Neural Connectivity Underlying Cognitive Control:

Variations in ADHD Participants

by

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Abstract

This project aimed to identify abnormalities in brain regions underlying cognitive control, including differences in activation within these regions and differences in connectivity between these regions, in participants with ADHD versus healthy controls. The Multi-Source Interference Task (MSIT) has been particularly effective for studying both response inhibition and attention control in neuroimaging by implementing both 'congruent' and contrasting 'incongruent' task conditions (Bush & Shin, 2006; Bush et al., 2003). The present study used the MSIT in conjunction with fMRI neuroimaging to examine the possible neural connectivity variations of regions specifically activated during the incongruent tasks between ADHD and healthy participants. We expected hypoactivation in cognitive control regions including the anterior cingulate cortex, supplementary motor cortex, and superior parietal cortex in ADHD participants, which would be consistent with typical clinical ADHD symptoms such as diminished attention regulation and response inhibition. The ultimate goals of the connectivity analysis were to help map the brain's cognitive control network and elucidate underlying causes of ADHD. The results, demonstrating *hyper*activation of cognitive control regions and increased region coupling in ADHD participants, support a compensatory hypothesis for ADHD participants' functional interconnectivity that invites interesting speculation and directions for future studies.

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Finding the Neural Correlates of Attention

The ability to willingly direct attention towards various internal and external stimuli is certainly one of the primary and vital components underlying concepts of free-will, human consciousness, and the archetypal definition of *choice*. Beyond conceptual significance, the mechanism for directing cognitive resources in a reasoned fashion holds limitless practical importance. An inattentive student is more likely to perform poorly on tests; an inattentive driver is more likely to cause an accident, and a person with less power to intentionally direct attention away from distracting stimuli (whether internally/endogenously or externally/exogenously generated) and towards a desired processing task (e.g. solving a puzzle or math problem) will likely take longer to accomplish a given task, produce an inferior result, or both. This final case can be taken to mean that a person with powerful control over deliberate attention attribution will possess more cognitive processing power (or simply, intelligence) than the same person with weak attention control. Thus when one considers the vast influence inherent to the control of attention, it is easy to understand why finding the neural correlates and activation variance (between humans) is of interest.

In attempting to develop an experimental task that can selectively activate a hypothetical "attention regulation circuit," researchers have begun to discover a necessity for classifying the various types of attention regulation employed by the brain. Modulation of attention is a complex mechanism that is not likely reducible to one or more brain structures or regions. Rather, evidence suggests multiple independent (yet likely interconnected) attention-modulation mechanisms including impulse control, interference processing, response selection, decision-

making, stimulus/response competition, and cognitive inhibition (Bush & Shin, 2006; Peterson et al., 1999; Kipp, 2005). In fact, it is reasonable to consider attention-modulation to be involved in *all* conscious neural activities, for attention is undoubtedly a core component of consciousness and cognitive control. However, while attention may be internally redirected and modulated in different ways to perform various mental deliberations or calculations, there still remains an overarching, distinct process of willful attention attribution. Such strategic directed attention is better defined in terms of actual mechanism of action. Purposely directing attention to a particular stimuli entails that there are multiple, competing stimuli to which attention *could* be attributed. In this light, the action mechanism is to contrast and *process* multiple *interfering* stimuli. Thus the activity of *intentional attention attribution* can be considered synonymous with *processing interfering stimuli* (henceforth referred to as PIS).

The first modern attempt to selectively and consistently activate the brain circuit responsible for PIS is known as the Stroop task. This task, developed by John Ridley Stroop, borrowed evidence discovered by James Cattell in 1886 that demonstrated how humans can read textual names of objects and colors much faster than they can name an image of the same object or color (MacLeod, 1991). Thus it takes longer for the average person to reply ‘blue’ when presented with a blue swatch of paper rather than the word "blue" printed on paper. Cattell proposed that reading text is automatic whereas recognizing and identifying images requires voluntary effort (MacLeod, 1991).

This finding led Stroop to postulate a task that could reliably evoke voluntary effort to produce a correct response. Thus he invented an *incongruent* stimulus, where the word text and color did not match (e.g. "blue" in green ink), and the desired response was the actual color of the stimuli, not the text. The automatic response to read the text must be overridden by voluntary

directed attention (at the actual color) in such incongruent trials, and produces what is now known as the Stroop effect. By comparing brain activation in congruent versus incongruent trials during a Stroop task, it seems possible that the neural correlates for processing interfering stimuli can be identified.

However, upon consideration, a subtraction method of brain activation in incongruent versus congruent Stroop tasks should not only result in regions used for processing interfering stimuli, but it should also display regions underlying impulse control. This is because during the incongruent trial a subject must not only distinguish the correct response based on the stimuli (PIS), but s/he must also inhibit the automatic response to read the text shown. Thus any functional magnetic resonance imaging (fMRI) study that uses the Stroop effect ought to purport a circuit that encompasses both neural mechanisms: PIS and impulse control.

Peterson et al. (1999) modeled the functional connectivity of said two mechanisms in their study: *An fMRI Study of Stroop Word-Color Interference: Evidence for Cingulate Subregions Subserving Multiple Distributed Attentional Systems*. Using data collected from 34 normal adult participants, this study analyzed patterns of correlations between brain regions using factor analysis and interpreted the resulting factors (i.e., brain networks) in terms of functions related to intentional attention attribution, including: "sensory tuning, receptive language, vigilance, working memory, response selection, motor planning, and motor response functions" (Peterson et al., 1999). This study led to the conclusion that the anterior cingulated cortex (ACC) modifies neural pathway strengths and allocates attentional resources by "reducing cross-talk between information processing modules," and thus acts to process interfering stimuli (Peterson et al., 1999). Thus, excitingly, this data proposes a major player in the PIS circuit (the ACC) and also supports the previously mentioned theory of multiple interconnected attentional

subsystems, which appear to be coordinated or integrated, at least in part, by the ACC.

In light of the ACC's widespread interconnectivity, it may be wise, for clarity, to link the term *attention* to the similar yet more encompassing phrase *cognitive control*, which refers to all flexible and adaptive processing that is utilized to satisfy task demands (e.g. impulse control and PIS in incongruent Stroop trials). PIS, therefore, can still be categorized as one of the processes of attention, which is itself a form of cognitive control.

Findings from multiple imaging studies as reported by Bush and Shin (2006) have contributed to the identification of a cognitive/attention network called the cingulo-frontal-parietal network (CFP network), which consists of the dorsal anterior midcingulate cortex (daMCC), dorsolateral prefrontal cortex (DLPFC) and superior portions of parietal cortex including the premotor and primary motor cortex, inferior temporal gyrus and the superior parietal lobule (Bush & Shin, 2006). This is believed to be the primary circuit for attention and cognitive processing mechanisms specifically related to PIS and similar task-based regulation pathways. It was discovered by analyzing and aggregating activation patterns produced from Stroop, Stroop-like, Eriksen Flanker-type and Simon task variants. These tasks are all designed to precipitate cognitive interference in the subject.

Stroop-like tasks include any variant of the original Stroop task, for example, a Stroop task using auditory instead of visual stimuli, or requesting the subject to sort or match the stimuli based on congruency, or changing part of the stimuli from names of colors to names of objects (MacLeod, 1991; Bush & Shin, 2006). Flanker-type tasks require the subject to identify the middle letter in a string of text, and use distracter letters for incongruent cases (e.g. AAAAA versus ZZAZZ) (Bush & Shin, 2006). Finally, Simon tasks evoke "cognitive interference produced by spatial incongruence between the target and response (e.g., given a two-button

response pad, it takes longer for participants to respond using the left button when the target appears on the right (and vice versa) than when the stimulus and response positions correspond)" (Bush & Shin, 2006). Inspecting the activation patterns for this array of incongruent tasks has allowed researchers to map the CFP network, which reliably shows activation when new cognitive interference tasks are administered (Bush, Seidman & Valera, 2005).

However, all of the aforementioned tasks entail a major setback that hinders future progress in both empirical and clinical realms. None of said tasks are robust enough to reliably evoke brain activation in single participants (Bush & Shin, 2006). Instead, activation patterns must be extrapolated from group-averaging techniques. This unfortunate situation produces three separate negative implications for existing task-based cognitive interference experiments. Firstly, since these experiments must rely on group-averaging they require a higher number of participants. Secondly, while the intention of these tasks is to elicit activation in regions that process cognitive interference, they are not robust enough to guarantee this outcome consistently and on the level of the individual. Thirdly, without a task that can produce CFP network activation on the level of the individual, clinical assessment cannot be performed on patients seeking diagnostic testing for cognitive dysfunction or impairment. These reasons demonstrate that a more powerful and reliable task should be developed.

Bush and Shin (2003 & 2006) sought to develop a task that could produce reliable and powerful activation of the CFP network. In creating an ideal task for cognitive interference processing studies, they devised a list of criteria to allow for maximal application value across subject and study type. They wished to be able to measure performance data including reaction times and accuracy of the participants to assess both cognitive and behavioral functioning. To prevent limitations on suitable participants (e.g. age or cognitive disposition), it was necessary

for the task be easily taught and retained. Additional criteria to ensure the broadest reach for a diversified set of applications included that the task was short, was not language specific, offered temporal stability for retesting and longitudinal studies, and finally, that it produced a narrow range of performance data for healthy participants so results could be "disorder specific" (Bush & Shin, 2006).

Bush and Shin successfully met these criteria with their invention of the multi-source interference task (MSIT). The MSIT was hypothesis driven, meaning that an understanding of the function of the CFP network led to the development of the task conditions (and not vice versa). The MSIT "reliably and robustly activates daMCC [and DLPFC and CFP network overall] within individuals, permits collection of concomitant imaging and performance data, [and] can be a useful task in studies of neuropsychiatric patients and normal volunteers" (Bush & Shin, 2006). This makes the MSIT a useful task for studying cognitive control relating to PIS. Furthermore, "single runs of the MSIT have produced CFP network activation in approximately 95% of tested participants" (Bush & Shin, 2006), which is an astonishing rate considering alternative tasks require multiple runs to achieve similar or worse activation (Bush, Holmes, Rosen, Shin & Vogt, 2003).

Bush et al. (2003) analyzed previous cognitive interference tasks such as the Stroop, Flanker and Simon task "in which the processing of one stimulus feature impedes the simultaneous processing of a second stimulus attribute" (Bush & Shin, 2006). This competing processing of simultaneous stimuli is the basis for PIS overall, and a necessity to "determine what types of activities or tasks would be likely to utilize the CFP network" (Bush & Shin, 2006). The goal of this analysis was to develop a set of experimental task conditions that would maximally activate the CFP network.

The MSIT displays a set of three numbers (that includes a particular combination of 1, 2,3 or 0), and instructs participants to respond with either index, middle or ring finger, which are each positioned over a separate button (correlating to a response of 'position 1,' 'position 2,' and 'position 3,' respectively, during trials utilizing the right hand), based on the value of the number in the set of three that does not match the other two (distracters), regardless of the spatial position. For example, if "003" is displayed, the appropriate response would be '3', indicated by pressing the third finger's button. Trials that displayed "322," "131," etc. would entail the same response (the third button) as the correct answer (because the differing digit is 3). Participants are informed that during some trials (which are control, or *congruent*) the target (unique) number will match the position, thus '1' would appear in the first position, '2' in the second, and '3' in the third. Distracter digits for control trials are always '0.' Thus the control trials are '100,' '020' and '003.'

In short, participating participants are instructed to identify the unique number's value from a set of three using a single button press from a choice of three buttons. Interference occurs when the unique number's *value* does not correspond with the *position* of the associated button. For example, the stimulus '131' would require a press of the button in the third position, despite the fact that the unique digit ('3') is in the second position of the set of three numbers.

One of the clinically relevant applications of this MSIT task, as outlined by Bush and Shin (2006) is that "it can be expected to serve as a useful fMRI probe in searching for the neural substrates of various neuropsychiatric disorders such as attention deficit disorder [ADD]." Because the MSIT requires willing modulation of attention between stimuli, it can help identify which individuals are better at response inhibition, impulse control, decision-making and processing interfering stimuli by looking at performance data coupled with fMRI results. This

makes the MSIT an ideal candidate for clinical diagnosis of ADD and the related attention-deficit hyperactivity disorder (ADHD).

Attention-deficit hyperactive disorder

Attention-deficit hyperactivity disorder (ADHD) is characterized by behavioral symptoms involving diminished attention-span and elevated activity believed to be caused by abnormalities in *inhibitory processing*, which is directly correlated to mechanisms for response inhibition, PIS, and attention. Typical ADHD manifestations such as inattention, impulsivity and motor restlessness can lead to undesired consequences for afflicted individuals such as poor performance (due to lack of focus) in school, work or personal life, and even impaired cognitive ability due to deficient ability to inhibit distracting stimuli. Such broad behavioral symptoms can be more easily investigated by identifying and contrasting specific neural mechanisms such as cognitive inhibition (which can be further sub-defined as automatic and intentional types), behavioral inhibition and resistance to interference (Kipp, 2005). These postulated neural correlates of ADHD share a great deal of similarity with the CFP network; both ADHD mechanisms and the CFP network involve a type of executive function dealing with attention, inhibition response and interference processing. As ADHD appears to demonstrate irregularity in the CFP network, it is worthwhile to outline the significance and impact of the disorder.

The neuropsychiatric disorder ADHD has an estimated prevalence of approximately 5-8% in children, making it one of the most common childhood neurobehavioral disorders (Bush, 2010). Not only does ADHD contribute to diminished academic, occupational and social functioning, as mentioned previously, but it often persists into adulthood (Bush, 2010). While multiple manifestations of the disorder exist in the population, ranging from a purely inattentive to a purely hyperactive form, the most common behavioral manifestation of ADHD is a

combination of diminished attention and overactive behavior (or hyperactivity). Bush (2010) states that "inattention, or the inability to direct and maintain selective attention to motivationally relevant tasks, is a key feature of the disorder." The other major attributes associated with ADHD, impulsivity and hyperactivity, both could be explained by dysfunction or abnormalities in neural circuits responsible for behavioral inhibition. Interestingly, this apparent deficit does not present itself consistently. At times, ADHD patients can perform tasks normally and even exceptionally, perhaps depending on interest or mood (Bush, 2010).

ADHD should not be solely considered an affliction, however. Many of the associated behavioral dispositions can also lead to attributes valued by society, such as creativity, fast reflexes, and hyper focus (Kipp, 2005). Thus understanding the neural mechanisms responsible for the manifestation of ADHD cannot only help improve negative conditions of the disorder, but also can help to understand the correlates for some of these potentially valuable characteristics.

What are the possible neural mechanisms for ADHD? Deficits in circuits responsible for inhibition were proposed, yet it is also possible that, conversely, circuits controlling action commands are extra sensitive and/or hyperactive in ADHD participants. If the latter proposition were the case, than for an ADHD subject to perform normally on a task, that subject would require extra activation of inhibitory circuits to compensate for the overactive action/command circuits. Thus we have now developed two hypotheses that could explain the behavioral outcomes of ADHD: one, an inhibitory-circuit deficit, and two, a hyper-activation of command-generating circuits and correlating compensatory inhibitory-circuit hyper-activation.

However, it is possible that other factors or abnormalities are resulting in deficits or hyperactivation of these circuits. If this were the case, than the two proposed explanations for ADHD in the previous paragraph would merely be symptoms of the disorder, not causes. Some

potential examples could range from irregular task-related reward or motivation attribution to inadequate ability to process interfering stimuli. Another candidate may be a neural disposition for attributing attention to a particular type of stimuli in a biased fashion (lacking adequate mediation or modulation of attention for PIS). This was proposed by Allport in 1980 and 1987 and also by Posner and Peterson in 1990 (Bush, 2010). The biasing of attention, also known as *selective attention,* was imagined to be 'selection for action' in ADHD participants (Bush, 2010).

Studies by Pardo et al. (1990) used PET imaging to contrast selective attention as produced by the Stroop task with a basic vigilance task to discover the brain regions responsible for the difference in task processing. The findings, supplemented with further studies by Corbetta et al. (1991), outline a circuit involving the ACC, frontal and parietal regions, also known as the cingulo-fronto-parietal (CFP) network (Bush, 2010). The resulting belief that this network is the primary circuit responsible for selective attention leads to questions regarding the abnormalities in ADHD patients for the CFP network.

Bush (2010) states that "the most consistent cross-study and cross-modality data identifying a region as dysfunctional in ADHD have been provided for the daMCC" which can also be referred to as the dorsal ACC. This region in particular is implicated in helping modulate motivational reward to influence motor responses (Bush, 2010). Specifically, the daMCC is believed to integrate information from multiple inputs to provide feedback-based decision-making mediation of the rest of the cognitive-reward-motor and CFP networks (Bush, 2010). A dysfunction of the daMCC could, therefore, reduce the efficacy of such modulation leading to inappropriate attention selection/PIS and altered decision-making due to abnormal feedback used for motivation attribution. These symptoms parallel those associated with ADHD.

If ADHD is produced from an activation abnormality, it would be of clinical relevance to

determine exactly how this abnormality can be detected. Furthermore, knowing the activation differences between ADHD and healthy participants could also help researchers further the understanding and theories relating to the CFP network and other circuits involved in attention, impulse regulation and response selection, among others. There are two possible magnitude deviations for a difference in region activation: increased or decreased activity. Decreased activation of the daMCC could likely support the theory that ADHD were a result of insufficient attention-regulation as it relates to aforementioned decision-making relevant feedback and motivation. Decreased activity in other regions of the CFP could communicate a deficiency in response inhibition. Alternatively, however, similar to the second hypothesis proposed in paragraph four of this section regarding inhibition, the daMCC or other CFP areas could present hyper-activation used for compensation of another (likely also hyper-activated) circuit.

Perhaps the most obvious neural candidate for ADHD is the circuit underlying response inhibition. Decreased ability to inhibit responses could likely be a result of altered mechanisms for reward, feedback-association, motivation attribution and attention selection as outlined above for the CFP network and, more specifically, daMCC. However, inhibition of response poses the most behaviorally-relevant process for ADHD behavior, for it can be implicated in all hallmark signs of ADHD: inattention, impulsiveness and hyperactivity. This hypothesis is supported by studies that demonstrate ADHD participants' increased likelihood to make errors of commission (false alarms), decreased ability to withhold a prepotent response or interrupt an ongoing response and slower response on tasks assessing inhibitory control (Menon, Reiss, Ringel & Tamm, 2004).

The 'Go/No-Go task' is often used by researchers to measure response inhibition in participants, and consists of frequent "go" trials and infrequent "no-go" trials that illicit an

inhibitory (of the typical "go") response in participants, and is generally used to evaluate prepotent tendencies. An fMRI study of this task by Schulz et al. (2004) compared ADHD to control participants to measure differences in region activation. The results of this study showed an increased activation of left and right ventrolateral inferior frontal gyrus, left anterior cingulate gyrus, and left medial frontal gyrus for ADHD participants during the inhibition tasks (Schulz et al., 2004). These data would support a compensatory activation of response inhibition for ADHD participants.

Tamm et al. (2004) also used fMRI in conjunction with the Go/No-Go task to measure neural activation differences relating to response inhibition for ADHD versus control participants. The findings show greater activation in the middle/inferior/superior temporal gyrus for ADHD participants, but greater activation in the right inferior frontal gyrus for control participants (Tamm et al., 2004).

Dickstein et al. (2006) performed a meta-analysis on similar studies using the "activation likelihood estimation" (ALE) technique to contrast neural activity across 16 neuroimaging studies. The results of this meta-analysis showed "significant patterns of frontal hypoactivity," including ACC (Bannon, Castellanos, Dickstein & Millham, 2006). A focus on response inhibition studies resulted in an increased likelihood for activation of the inferior prefrontal cortex, medial wall regions (including ACC), inferior frontal and precentral gyrus in control versus ADHD participants (Dickstein et al., 2006). These data leads to disagreement regarding a primary sub-region responsible for ADHD, but rather supports the hypothesis of an overall dysfunction in frontal-based circuitry.

The logical next step in determining neural circuits responsible for ADHD should address the findings of the ALE performed by Dickstein et al. (2006). Since no individual sub-region has

been identifiable for response-inhibition deficits in ADHD participants, but rather, findings have shown mixed results supporting either hyperactive compensation or hypoactive inhibition, a study is needed to measure the connectivity within the response inhibition network during an interference processing task to contrast ADHD and control participants. Based on the results of many of the studies outlined herein and the premise that ADHD participants have a deficit in inhibitory control, we predicted that ADHD participants would show a hypoactivation of neural circuits responsible for inhibitory control.

Method

Procedure Overview

The present study was designed to assess connectivity in the response inhibition network between ADHD and control participants. The multi-source interference task (MSIT) was selected as the event-based producer of interference processing and inhibition response due to its robust CFP network activation that can be consistently observed even in single participants. This allowed greater data confidence despite a relatively low number of participants. Participants performed the MSIT while undergoing fMRI for 120 incongruent, 120 congruent and 60 fixation trials.

Participants

Four patients with pediatric ADHD (14.65 +/- 3.01, range 10-17 years; 2 females, 2 males) and four healthy participants (13.85 +/- 2.66, range 10-16 years; 4 females) were studied as the experimental and control group, respectively. All participants were trained to be able to perform at greater than 70% accuracy. Movement during the experiment was considered acceptable if there existed less than 2 mm displacement and less than 2° rotation.

Imaging

Data acquisition was executed using a 3.0 T GE Signa scanner. The standard Psychiatric Affective Neuroimaging Laboratory (PANLab) technique for normalization was employed to allow for contrast and analysis of images. Outlined briefly, this process entailed a reverse spiral image acquisition sequence to measure the blood-oxygen-level dependence (BOLD) signal. This sequence acquired 40 brain image 'slices' at 3.0mm per slice every two seconds. The reverse spiral sequence attempts to minimize artifacts and signal dropout in key regions to allow the greatest accuracy during analysis.

Statistical Parametric Mapping 2 software (SPM5; Wellcome Department of Cognitive Neurology, London; www.fil.ion.ucl.ac.uk/spm) was used to complete the normalization sequence, which included standard preprocessing steps such as motion correction, stretching of images and noise removal. To align images onto the same anatomical space, a low resolution SPGR (Spoiled Gradient Echo) was taken around the same time as the functional imaging. The low-resolution images were used to align the reverse spiral sequence, and then high resolution SPGR images (taken disparate in time from the functional and low-resolution images) were used to enhance detail.

For a more detailed explanation of the neuroimaging methods used in this study, please refer to the appended document, "Neuroimaging methods," which is standardized language used by many researchers in the PANLab at the Department of Psychiatry of the University of Michigan.

Analysis: Aim Summary and Action Plan

The aim of this study was to measure and assess the connectivity within the response inhibition network during an interference processing task to contrast ADHD and control participants. This aim can be broken down into several interrelated questions:

A) Which brain regions are selectively activated during response inhibition and PIS as precipitated by the incongruent task scenario of the MSIT?

B) Of the regions identified in A, which region shows the strongest activation across all participants?

C) Which brain region more strongly matches region B in BOLD oscillation pattern during incongruent trials than congruent trials?

D) Which group exhibits a stronger 'coupling' or oscillation match of region C with region B, ADHD or control participants?

Answering these questions entailed many steps of image processing and analysis after data collection. Firstly, to analyze neural connectivity underlying a particular neural mechanism, a 'seed' region must be identified. Many regions of the brain are activated and exhibit 'coupling' or interconnectivity during virtually any task, thus it was necessary to isolate a region specifically implicated in PIS and response inhibition (questions A & B), which are the neural mechanisms meant to be investigated by this study, to function as the 'seed' region. Second, the seed region's BOLD oscillation pattern needed to be mapped and contrasted with all other brain regions to find regions with strong 'coupling' or connectivity (question C). Finally, the ADHD connectivity map needed to be contrasted with the control group's map (question D). Here is a breakdown of these steps employed to accomplish these ends:

1. Create individual BOLD image maps for each subject of both congruent trials and incongruent trials
2. For each individual, subtract the congruent activation map from the incongruent map
3. Average the resulting maps for both groups, control and ADHD, to isolate

activation in shared regions of interest (ROI) implicated in response inhibition and PIS

4. Use the strongest common ROI to perform independent connectivity analyses for each group
5. Compare the two resulting connectivity maps, ADHD versus control

While this thesis is solely meant to answer question D by reporting on steps 4 and 5, it is important to outline the necessary data and analysis used to accomplish this aim.

Analysis: Identifying the Seed Region

The original study used for this thesis was performed by Suzanne C. Perkins, Chandra Sripada, James Swain, Kate Fitzgerald, Julie Kaplow and Israel Liberzon (2010) of the Department of Psychiatry in the University of Michigan. Led by Perkins, the study aimed to isolate the brain regions selectively activated during the MSIT and discover any variations between ADHD and control. Thus the findings helped answer questions A and B and consisted of analysis steps 1-3 in addition to further steps done to contrast the activation patterns between groups. These additional steps and their results are just outside of the scope of this thesis, but will nonetheless be outlined in an attempt to give proper credit to Perkins et al.

Perkins et al. (2010) first derived activation maps for individual participants to contrast the incongruent versus congruent trial image data using MATLAB (2007a, The MathWorks, Natick, MA; www.mathworks.com/matlabcentral) (steps 1 and 2). Resulting maps were averaged within each group, ADHD and control, before a whole brain analysis was performed to compare incongruent versus congruent image data (step 3). Another contrast of incongruent versus congruent was performed for all participants. All analyses used a *p* value of .005 and a cluster size threshold of 5. Such a stringent *p* value was needed because of the huge number of

statistical tests computed for neuroimaging (one test for each voxel in the image), and further, a low *p* value helped control for false positives. A 'cluster' refers to the number of contiguous activated voxels. Voxels are essentially individual pixels in a brain map image.

Assessing Connectivity with a Psycho-physiological Interaction Analysis

Following the analysis of Perkins et al., the present study performed additional computations and comparisons using MATLAB. To determine connectivity between brain regions, a psycho-physiological interaction (PPI) analysis was executed. A PPI analysis aims to elucidate interactions between brain regions (physical component) in relation to the task environment (psychological component) as designed by the experiment. Thus, brain activity during the congruent and incongruent tasks was analyzed in relation to the activity of a seed region found by Perkins et al. that displayed robust and shared selective activation during the incongruent task. A PPI analysis attempts to report interactions in the brain by examining the degree of activity synchronization each brain region exhibits to the seed region. For this to make sense, one must first understand how regional activity appears in fMRI data.

As stated earlier, the fMRI data is based on the BOLD signal, which can be thought of as a measure of neural activity. When plotted over time for any particular region, this activity exhibits a wavelength pattern, with peaks and valleys, where each oscillation pattern (wavelength) tends to last between 1-10 seconds. To assess connectivity, the PPI analysis compares the oscillation pattern of a seed region to every other region of the brain. The greater a region matches in oscillation to the seed region, the greater connectivity or 'coupling' that region exhibits with the seed. Figure 1 shows two cases: correlated oscillation between two regions and anti-correlated oscillation between two regions. The former case entails a coupling of regions, whereas the latter does not (instead, the regions are likely disjointed).

Thus a PPI analysis was done across subject groups and between congruent and incongruent data, using a seed region discovered by Perkins et al. with a p-value of .005. Within each group, correlation statistics were computed for voxels in both congruent and incongruent trial data. For each group, voxels displaying enhanced seed coupling during incongruent trials were mapped for each group by subtracting the congruent correlation statistics from the incongruent correlation statistics (step 4). Finally, the two PPI maps (ADHD and control) were contrasted against each other to determine variations in connectivity (step 5).

Results

Imaging Data

The MSIT produced robust activation of CFP network regions during the incongruent trials. The analysis done by Perkins et al. comparing congruent to incongruent image data averaged for all participants yielded an activation map showing significantly ($p < .005$) higher activation in the posterior medial frontal cortex ($Z = 3.06$; 0, 9, 51) and specifically in the supplementary motor area (including pre-SMA), right inferior frontal gyrus, insula and operculum during the incongruent trials. This map is shown in Figure 2. The same activation map resulted from incongruent - congruent analysis for each group (ADHD and control), yet when group maps were contrasted, the ADHD participants' map exhibits increased ACC activity (Figure 3).

The pre-SMA exhibited the most consistent, robust and non-group-specific activation from the incongruent - congruent contrasts performed by Perkins et al. (2010), thus, the pre-SMA was used as the seed region for the double-contrast PPI connectivity analysis. In each group, the right inferior frontal gyrus (rIFG) demonstrated the highest degree of coupling with the seed region (pre-SMA). Next, the PPI map of the ADHD participants was contrasted to that of the

control participants. The resulting map (Figure 4) demonstrates increased oscillation (positive connectivity) correlation of the rIFG with the pre-SMA seed region for ADHD versus control participants, at MNI co-ordinates: x = 51, y = 27, z = -9 and t = 4.68, which coincides with a *p* value of less than .001.

Behavioral Data

There was no performance difference between subject groups on the MSIT.

Discussion

As attention regulation, interference processing and response inhibition ability all profoundly influence behavior, intelligence and task-performance, it is of great scientific and clinical interest to determine underlying neural mechanisms. Combining the MSIT, a robust task capable of activating interference processing circuits, with a set of ADHD participants who exhibit symptoms of a deficit in the same interference processing circuits allows for a powerful and data-rich neuroimaging study that can hopefully help elucidate the neural underpinnings of response inhibition. While single-contrast analyses in this field of study have left researchers with inconclusive results implicating any particular sub-region for ADHD or response inhibition, this study employs a wholly new (for this field) mechanism of double-contrast PPI analysis, which should dramatically enhance the likelihood for the correct identification of underlying neural circuits.

The analysis by Perkins et al. yielded activation data consistent with previous studies of PIS and response inhibition, which was the desired result of the MSIT. The pre-SMA was chosen as the seed region due to both its strong activation in this study and because PANLab has performed over four other MSIT studies whose results also showed the pre-SMA to have the most reliable activation in incongruent – congruent trials. The present study demonstrated a

hyperactivation of the pre-SMA in ADHD versus control participants, which was contrary to the hypothesis, but consistent with several other studies (Tamm et al., 2004), (Schulz et al., 2004). Dickstein et al. (2006) suggests that the finding of higher pre-SMA activity is more reliable in kids than adults, and says insula/inferior frontal gyrus is higher in ADHD than controls, which may also help explain the findings. However, it is clear that future studies are needed to clarify the role of the SMA and IFG in cognitive control in light of the findings of this study, particularly pertaining to ADHD.

ADHD participants demonstrated greater rIFG coupling with pre-SMA during incongruent trials than control participants. In simpler terms, ADHD participants exhibited greater inhibition circuit connectivity, because the rIFG purportedly 'talked' more to the pre-SMA in ADHD than control participants, which suggests that the inhibitory control network is more interconnected (and perhaps functioning more powerfully) in ADHD participants. This finding supports a compensatory hypothesis, meaning that this increased connectivity and activation within inhibitory circuitry is needed for ADHD participants to perform tasks as well as controls. However, this conclusion requires further research to determine why the compensation is necessary.

Perhaps the rIFG's signal is hindered or in some way diminished in ADHD participants, and thus requires greater activation to achieve the same behavioral result. Another possibility is that there is greater activation or salience for a particular set of actions or command/impulse generating circuits, and so the rIFG must be activated more strongly to compensate. Future research is needed to determine what specific process is controlled by the coupling of pre-SMA with rIFG.

This was one of the first MSIT incongruent versus congruent contrast coupling studies

ever performed. All data presented demonstrates increased activation in neural regions and circuitry implicated in processing interfering stimuli, inhibiting response and focusing attention for ADHD participants than in controls. This is truly a puzzling finding without any evidence for hyperactivation in impulse-generating circuitry. Hopefully future research will address this discrepancy and determine for what this increased inhibitory activity is needed to compensate. By continuing to map inhibition response and PIS neural circuitry in future research, it may be possible to determine causes and treatments for ADHD.

However, there are several limitations to the PPI analysis technique employed in addition to other aspects of the study. The 'findings' of the PPI connectivity analysis are based on *correlations* in oscillation pattern. Thus, the PPI analysis is an indirect measure of connectivity between brain regions, and certainly does not prove causation. Instead, regions that match in oscillation pattern are merely likely candidates for having connectivity with one another; thus, researchers cannot truly be sure what ‘tighter’ ‘coupling’ actually entails. Future research is required to explicate coupling and interconnectivity both overall and specifically in the CFP network. Finally, the sample size for this study was very small, with only 8 participants analyzed.

Future studies can help determine if the implications from the findings of this study are correct. If methylphenidate and other pharmaceuticals directly address the neural abnormalities of ADHD patients, than it would be feasible for a similar study, which substituted ADHD participants on placebo for the control group and ADHD participants on methylphenidate for the experimental group, to demonstrate the same findings. In addition to validating these findings, it is important for future studies to continue mapping neural coupling in regions associated with cognitive control to help understand why compensatory activity occurs in ADHD participants.

Discovering the details of these mechanisms will not only help with the diagnosis and treatment of ADHD, but may also suggest new ways for enhancing cognitive control.

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Figure 1. Demonstration of BOLD signal oscillation patterns. The image on the left depicts correlated oscillation between two regions while the image on the right depicts anti-correlated oscillation between two regions. The former case entails a coupling of regions, whereas the latter does not (instead, the regions are likely disjointed).

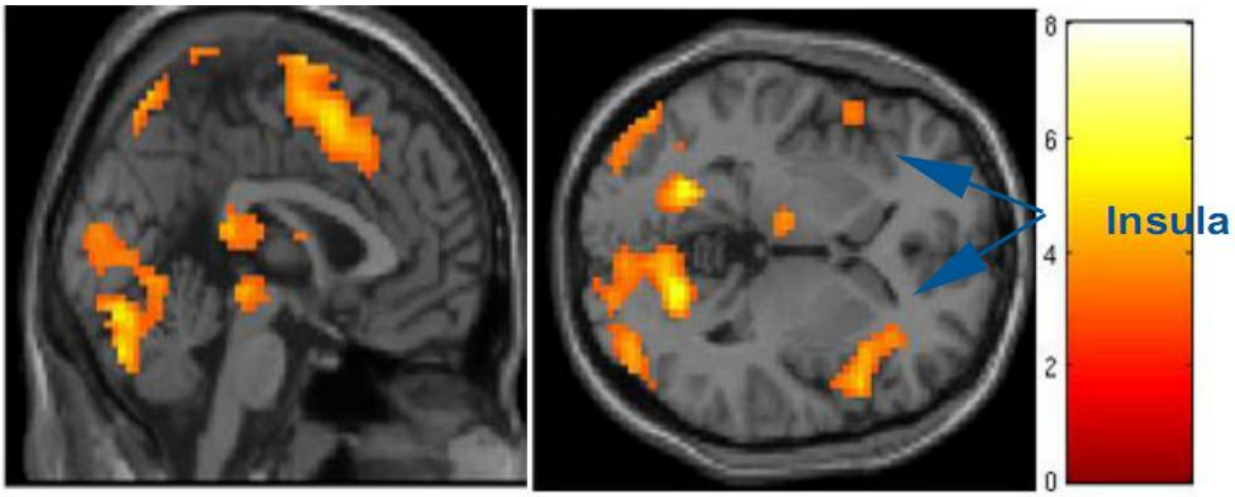

Figure 2. Analysis done by Perkins et al. (2010) comparing congruent to incongruent image data for all participants. This map shows significantly ($p < .005$) higher activation in the posterior medial frontal cortex ($Z = 3.06$; 0, 9, 51) and specifically in the supplementary motor area (pre-SMA), right inferior frontal gyrus, insula and operculum during the incongruent trials.

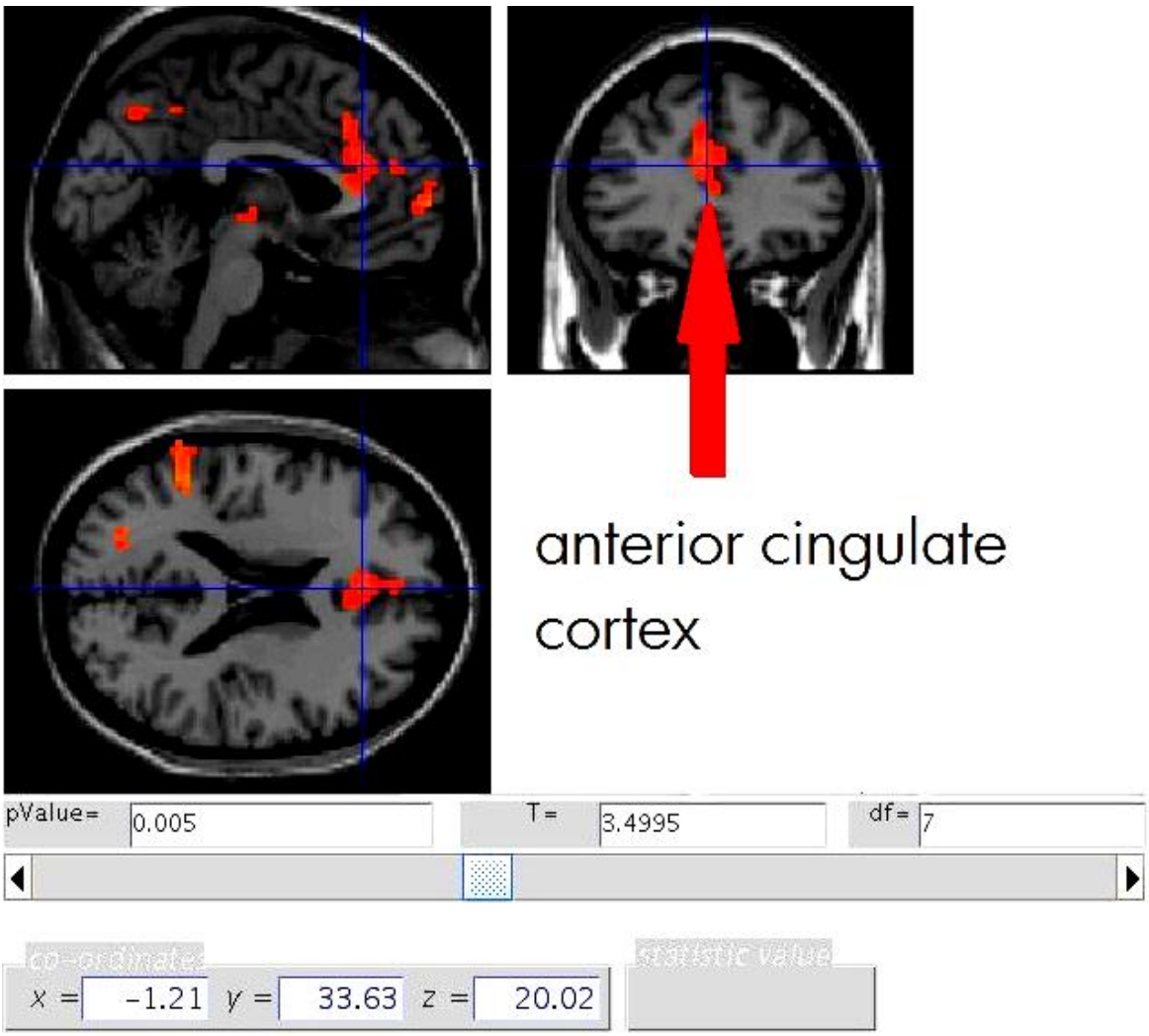

Figure 3. ADHD versus control contrast of incongruent - congruent activation maps. This figure demonstrates that the ADHD group's activation map for incongruent versus congruent tasks exhibited increased ACC activity as compared to the control group's map.

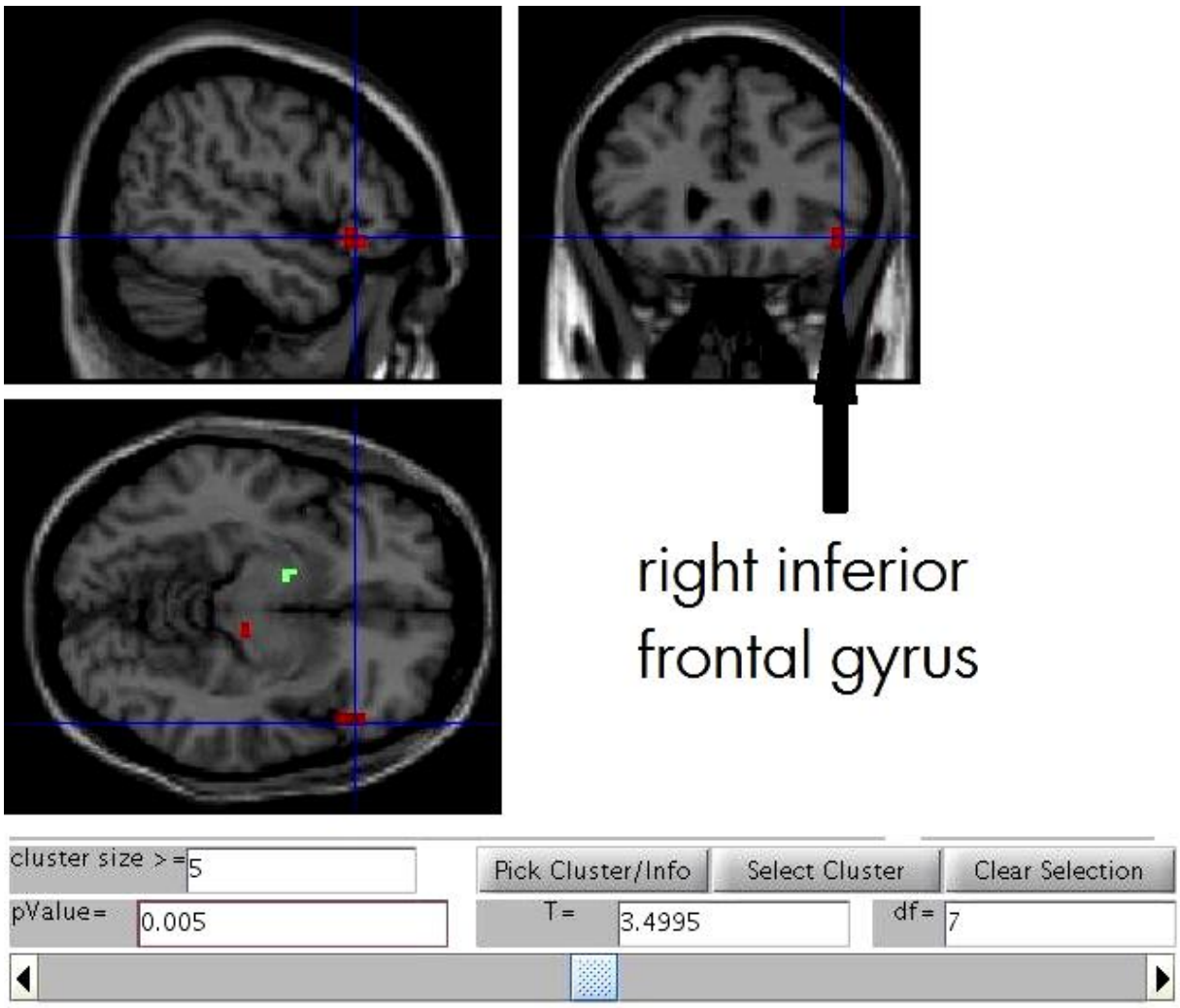

Figure 4. Contrast of ADHD group's PPI map with control's map. The ADHD group exhibited greater coupling of the rIFG to the pre-SMA seed than the control group.

Appendices

Neuroimaging methods

MRI scanning occurred on a General Electric (Waukesha, WI) 3T Signa scanner [LX (8.3) release, neurooptimized gradients]. Scanning began with structural acquisition of a standard T1 image (T1-overlay) for anatomic normalization and alignment. A T2*-weighted, reverse spiral acquisition sequence [GRE; repetition time, 2000 ms; echo time, 30 ms; flip angle, 90°; field of view (FOV), 20 cm; 40 slice; thickness/skip, 3.0/0 mm matrix size equivalent to 64 X 64], which has been shown (Glover and Law 2001) to minimize signal drop-out in regions such as ventral striatum and orbitofrontal cortex that are vulnerable to susceptibility artifact. After discarding four initial volumes to permit thermal equilibration of the MRI signal, 200 volumes were acquired per run. After acquisition of functional volumes, a high-resolution T1 scan was obtained for anatomic normalization [three-dimensional spoiled gradient-recalled acquisition in a steady state (SPGR); 24 FOV; thickness/skip, 1.0/0 mm]. Stimuli were presented and responses recorded using a computer running E-prime (Psychology Software Tools, Pittsburgh, PA), interfaced to project stimuli onto MR-compatible liquid crystal display goggles (Resonance Technology, Northridge, CA). Choices were made using an MRI-compatible button box.

Neuroimaging Analysis

Data from all 8 participants met criteria for high quality (uniformity and homogeneity of T2* images in regions such as ventral striatum and orbitofrontal cortex prone to susceptibility artifact) and scan stability (motion correction <2mm displacement), and were subsequently

included in the data processing. Preprocessing steps were implemented using Statistical Parametric Mapping 2 software (SPM5; Wellcome Department of Cognitive Neurology, London; www.fil.ion.ucl.ac.uk/spm). Preprocessing followed conventional procedures: 1) slice time correction; 2) spatial realignment; 3) normalization to the structural (T1-weighted) Montreal Neurologic Institute (MNI) template through the use of nonlinear warping algorithm followed by resampling by sync interpolation resulting in a voxel size of 3x3x3mm; 4) spatial smoothing through the use of a Gaussian 5mm full-with-half-maximum kernel; 5) high-pass temporal filtering with a cut-off of 128 s to remove low-frequency drifts in signal. After preprocessing, statistical analyses were performed at the individual and group level using the general linear model (GLM) and Gaussian random field theory as implemented in SPM5.

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