *J Child Psychol Psychiatr*, 58, p. 810–818.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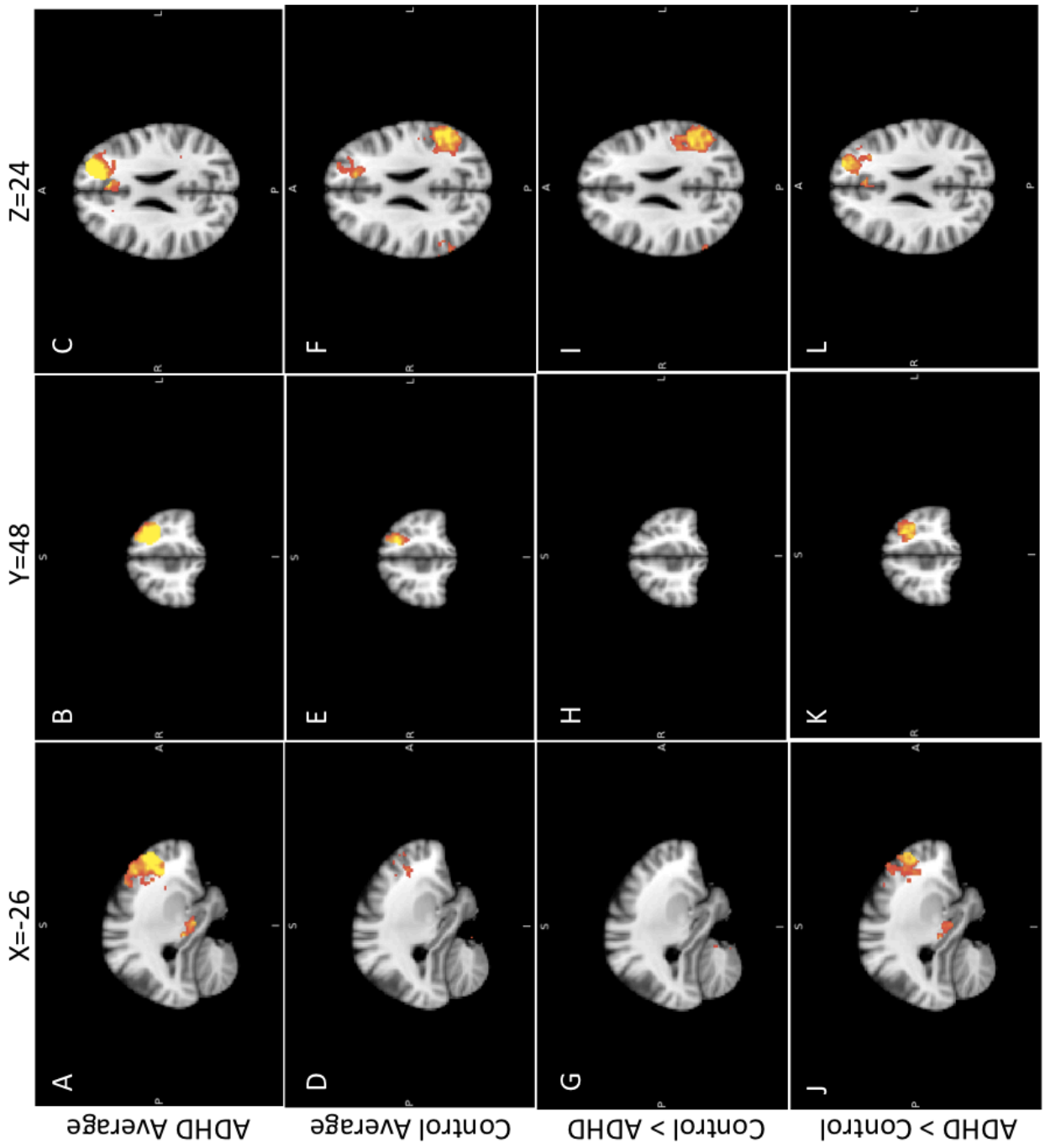
R
L
P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J
K
L
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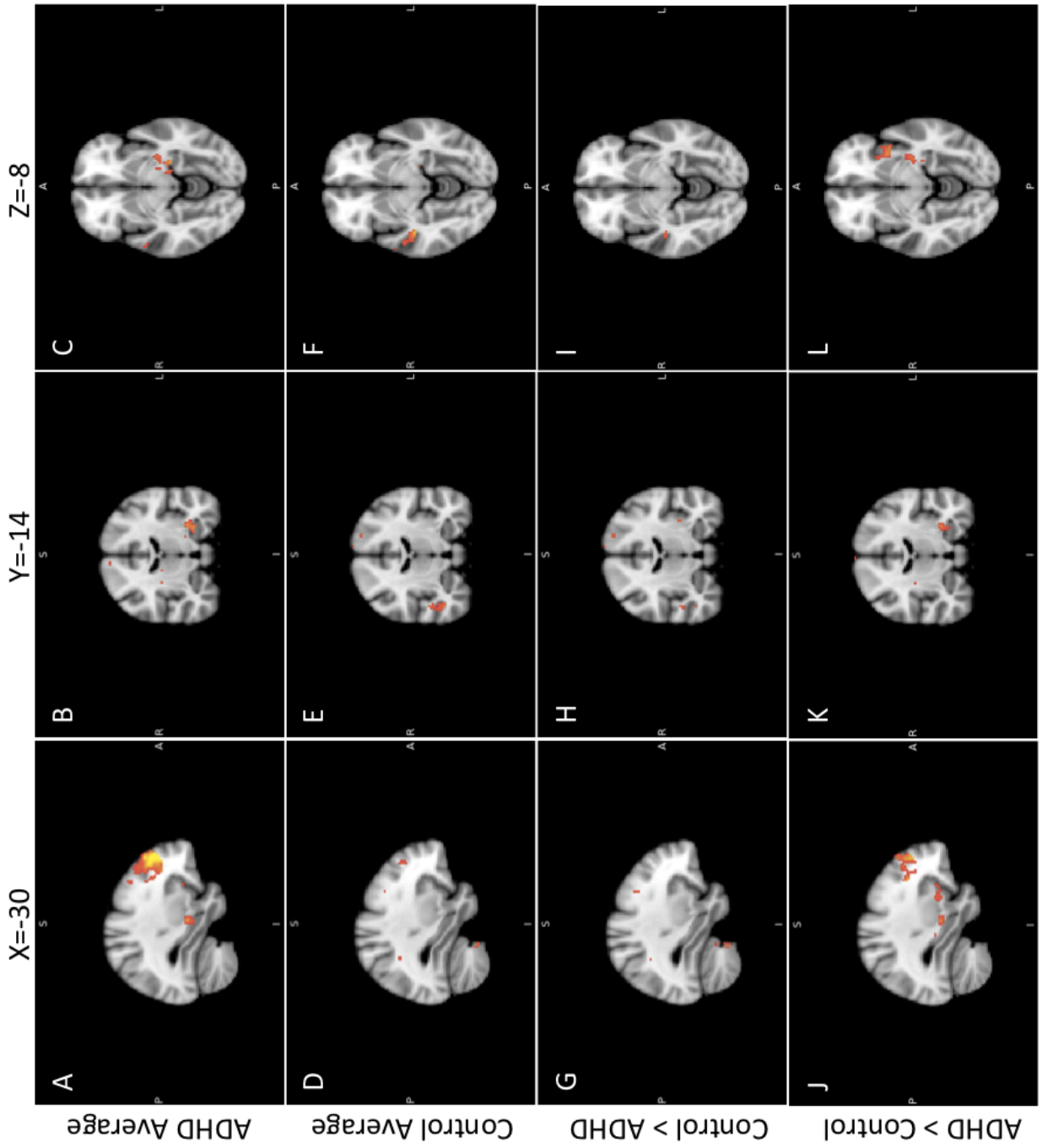
Control Average
Control > ADHD
ADHD > Control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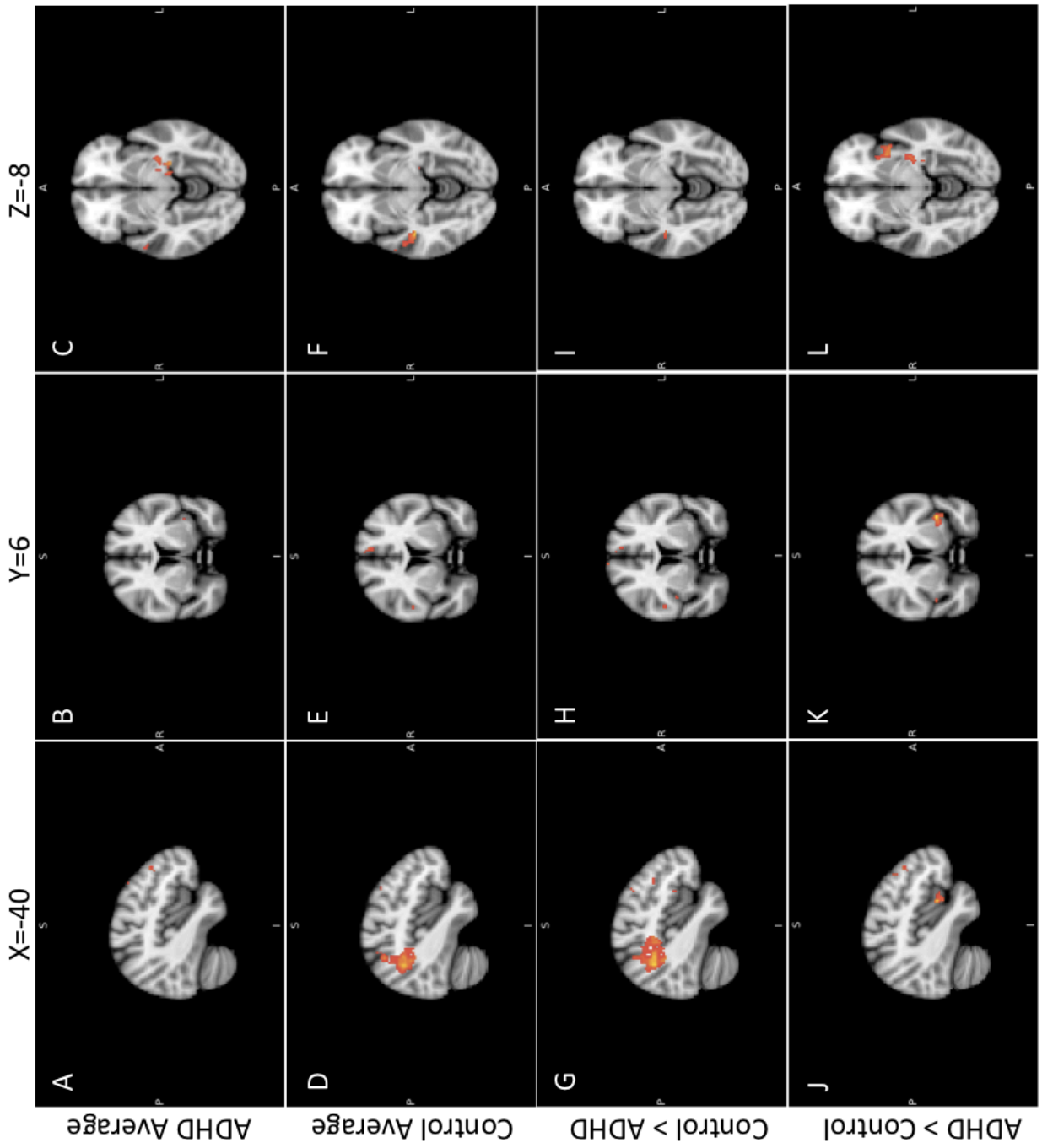
Control > ADHD
ADHD > Control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L
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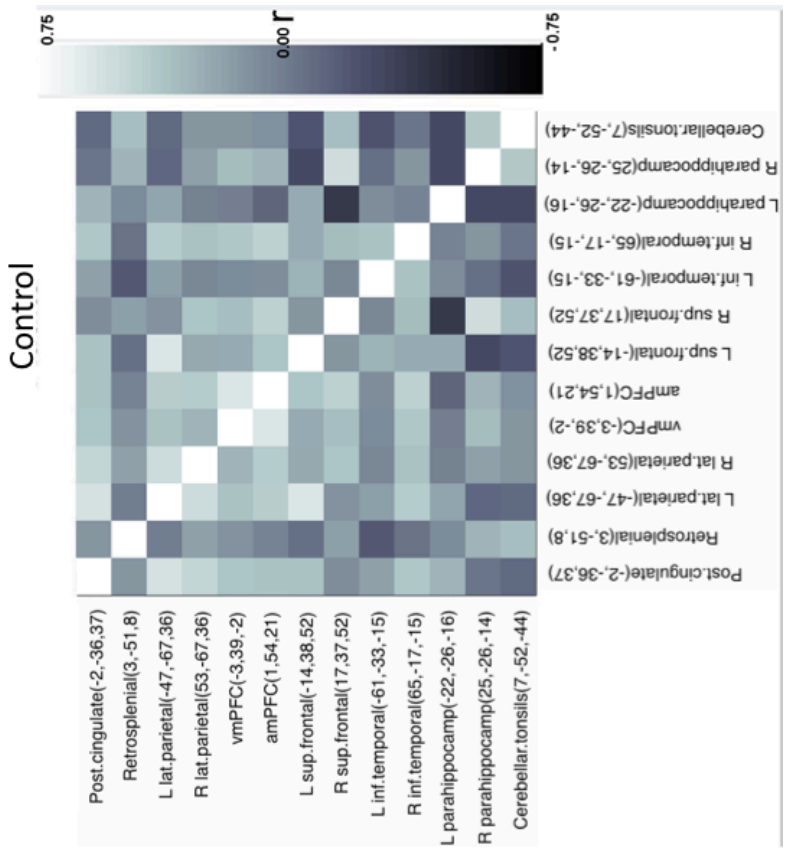
Control > ADHD
ADHD > Control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0.00
r
-0.75
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Retrosplenial(3,-51,8)
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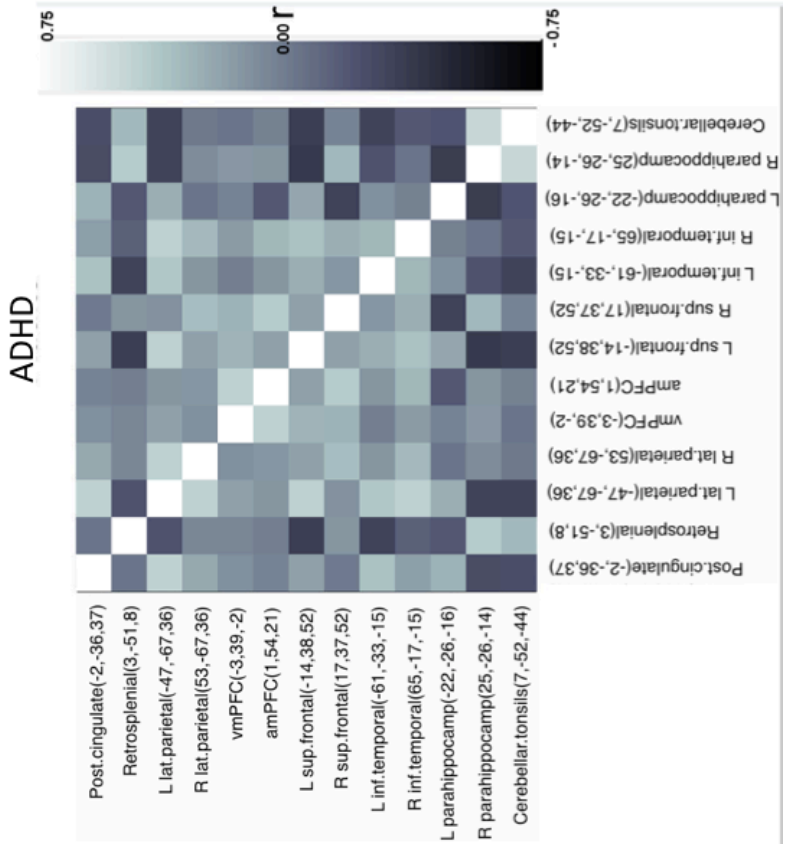
R lat.parietal(53,-67,36)
vmPFC(-3,39,-2)
amPFC(1,54,21)
L sup.frontal(-14,38,52)
R sup.frontal(17,37,52)
L inf.temporal(-61,-33,-15)
R inf.temporal(65,-17,-15)
L parahippocamp(-22,-26,-16)
R parahippocamp(25,-26,-14)
Cerebellar.tonsils(7,-52,-44)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Retrosplenial(3,-51,8)
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R sup.frontal(17,37,52)
L inf.temporal(-61,-33,-15)
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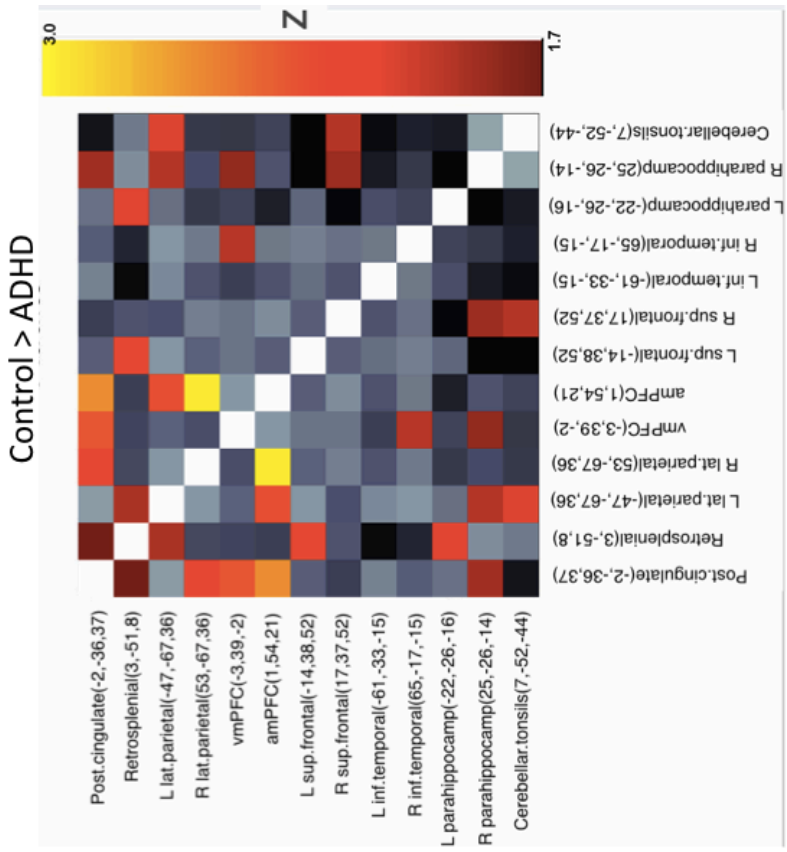
Cerebellar.tonsils(7,-52,-44)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L inf.temporal(-61,-33,-15)
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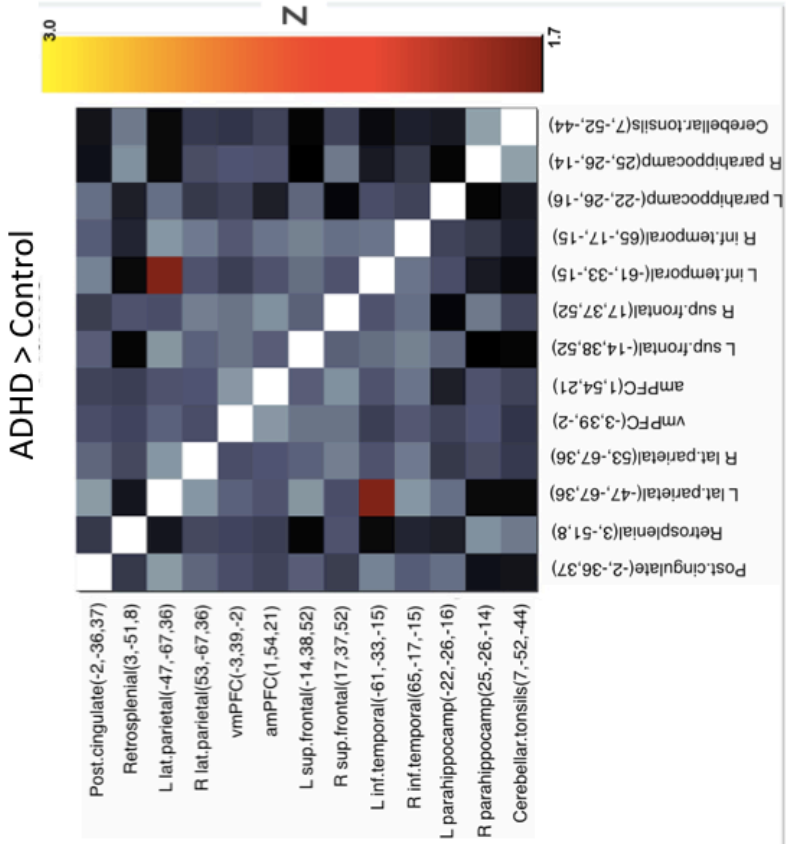
Cerebellar.tonsils(7,-52,-44)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3.0
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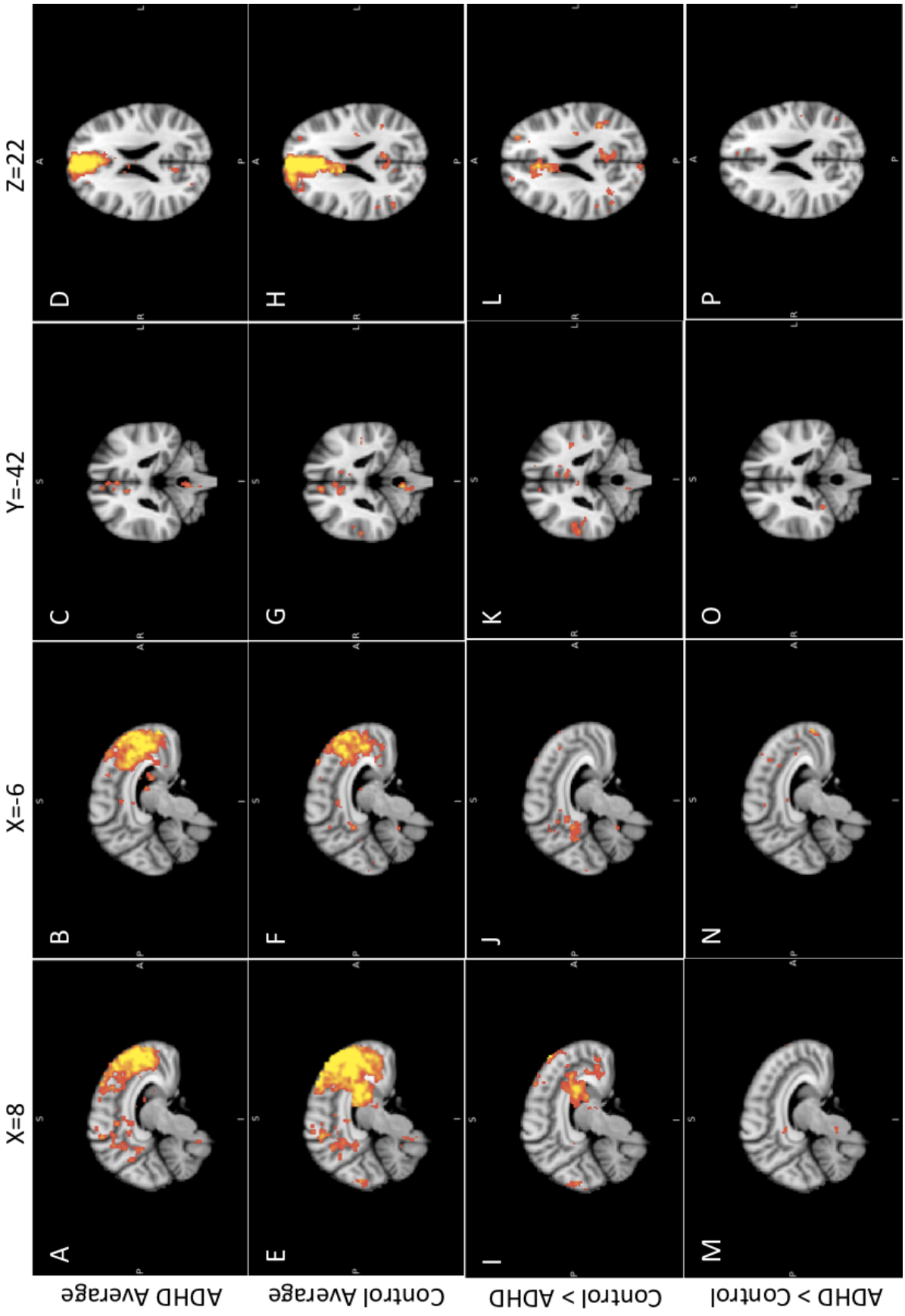
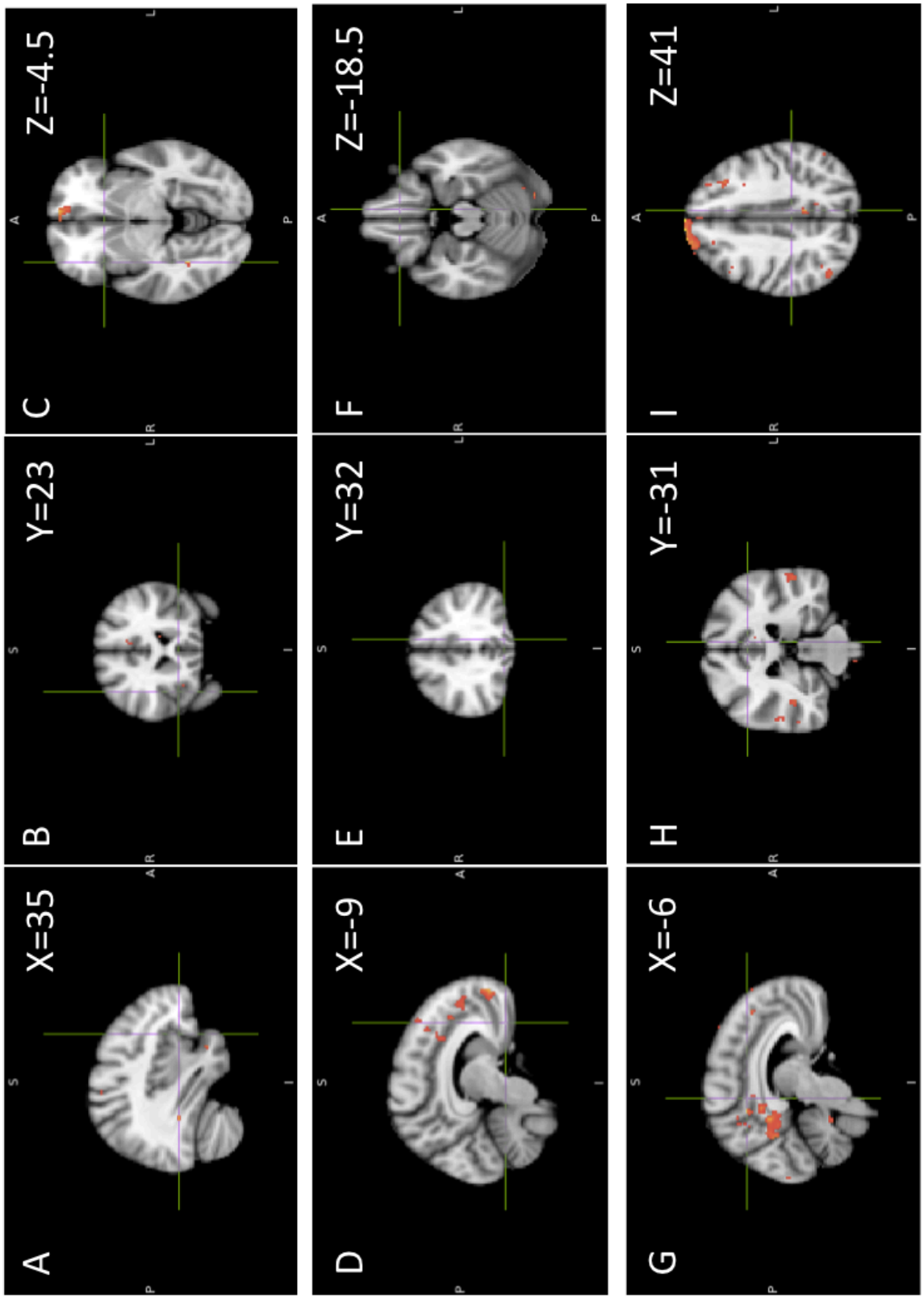
Post.cingulate(-2,-36,37)
Retrosplenial(3,-51,8)
L lat.parietal(-47,-67,36)
R lat.parietal(53,-67,36)
vmPFC(-3,39,-2)
amPFC(1,54,21)
L sup.frontal(-14,38,52)
R sup.frontal(17,37,52)
L inf.temporal(-61,-33,-15)
R inf.temporal(65,-17,-15)
L parahippocamp(-22,-26,-16)
R parahippocamp(25,-26,-14)
Cerebellar.tonsils(7,-52,-44)


X=8
X=-6
Y=-42
Z=22
ADHD Average
Control Average
Control > ADHD
ADHD > Control
A
B
C
D
E
F
G
H
I
J
K
L
M
N
O
P


A
X=35
B
Y=23
C
Z=-4.5
D
X=-9
E
Y=32
F
Z=-18.5
G
X=-6
H
Y=-31
I
Z=41
1
2
3