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Neural correlates of inhibitory control in adult ADHD: Evidence from the Milwaukee longitudinal sample

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Abstract

Only a few studies have investigated the neural substrate of response inhibition in adult ADHD using Stop-Signal and Go/No-Go tasks. Inconsistencies and methodological limitations in the existing literature have resulted in limited conclusions regarding underlying pathophysiology. We examined the neural basis of response inhibition in a group of adults diagnosed with ADHD in childhood and who continue to meet criteria for ADHD while addressing limitations present in earlier studies. Adults with ADHD ($n=12$) and controls ($n=12$) were recruited from an ongoing longitudinal study and were matched for age, IQ, and education. Individuals with comorbid conditions were excluded. Functional MRI was used to identify and compare the brain activation patterns during correct trials of a response inhibition task (Go/No-Go). Our results showed that the control group recruited a more extensive network of brain regions than the ADHD group during correct inhibition trials. Adults with ADHD showed reduced brain activation in the right frontal eye field, pre-supplementary motor area, left precentral gyrus, and the inferior parietal lobe bilaterally. During successful inhibition of an inappropriate response, adults with ADHD display reduced activation in fronto-parietal networks previously implicated in working memory, goal-oriented attention, and response selection. This profile of brain activation may be specifically associated with ADHD in adulthood.

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Keywords

functional magnetic resonance imaging (fMRI); attention deficit hyperactivity disorder; response inhibition; adult psychiatry; attention; impulsivity

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a neurobehavioral disorder characterized by developmentally inappropriate levels of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 1994). ADHD is often considered a childhood disorder, as it occurs in 1-5% of children (Faraone and Biederman, 2005). However, ADHD also occurs in 1-7% of adults (Simon et al., 2009), and prospective longitudinal follow-up studies show that rather than normalizing with increasing age, ADHD persists into adulthood in 4-66% of individuals diagnosed in childhood (Weiss et al., 1985; Mannuzza et al., 1998; Rasmussen and Gillberg, 2000; Barkley et al., 2002).

Psychological theories have proposed that ADHD symptoms follow from a primary deficit in inhibitory control (Barkley, 1997; Quay, 1997). Functional neuroimaging studies suggest that a network of fronto-parietal brain regions is implicated in motor response inhibition as assessed by Stop-Signal and Go/No-Go tasks. Brain regions implicated include inferior prefrontal, medial prefrontal (including the pre-supplementary motor area), and inferior parietal areas (for review see Chambers et al., 2009). Lesion and transcranial magnetic stimulation (TMS) studies suggest that two subregions of prefrontal cortex, the right inferior frontal gyrus (IFG) and the pre-supplementary motor area (pre-SMA), are critically involved in inhibitory control, as patients with lesions to these regions and healthy participants undergoing TMS to these regions perform “Stop” and “No-Go” trials of the Stop-Signal and Go/No-Go tasks more slowly and less accurately than healthy controls (Aron et al., 2003; Chambers et al., 2006; Floden and Stuss, 2006; Picton et al., 2007; Chen et al., 2009). Taken together, these studies provide compelling evidence that the frontal lobes play a critical role in response inhibition, and that the pre-SMA and the right IFG represent subregions of the frontal lobes that are critically related to inhibitory control.

The theory that individuals with ADHD have deficits in response inhibition that follow from dysfunction of the frontal lobes is consistent with several different lines of research. Individuals with ADHD demonstrate behavioral impairments relative to healthy control participants on “Stop” and “No-Go” trials of the Stop-Signal and Go/No-Go paradigms. Differences in performance have been observed in samples of ADHD children (Trommer et al., 1988; Tamm et al., 2004; Lijffijt et al., 2005) and in samples of ADHD adults (Bekker et al., 2005; O'Connell et al., 2009; Burden et al., 2010). Functional neuroimaging studies have shown that when children with ADHD perform “Stop” and “No-Go” trials on the Stop-Signal and Go/No-Go paradigms they display reduced activation in the frontal lobes compared to matched healthy control participants (Dickstein et al., 2006; Rubia et al., 2008; Suskauer et al., 2008; Passarotti et al., 2010). Clinical reports and longitudinal data have also shown that adults with ADHD exhibit a pervasive pattern of disinhibition in several major life activities including money management, excessive substance abuse, and gambling (Barkley, 2008). Taken together, this data suggests that the neural correlates of inhibitory control are dysfunctional in adults with ADHD.

Functional neuroimaging studies have only very recently begun to investigate the neural correlates of response inhibition in adults with ADHD using Stop-signal and Go/No-Go tasks. Five fMRI studies that compared groups of adults diagnosed with ADHD to matched controls while each group performed the same Stop-Signal or Go/No-Go task have yielded

inconsistent findings (Epstein et al., 2007; Dibbets et al., 2009; Cubillo et al., 2010; Dillo et al., 2010; Kooistra et al., 2010). Three of the studies reported that adults with ADHD demonstrate increased prefrontal activation while inhibiting a motor response (Epstein et al., 2007; Dibbets et al., 2009; Kooistra et al., 2010). This is consistent with a recently proposed hypothesis suggesting that adults with ADHD may rely on the frontal lobes to compensate for primary dysfunction in other brain regions (Halperin and Schulz, 2006). However, two studies have reported that adults with ADHD demonstrate reduced activation of frontal brain regions while inhibiting a motor response (Epstein et al., 2007; Cubillo et al., 2010). This supports the alternative claim that dysfunction of frontal lobes is directly related to deficits in response inhibition in individuals with ADHD (Rubia et al., 1999; Booth et al., 2005).

There may be several reasons for the inconsistent findings. First, prospective longitudinal follow-up studies suggest that retrospective self-report of ADHD symptoms may be inaccurate (Barkley et al., 2002; Mannuzza et al., 2002), calling into question whether the participants in three studies that used retrospective diagnosis of ADHD (Epstein et al., 2007; Dibbets et al., 2009; Dillo et al., 2010) were assigned to the appropriate experimental group.

Secondly, the potential influence of comorbid psychiatric disorders on the outcome of functional neuroimaging studies should also be considered. Although four of the studies reported that they excluded comorbid conditions, two studies excluded participants based on report of psychiatric disorder rather than on the results of structured psychiatric interviews (Dibbets et al., 2009; Kooistra et al., 2010). Furthermore, two studies did not exclude comorbidities that are commonly present in adults with ADHD including learning disabilities and current use of substances (Epstein et al., 2007; Cubillo et al., 2010). These approaches raise questions as to whether the functional neuroimaging patterns described in these studies were specifically related to ADHD (Adler et al., 2005; Leibenluft et al., 2007; Paloyelis et al., 2007; Cubillo and Rubia, 2010).

Thirdly, methodological issues may have contributed to the inconsistent findings. Four of the studies used an event-related design, while one study utilized a block design. Interestingly, the four that used event-related examined activation associated with correct trials only and found that ADHD and control participants activated the prefrontal cortex to a different degree during inhibition of a prepotent motor response (Epstein et al., 2007; Dibbets et al., 2009; Cubillo et al., 2010; Kooistra et al., 2010), while the study that used a block design did not find activation differences in the frontal lobes (Dillo et al., 2010). Several authors have noted that block designs may be more susceptible to a variety of functional neuroimaging confounds, including effects of task difficulty, response preparation, habituation, different stimuli, maintenance of stimulus-response associations, changes in set, stimulus analysis, processing of conflict and error, novelty processing, mixed event types, and frequency of motor events (Garavan et al., 2002; Tamm et al., 2004; Paloyelis et al., 2007; Simmonds et al., 2008). Additionally, it is not possible to examine brain activation associated with correct trials within the context of a block design.

Finally, a recent meta-analysis that examined the neural correlates of response inhibition in healthy samples noted that another possible factor that could contribute to variable functional neuroimaging findings when using the Go/No-Go task is contrast of “Go” and “No-Go” trials (Simmonds et al., 2008). The meta-analysis examined the results of 11 event-related fMRI studies that administered the Go/No-Go task to healthy individuals, and suggested that although the contrast of “No-Go” and “Go” trials would reveal areas of the brain that were uniquely involved in response inhibition and selection, this type of contrast would also fail to associate any brain region that contributed to both cognitive processes, such as the pre-SMA. Interestingly, none of the five studies that examined the neural correlates of response inhibition in adults with ADHD contrasted brain activation patterns

associated with “No-Go” trials against implicit task baseline, and, likely, this is why none of these studies found activation differences between ADHD and control participants that were located in the pre-SMA despite this region's critical role in response inhibition.

The five previous studies in adults with ADHD provided inconsistent results and may have been confounded by issues that were related to sample assessment, functional neuroimaging design and analysis. For this reason, the aim of the current study was to examine the neural correlates of response inhibition in adults with ADHD while addressing these previous limitations. To ensure that adults in our sample had symptoms of ADHD in childhood as well as in adulthood and were therefore assigned to the correct experimental group, we examine an adult ADHD sample that was recruited from an ongoing longitudinal study (Barkley, 2008). To confirm that resulting brain activation patterns were specifically associated with ADHD, we exclude individuals with current psychiatric or neurological comorbidities. To avoid potential confounds associated with fMRI block designs and to be able to compare our neuroimaging findings with those of other studies that have used the same task, we administer an event-related version of the Go/No-Go task that has been studied within samples of healthy participants (Garavan et al., 1999; Garavan et al., 2002; Garavan et al., 2003; Hester et al., 2004a; Kelly et al., 2004). To reveal activation in a network of brain regions associated with the act of inhibiting a prepotent response without eliminating brain regions that may play an important role in both response selection and inhibition we contrast activation associated with “No-Go” trials against an implicit task baseline. We perform this contrast prior to testing whether ADHD and control participants demonstrate differences in mean hemodynamic response during the correct performance of “No-Go” trials within the boundaries of functionally-defined brain regions of interest defined by the contrast of “No-Go” trials with implicit task baseline.

In keeping with the theory that dysfunction of the frontal lobes is associated with deficits in response inhibition in individuals with ADHD, we hypothesized that our sample of adults with ADHD would demonstrate less accurate performance and less prefrontal activation than controls during “No-Go” trials. More specifically, we predicted that our group of adults with ADHD would demonstrate reduced activation in subregions of prefrontal cortex thought to play a critical role in response inhibition, such as the right IFG and the pre-SMA.

2. Methods

2.1 Participants

Participants were recruited from a long-term, prospective, longitudinal study of “hyperactive” and IQ-matched control children ($n = 158$) (Barkley et al., 1985; Barkley et al., 2002; Barkley, 2008). ADHD participants were originally recruited from consecutive clinic referrals, and continue to meet criteria for combined type ADHD. Individuals in the longitudinal control group ($n = 81$) were originally recruited using a “snowball” technique in which parents of the hyperactive children provided names of friends who had children within the same age range of the hyperactive participants.

We recruited 12 adult males from the original longitudinal “hyperactive” group and 12 adult males from the original control group. All ADHD participants met diagnostic criteria for ADHD in adulthood based on their parents' report of current DSM-IV ADHD symptoms (number of current ADHD symptoms > 1.5 SD of control group mean) (Barkley et al., 2002). Exclusion criteria for both groups included: 1) DSM-IV Axis I diagnosis, as defined by the Structured Clinical Interview for the DSM-IV, non-patient version (SCID-NP); 2) history or current evidence of learning disability, operationally defined by any Wide Range Achievement Test–3rd edition (WRAT-3) score below the 7th percentile; 3) Wechsler Adult Intelligence Scale–3rd edition (WAIS-III) Vocabulary and Block Design scaled scores < 6 ;

4) history of neurological disorders/conditions; 5) dependence on or daily use of alcohol or marijuana, as determined by the SCID-NP; 6) current use of cocaine, illicit stimulants, hallucinogens or inhalants; or 7) evidence of recent alcohol or psychoactive drug use as determined by breath and urine testing. Each of the formerly “hyperactive” subjects had, at minimum, a three-week, double-blind, placebo-controlled stimulant trial (Barkley, 2008). Many of the participants were on a stimulant for longer periods of time during their childhood and adolescence. Only one of the ADHD subjects was taking a stimulant at the time of the study, and he was required to go off his medication 48 hours before he participated in the fMRI session. All participants were right-handed. The two groups did not differ significantly in age, years of education, or overall estimated IQ, but the control group scored higher on WAIS-III Vocabulary (Table 1). All participants provided written informed consent approved by the institutional review board at Medical College of Wisconsin, and \$50.00 was offered as compensation for participation in the study.

2.2 Response inhibition task, Go/No-Go

Our version of the Go/No-Go task followed a format described previously (Garavan et al., 1999). Participants saw a series of lower case letters replacing one another (500 ms/letter). During an initial practice session to establish a prepotent response to target letters, participants were instructed to make a button press response quickly and accurately whenever certain target letters (“x” or “y”) were presented within a series of distracter letters (2 runs, 250 letters, 75 targets). Following practice, a switch in the rules was made which stipulated that responses to “x” or “y” should only be made if the two target letters alternated in the presented series (Figure 1). Response to targets constituted the “Go” condition of this task whereas the presentation of “lure” letters, to which a prepotent response has been practiced but becomes inappropriate, constituted the “No-Go” condition. Participants completed 6 runs of the alternation task in the scanner with 250 letters per run (1500 total letters). “No-Go” letters were presented every ~ 20 s and targets every 3.5 s. The six scanning runs and the last practice run consisted of an average of 36 “Go” letters and 7 “No-Go” letters per run. Response prepotency was maintained by including five times more valid “Go” letters than “No-Go” letters and through prior instructions that stressed fast responding. Participants were encouraged to respond while the stimulus was still on screen, but responses were considered valid if they responded within 1000 ms of stimulus onset.

2.3 Magnetic resonance imaging and processing

Whole-brain imaging was performed on a Signa GE 1.5 Tesla scanner equipped with a prototype 30.5 cm i.d. three-axis local gradient head coil and an elliptical endcapped quadrature radio frequency coil. Prior to functional imaging, high resolution, 3D spoiled gradient-recalled at steady state anatomic images were collected [TE = 5 ms; TR = 24 ms, 40 flip angle, slice thickness = 1.2 mm, FOV = 24² cm, matrix size = 256 × 192] for precise anatomical reference.

Multi-scan series of images were acquired using a single-shot, gradient-echo echo-planar pulse sequence with initial pi/2 pulse [TE = 40 ms; TR = 2500 ms; 90 flip angle; slice thickness = 6 mm; FOV = 24 cm; matrix size = 64²]. To provide coverage of the entire brain 22 contiguous sagittal slices were selected. Data were acquired from six runs of 66 sequential echo-planar images collected within 165 s per run with an interscan interval of ~30 s.

Image processing and analyses were performed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). After discarding the first three images from each run, linear de-trending algorithms available within the AFNI program were applied to the functional

data. Images were then concatenated by run and spatially registered in three-dimensional space using an iterative linear least squares algorithm.

2.4 fMRI analysis

2.4.1 Individual models of functional activity—To derive the magnitude of hemodynamic response to each task condition, variations in the linearly-detrended, motion-corrected, concatenated time-series data were then modeled using onset times associated with each trial type, a γ -variate function, and a nonlinear regression optimization procedure (Garavan et al., 1999). The maximum hemodynamic lag associated with the γ -variate function was constrained to a range similar to previously published estimates (Cohen et al., 1997), and the magnitude parameter of the model was free to vary. The regression yielded a separate estimate of the peak hemodynamic response to correct “Go” and “No-Go” trials within every voxel in the brain, making no assumptions about relative magnitude. Estimates of motion from each dimension of space were included in the individual model as covariates of no interest. Baseline hemodynamic activity during distracter letters was also allowed to vary freely in the model.

2.4.2 Group activation maps associated with the contrast of correct “Go” and “No-Go” trials—Data for all participants were transformed into stereotaxic space (Talarach and Tourneaux, 1988) to allow direct voxel-by-voxel statistical comparisons to be performed across participants. The stereotactically resampled statistical parametric maps were spatially averaged over a 6 mm radius. In an attempt to identify a network of brain regions specifically associated with response inhibition, peak hemodynamic changes associated with correct “Go” trials and “No-Go” trials were contrasted directly against each other using voxelwise two-sample, two-tailed t-test comparisons (uncorrected $\alpha = p < 0.0005$). Separate voxelwise maps were constructed for the ADHD and the control groups so that brain regions exhibiting greater magnitude during “No-Go” trials could be identified in either group (see section 2.4.4 “fMRI-fROI analysis”). Voxels not spatially contiguous to a cluster with a minimum volume of 350 μ l were removed in order to control for Type I error. This approach accords to theory suggesting that as the number of contiguous voxels that make up a cluster of voxels considered to be activated increases the likelihood that this cluster was falsely identified by chance decreases (Forman et al., 1995). Additionally, p values estimating the probability that a particular cluster may have been falsely identified using our uncorrected α and minimum cluster size thresholds (Type I error) were generated on a cluster by cluster basis using a Monte Carlo permutation procedure implemented in AFNI (AlphaSim). The program estimated the probability that each cluster identified within the map at a particular uncorrected α level was the result of Type I error based on its size, the level of smoothness associated with the data, and 1,000 random image permutations. To protect against the possibility that our thresholding procedures were too stringent in relation to this contrast and that the resultant activation maps may have suffered from Type II error, we also considered activation patterns present at a more lenient threshold (uncorrected $\alpha = p < 0.005$, 200 μ l minimum cluster volume).

2.4.3 Group activation maps associated with correct “No-Go” trials—To reveal a network of brain regions associated with “No-Go” trials including those brain regions that may make significant contributions to “Go” and “No-Go” trials, peak change associated with correct “No-Go” trials was contrasted against an implicit task baseline (i.e., 0) through use of voxelwise one-sample, two-tailed t-test comparisons at uncorrected $\alpha = p < .0005$ and minimum cluster volume of 350 μ l. We again attempted to estimate the probability of Type I error associated with each cluster observed in the resultant maps using the same Monte Carlo procedures described above, and again constructed separate voxelwise maps for the

ADHD and the control groups so that brain regions recruited by either group could be identified (see below).

2.4.4 fMRI-fROI analysis—As a follow-up to the voxel-wise analyses, a functional region of interest (fROI) analysis using a conjunctive “OR” mask was conducted (Poldrack, 2007). Use of a conjunctive “OR” mask is a common method for creating functionally defined ROIs based on identifying a set of task-associated brain regions recruited by either group (Celone et al., 2006; Mitsis et al., 2008; Roberts et al., 2009; Seidenberg et al., 2009). This method permits hypothesis testing within the spatial extent of meaningfully defined regions of interest while minimizing bias towards either group, and it has improved statistical power over voxel-wise approaches. To create the “OR” mask, a single fROI map was generated by conjoining activated regions identified in the voxelwise analysis across the groups. Any voxel considered to be “activated” in the “No-Go” versus implicit task baseline comparison contributed to the final conjunctive fROI map. To perform follow-up comparisons that examined group differences in hemodynamic response within each fROI, an averaged peak hemodynamic response was calculated for all voxels within an fROI for each participant. Two-sample, two-tailed unequal variance t-tests were used for all comparisons given the small sample size.

2.4.5 Common Areas of Recruitment: Go and No-Go trials—To identify brain regions that may have made contributions to both “Go” and “No-Go” trials, a conjunction analysis (i.e., “AND” mask) was also performed following the Minimum Statistic compared to the Conjunction Null method (MS/CN) described by Nichols et al. (2005). This was achieved in a series of steps. First, peak changes associated with correct “Go” and “No-Go” trials were each contrasted separately against an implicit task baseline (i.e., 0) through use of voxelwise one-sample, two-tailed t-test comparisons at uncorrected $\alpha = p < .0005$ and a minimum cluster volume of 350 μl . Separate voxelwise maps for the ADHD and the control groups were constructed so that brain regions recruited by either group during the performance of each trial type could be identified. Second, separate “OR” maps were constructed in relation to “Go” and “No-Go” trials that described activation demonstrated by either group during the performance of each trial type. Third, maps associated with each trial type were then converted to binary code (1 = activated, 0 = not activated) and added to one another in order to identify brain regions common to both trial types (as demonstrated by either group). To perform follow-up comparisons that examined group differences in hemodynamic response within each fROI identified within this “AND” mask, an averaged peak hemodynamic response was calculated for all voxels within an fROI for each participant in relation to each trial type.

3. Results

Mean accuracy ($\pm$ SD) on “Go” trials was 94% ($\pm$ 3%) for the control group and 94% ($\pm$ 3%) for the ADHD group. Mean accuracy ($\pm$ SD) on “No-Go” trials was 89% ($\pm$ 8%) for the control group and 79% ($\pm$ 25%) for the ADHD group. There was no significant difference between the ADHD and Control groups' performance on “Go” [$t(1, 21) = 0.08, P = 0.94, d = 0.03$] or “No-Go” trials [$t(1, 13) = 1.31, P = 0.21, d = -0.53$].

Direct contrast of peak activation associated with “Go” and “No-Go” trials failed to reveal any significantly activated brain regions in either group at our selected voxelwise and minimum cluster volume thresholds. When we relaxed our thresholds (uncorrected $\alpha = p < 0.005$, 200 μl minimum cluster volume), one region, the right angular gyrus, was identified as exhibiting greater activation during “No-Go” trials than during “Go” trials in at least one of our experimental groups (Table 2). However, posthoc estimation of the probability of Type I error associated with this cluster using Monte Carlo permutation suggested that we

could not reject the possibility that this cluster may have been identified as activated by chance (Table 2; $p < 0.99$). Follow-up analyses of mean magnitude of response within this brain region did suggest, however, that the control group demonstrated significantly greater activation than the ADHD group within this brain region during the performance of correct “No-Go” trials.

During correct “No-Go” trials, the pattern of brain regions activated by each group was similar for ADHD and control participants (Figure 2). Conjunctive “OR mask” fROI analyses were performed to identify regions activated by either group (Table 3, Figure 2, Figure 3). Follow-up analyses revealed areas of significant difference in magnitude of brain response between groups (Table 3, Figure 3).

The control group demonstrated significantly greater mean magnitude of activation than the ADHD group in six regions during the correct performance of “No-Go” trials: right frontal eye field (FEF), right pre-SMA, right inferior parietal lobe, left inferior parietal lobe, left precentral gyrus, and left precuneus (Table 3, Figure 3). However, Monte Carlo permutation suggested that we could not reject the possibility that the cluster located in left precuneus may have been identified as activated by chance (Table 2; $p < 0.19$). There were no brain regions in which the ADHD group demonstrated significantly greater magnitude of activation than the control group.

Zero-order correlations calculated between “No-Go” related brain activity and accuracy of performance and between “No-Go” related brain activity and current ADHD symptoms were not significant.

The results of the conjunction analysis using the MS/CN method showed that there were five regions in which the ADHD group or the control group demonstrated common activation during the correct performance of “Go” and “No-Go” trials (Table 2): right FEF, right pre-SMA, right IFG, and bilateral inferior parietal lobe. Follow-up analyses of mean magnitude of response within these brain regions suggested that the control group did not demonstrate significantly greater mean activation than the ADHD group within any of these commonly recruited brain regions during the correct performance of “Go” trials (Table 2). However, during correct performance of “No-Go” trials, the control group demonstrated greater mean activation magnitude than the ADHD group in some of the regions that were commonly recruited during “Go” and “No-Go” trials (Table 2) including regions of the right FEF and the right pre-SMA.

4. Discussion

The current study examined a well-characterized sample of adults with ADHD from an ongoing longitudinal study that did not include individuals with comorbid conditions. As such, the observed differences in brain activation between individuals with ADHD and controls are unlikely to be due to factors that may be related to inaccurate retrospective assessment of ADHD symptoms or due to disorders that are often comorbid with ADHD. Consistent with the hypothesis that dysfunction of the frontal lobes is present in individuals with ADHD and consistent with functional neuroimaging studies that have investigated the neural correlates of response inhibition in ADHD children (Dickstein et al., 2006; Rubia et al., 2008; Suskauer et al., 2008; Passarotti et al., 2010), our study suggests that ADHD adults display less activation than controls during inhibition of a prepotent motor response.

Participants in our two experimental group were observed to activate a predominantly right-lateralized frontoparietal network of brain regions during the correct performance of “No-Go” trials. Regions identified through contrast of “No-Go” trials with implicit task baseline included areas that have been previously associated with inhibitory control such as the right

IFG and medial prefrontal cortex (pre-SMA) as well as other areas that have frequently been observed to be co-activated during the correct performance of “No-Go” trials including premotor cortex (FEF), right anterior insula, and the bilateral inferior parietal lobes (Garavan et al., 2006; Simmonds et al., 2008). Although inferior occipital and left precuneus regions were also identified as being activated at our originally selected thresholds, post hoc Monte Carlo permutation procedures suggested that we could not reject the possibility that these clusters could have been identified as being active by chance (Table 3).

In a meta-analysis of event-related functional neuroimaging studies that compared the neural correlates of “simple” and “complex” versions of the Go/No-Go task, Simmonds and colleagues (2008) proposed that contrast of “No-Go” trials against implicit task baseline and use of a “complex” version of the Go/No-Go task identical to the one used in the present study likely elicits brain activation associated with response inhibition amongst other cognitive abilities including selective attention, stimulus recognition, working memory (*i.e.*, updating of stimulus-response associations), and response selection, including selecting not to respond. Consistent with their hypothesis, their results showed that in addition to brain regions thought to be critically involved in response inhibition, such as the pre-SMA, “complex” versions of the Go/No-Go task that involved additional cognitive task demands such as selective attention and updating of working memory were observed to elicit additional activation in a predominantly right-lateralized network including regions in the right middle/inferior frontal gyrus and bilateral inferior parietal regions. The authors interpreted this evidence to suggest that the neural basis of response inhibition may vary depending on task demands. This interpretation is consistent with the results of a prior study suggesting that the pre-SMA is recruited during the performance of “No-Go” trials regardless of whether a “simple” or “complex” versions of the Go/No-Go task are administered, but an additional frontoparietal network is recruited as working memory demands associated with the Go/No-Go task are added (Mostofsky et al., 2003). This evidence suggests that the neural basis of response inhibition may be made up of a network of brain regions some of which play a critical role in supporting response inhibition and others that may be recruited to play a more auxiliary role depending on task demands. However, it is also possible that use of a “complex” version of the Go/No-Go task and contrast of “No-Go” related activity against implicit task baseline may reveal activation patterns that are associated with cognitive operations co-occurring with the performance of response inhibition tasks rather than with the cognitive operation of canceling a response itself.

Contrast of “Go” trials and “No-Go” trials may be one way to address this issue as it is conceivable that “Go”-related activation may be subtracted from “No-Go”-related activation in order to identify activation uniquely and therefore specifically associated with response inhibition. However, as was discussed in the introduction, contrast of “Go” trials and “No-Go” trials may also fail to identify areas that make critical contributions to the performance of both trial types. The results of our own analysis suggested that direct contrast of activation associated with “Go” and “No-Go” trials produced null findings (Table 2), suggesting that several areas that contributed to “No-Go” trials also contributed to “Go” trials, a hypothesis that our follow-up MS/CN conjunction analyses supported (Table 2). Furthermore, areas of the pre-SMA and the right IFG were also identified among the set of regions that were commonly recruited during “Go” and “No-Go” trials, consistent with the idea that areas that may be critically involved in response inhibition may be recruited during the performance of both trial types. Although the results of our conjunction analysis could also be interpreted to suggest that areas recruited during both trial types are not uniquely related response inhibition and are therefore not specifically related to response inhibition, we find this interpretation to be less likely for two reasons: 1) as mentioned above, recent work has identified a critical role for the pre-SMA and the right IFG in response inhibition;

and 2) the results of our follow-up fROI analyses suggested that areas of the pre-SMA that were commonly recruited during both trial types were differentially activated by our ADHD and control groups depending on whether they were performing “Go” or “No-Go” trials. More specifically, our control group demonstrated greater mean activation of this region than our ADHD group only while correctly performing “No-Go” trials (Table 2) suggesting that this region is specifically involved in response inhibition despite its recruitment during “Go” and “No-Go” trials.

Although we cannot rule out the possibility that activation described by the contrast of “No-Go” related activation and implicit task baseline may be associated with co-occurring cognitive processes including but not limited to selective attention, updating of working memory, task switching, response selection (including selecting not to respond), and performance monitoring, several studies have suggested that brain regions associated with these cognitive operations may make significant contributions to the performance of response inhibition tasks (for reviews see Garavan et al., 2006; Chambers et al., 2009). If this were confirmed, brain regions identified by the contrast of “No-Go” related activation with implicit task baseline may in fact describe a network of brain regions associated with response inhibition. Within the context of this literature, our results are most consistent with the view that contrast of “No-Go” related activation with implicit task baseline using a “complex” version of the “No-Go” task reveals a network of brain regions some of which are critically involved in response inhibition and others which may play a more auxiliary role depending on additional task demands.

There were no areas within the network of brain regions defined by this contrast in which our group of adults with ADHD exhibited greater activation than controls or demonstrated activation outside of this network. As we predicted, areas in which a significant reduction in activation was observed included the pre-SMA, a functionally-defined sub-region of medial prefrontal cortex that is considered to be a critical node within the network of brain regions associated with inhibitory control (Floden and Stuss, 2006; Picton et al., 2007; Chen et al., 2009). Additional reductions in activation were also observed in a premotor area (right FEF), the left precentral gyrus (motor cortex), and in the inferior parietal lobes bilaterally.

Our findings are supported by the results of the study by Cubillo and colleagues (2010) another study that examined the neural correlates of response inhibition in a prospectively defined sample of adults with verifiable symptoms of ADHD in childhood and adulthood. Examining a sample of 11 ADHD adults and 14 age-matched controls, the authors reported that their group of adults with ADHD exhibited less activation than controls during the performance of “Stop” trials of a Stop Signal task. Significant reductions in activation were observed in the right caudate, thalamus, and putamen as well as bilateral premotor, bilateral inferior frontal/anterior insula, and medial prefrontal brain regions including the anterior cingulate and the SMA. Our study also found evidence that adults with ADHD exhibited less activation than controls in premotor and medial prefrontal cortex during inhibition of a prepotent motor response. Furthermore, similar findings were observed between the two studies despite differences in sample exclusion criteria as the previous study did not exclude participants with conditions that were commonly comorbid with ADHD. Nevertheless, there were some inconsistencies between the two studies as our study did not confirm that adults with ADHD exhibit less activation than controls in the inferior frontal gyrus and subcortical brain regions, and the previous study did not report that adults with ADHD display less activation than controls in the pre-SMA, the left precentral gyrus, the left precuneus, and the inferior parietal lobe bilaterally.

There are several possible explanations that may account for the inconsistent findings. For one, Cubillo and colleagues contrasted successful “Stop” trials against successful “Go” trials

rather than contrasting “Stop” trials against implicit task baseline. As was reviewed earlier, contrast of “Stop” and “Go” trials may succeed in revealing brain regions that are uniquely related to inhibitory control, but may also fail to reveal any brain region that makes equivalent contributions to the performance of both trial types including regions that may make critical contributions to inhibitory control such as the pre-SMA. For example, because the pre-SMA has been implicated in processes related to both response selection and response inhibition (for review see Mostofsky and Simmonds, 2008), it is possible that these investigators did not find activation differences that were located in the pre-SMA due to the similar recruitment of this brain region during both trial types.

Another possibility that may account for the inconsistent findings between the present study and that of Cubillo and colleagues (2010) may be related to the possibility that the Stop Signal and the Go/No-Go tasks may measure different aspects of response inhibition. Some authors have proposed that this explanation can potentially account for differences in the neural correlates of these two tasks (Rubia et al., 2001; Aron and Poldrack, 2006; Zheng et al., 2008). The Go/No-Go task has been described as a measure of response inhibition (Chambers et al., 2009), but unlike the Stop Signal task, the cognitive abilities involved in successful performance of this task may not be limited to cancellation of an already initiated motor response (Aron and Poldrack, 2006). Whereas the Stop Signal task may measure processes related to the “cancellation” of an already initiated motor response, the Go/No-Go task may place a greater demand on “restraint” during stimulus presentation (Schachar et al., 2007). Thus, ADHD-associated dysfunction of brain regions during inhibition of a motor response may vary depending on the point in time when the motor plan is countermanded. Thus, the results of our study may describe ADHD-associated dysfunction in a fronto-parietal network of brain regions that may be present during inhibition of a prepotent cognitive bias while Cubillo and colleagues' study may describe ADHD-related dysfunction in a fronto-striatal network of brain regions evident during cancellation of an already initiated motor response. Future studies may consider evaluating differences in the time course of neural processes related to response inhibition in samples of adults with ADHD more explicitly.

Cubillo and colleagues (2010) also found evidence of differences in activation between adult ADHD and control participants that were located in the right IFG. We also expected to find activation differences located in this brain region. Although our group of healthy control participants exhibited activation in *pars opercularis* of the right IFG, a region of the brain thought to be critically related to inhibitory control (Aron et al., 2003), we observed no statistical difference between ADHD and controls in this brain region. Another previous study also administered a Go/No-Go task to a group of adults with ADHD (ADHD, $n = 9$; Controls, $n = 9$) also found evidence of reduced activation in the IFG during the performance of “No-Go” trials (Epstein et al., 2007). However, that study also did not exclude individuals with common comorbidities, calling into question whether their findings were specifically associated with ADHD. It is possible that reduced activation of the right IFG may not account for deficits in inhibition in adults with ADHD. This possibility would also be consistent with recent fMRI studies that have challenged the notion that the right IFG directly controls response inhibition and favor attributing this role to the pre-SMA (Duann et al., 2009; Sharp et al., 2010).

Consistent with our hypotheses and with the results of fMRI studies of ADHD children (Tamm et al., 2004; Rubia et al., 2008; Suskauer et al., 2008), our group of adults with ADHD was observed to display reduced activation during the correct performance of “No-Go” trials in a medial prefrontal region located rostral to the SMA known as the pre-SMA (Picard and Strick, 2001). Several authors have suggested that the pre-SMA may play a critical role during successful response inhibition by maintaining stimulus-response

associations used to select a response (or the inhibition of a response) (Floden and Stuss, 2006; Picton et al., 2007; Mostofsky and Simmonds, 2008; Simmonds et al., 2008; Chambers et al., 2009; Chen et al., 2009). This interpretation would be consistent with the results of a study that used a variation of the Go/No-Go task used in the present study to investigate whether activation patterns associated with response conflict could be dissociated from activation patterns associated with error processing (Garavan et al., 2003). The study attempted to vary the level of response conflict present during inhibition of a prepotent response through administration of different stimulus presentation rates that elicited “fast” and “slow” responding while activation patterns associated with both of these conditions were examined separately in association with correct and incorrect trials. The results of that study suggested that an area of the anterior cingulate cortex (ACC) showed significant responses to errors of commission, but was not sensitive to the task's changing conflict demands whereas an area of the pre-SMA was sensitive to response conflict but not to errors of commission. Taken together, this evidence suggests that the pre-SMA is sensitive to manipulations that may disrupt the maintenance of stimulus-response associations within the context of performing a task requiring response selection or inhibition. By contrast, the ACC may be more important for monitoring of performance. It is unlikely that our observed results within the pre-SMA may be ascribed to differences in the neural correlates of error monitoring as we examined activation associated with correct trials only. This may explain why contrast of activation associated with correct “No-Go” trials with implicit task baseline did not reveal activation in the ACC. As we were unable to examine error-related activation within the context of this study due to an insufficient number of trials, it remains possible that adult ADHD and control participants demonstrate differential activation in the ACC during error processing, a hypothesis that should be explored in future studies.

A recent paired-pulse transcutaneous stimulation study demonstrated that the pre-SMA modulates activity in motor cortex in the presence of cognitive conflict but this is not observed when the same actions are performed in the absence of conflict (Mars et al., 2009). This raises the possibility that our group of adults with ADHD displayed less activation than controls in left precentral gyrus (motor cortex) during inhibition trials due to underactivation of the pre-SMA. Future studies might test this hypothesis using effective connectivity methods.

Our ADHD group also displayed reduced activation in the parietal lobes and the right FEF bilaterally consistent with structural neuroimaging evidence indicating that the inferior parietal lobe may be underdeveloped in adults with ADHD (Makris et al., 2007) and with functional neuroimaging evidence suggesting that adults with ADHD demonstrate reduced activation in premotor cortex during the performance of inhibitory control tasks (Cubillo et al., 2010). Activation of the parietal lobes has been reliably observed during the performance of response inhibition tasks, but magnetic stimulation of this region does not result in worse performance on the Stop-Signal task (Chambers et al., 2006). This suggests that the right inferior parietal lobe may not be critically related to successful response inhibition or that this brain region may not be related to the act of inhibiting an already initiated motor response. It is possible that recruitment of right inferior parietal lobe during inhibition trials may reflect a phasic increase in a more general attentional process (Garavan et al., 1999) that may co-occur with inhibition of a prepotent cognitive bias such as during sustained attention (Fassbender et al., 2004) or triggering shifts of attention (Corbetta and Shulman, 2002). Alternatively, the bilateral inferior parietal lobes may be necessary for maintenance of items in working memory during the performance of response inhibition tasks (Hester et al., 2004a). The FEF is important for volitional eye saccade movements (Pierrot-Deseilligny et al., 2004). As such, this brain region may play an important role in support of stimulus recognition during the performance of a manual version of the Go/No-

Go task not involving inhibition of eye movements. By contrast, left parietal cortex has been implicated in response selection (Bunge et al., 2002), an important component process that may contribute to more deliberative aspects of response inhibition (Garavan et al., 2002). Within the context of this literature our results suggest that adults with ADHD may demonstrate reduced activation in brain regions that support higher order attentional, working memory, and response selection processes that contribute to inhibition of a prepotent cognitive bias.

Our behavioral finding that adults with ADHD did not perform significantly worse than controls on “No-Go” trials (10% worse) was unexpected. Post-hoc analyses suggested that the association between ADHD and response inhibition was moderate ($d = -0.53$), consistent with results of a meta-analysis including 17 studies and nearly 1200 children ($d = 0.58$) (Lijffijt et al., 2005). This power analysis suggested that in order to detect a group difference in behavioral performance for response inhibition with 0.80 power ($\alpha=0.05$), 57 participants per group would be necessary. Since significant differences in brain activation were nonetheless observed in six brain regions, these results are consistent with the view that functional neuroimaging methods may be more sensitive than behavioral measures in the detection of brain disorders. However, an undetected difference in accuracy of “Go” trial performance was not likely since ADHD and control participants performed very similarly on these trials ($94\% \pm 3\%$ vs. $94\% \pm 3\%$). This suggests that potential differences between the ADHD and control groups with regard to performance of “No-Go” trials were not likely to be due to primary ADHD deficits in working memory or attention.

Limitations to our study deserve consideration. As was mentioned earlier, it is possible that our choice to contrast activation associated with “No-Go” trials against an implicit task baseline may have revealed areas of activation that were not specifically related to response inhibition. As such, these brain regions may have been associated with cognitive operations co-occurring with the performance of response inhibition tasks rather than with response inhibition itself (Type I error). Although we acknowledge this possibility, we chose to perform this contrast in order to avoid exclusion of brain regions that may make significant contributions to both “Go” and “No-Go” trials (Type II error). Furthermore, the results of our conjunction and follow-up fROI analyses suggested that some of the brain regions that were recruited during both trial types may be specifically and critically implicated in inhibitory control. Finally, we cannot reject the possibility that brain regions that are associated with cognitive processes co-occurring with response inhibition are not part of the network associated with inhibitory control although they may not be critical nodes within this network.

Our exclusion criteria to eliminate common comorbidities likely limited our sample. As such, our low sample size may have limited our power to detect behavioral differences under the “No-Go” condition. However, if this were the case, then it is likely that the five previous fMRI studies that attempted to examine the neural correlates of response inhibition in adults with ADHD may have been similarly underpowered as the sample sizes in these studies ranged between 9 and 17 participants per group. In fact, not one of the five studies reported that they observed a significant difference between ADHD and control participants with regard to accuracy of performance during inhibition trials while studies with higher sample sizes reportedly found significant differences (Bekker et al., 2005; O’Connell et al., 2009). In the event that our study was underpowered to detect behavioral differences in performance of this task, the differences in activation that were observed between ADHD and control participants could be attributable to differential task difficulty rather than to dysfunction of brain regions (Price and Friston, 1999). We attempted to address this problem by modeling activation of correct trials only. Future studies should attempt to replicate our findings using higher sample sizes.

All of our ADHD participants were clinically referred during childhood and had a previous history of stimulant medication. A recent study suggested that chronic exposure to stimulant medication may have an effect on brain function in individuals with ADHD (Konrad et al., 2007). Our study could not rule out the possibility that history of stimulant medication impacted upon our findings, but it should be noted that history of treatment with stimulant medication may also be correlated with greater severity of ADHD symptoms (Barkley et al., 2003). Future studies should attempt to repeat our procedures with a medication naive group.

In sum, our results suggest that adults with ADHD demonstrate less activation than matched controls within a fronto-parietal network of brain regions that has been previously associated with inhibition of a prepotent cognitive bias. Areas in which reduced activation was observed include premotor, medial prefrontal, and inferior parietal brain regions. As each of these brain regions may play a different role within the execution of response inhibition, it is possible that adults with ADHD have more difficulty with the component abilities that contribute to successful response inhibition, namely working memory, goal-oriented attention, and selection of a motor response. Considering that individuals with common comorbid conditions were excluded, the profile of reduced activation demonstrated may be specifically associated with persistent symptoms of adult ADHD. Future studies should determine whether this pattern of reduced activation varies with task demands or if it can be used for the purpose of diagnosis.

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Figure 1. Go/No-Go task

Participants were instructed to respond to target letters “x” and “y”, and withhold response on nonalternating presentations of target letters. Response to targets (“x” or “y” alternating) constituted the “Go” condition of this task whereas the presentation of “lure” letters, to which a prepotent response has been practiced but becomes inappropriate (“x” followed by “x” or “y” followed by “y”), constituted the “No-Go” condition. There were 5 more times as many “targets” as “lures” to emphasize a prepotent response.

Figure 2. Brain Regions Activated During Correct “No-Go” Trials

In ADHD and Control columns, red indicates regions demonstrating significantly greater peak activation during “No-Go” trials than at implicit task baseline (i.e., 0) at uncorrected $p < .0005$, minimum cluster volume = 350 μl ; blue indicates de-activation regions (No-Go < 0) identified at the same thresholds. In the final column, regions activated by either group are displayed in the same stereotactic space; different colors indicate distinct fROIs used in between-group contrasts. Numbers correspond to regions described in Tables 2 and 3.

Figure 3. Comparison of BOLD Signal in ROIs Active During Correct Response Inhibition Trials

Mean magnitude of BOLD response ($\pm$ SEM) for control participants (white; $n = 12$) and ADHD participants (black; $n = 12$) in each ROI during correct “No-Go” trials. Numbers on the x axis correspond to regions described in Tables 2 and 3. Numbers on the y-axis correspond to average parameter estimates of peak change in event-related hemodynamic signal during correct “No-Go” trials. $*p < 0.05$.

Table 1

Demographic, intelligence, and parental ADHD ratings for the adult ADHD and Controls Groups.

	ADHD	Controls
<i>Adult Evaluation</i>		
Age	31.6 (2.5)	29.9 (1.4)
Years of Education	13.3 (2.5)	15.0 (1.9)
Prorated IQ	105.6 (15.2)	116.1 (8.6)
Vocabulary *	10.8 (3.5)	13.7 (2.4)
Block Design	11.5 (3.3)	13.1 (2.0)
Parent ADHD rating *	9.4 (3.8)	1.4 (2.2)

Note. Means (SD) are provided. Adult IQ prorated from Block Design and Vocabulary subtests of the WAIS-III. Adult parental ratings of ADHD symptoms derived from DSM-IV criteria.

* $p < 0.05$

Table 2
Brain Regions Revealed In the Comparison of Activation During Correct “Go” and “No-Go” Trials of the Go/No-Go Task

Brain Region	Vol (μl)	x	y	z	p ¹	ADHD (SD)	CTRL (SD)	df	t	p ²	d
No-Go > Go^{**} (No-Go trials)											
<i>Parietal</i>											
R Angular Gyrus (BA 39)	346	37	-58	35	0.99	0.21	(0.36)	0.76	(0.34)	21	3.85 <0.01* 1.57
No-Go & Go^{***} (Go trials)											
<i>Frontal</i>											
(1) R FEF (BA 6)	456	32	-2	51	N/A	0.39	(0.19)	0.54	(0.47)	14	1.03 0.32 0.42
(2) R Pre-SMA (BA 6)	1,429	4	9	46	N/A	0.70	(0.19)	0.78	(0.47)	14	0.55 0.59 0.22
(4) R IFG [†] (BA 44)	722	45	3	28	N/A	0.49	(0.24)	0.47	(0.41)	17	-0.15 0.89 -0.06
<i>Parietal</i>											
(7) R Inferior Parietal Lobe (BA 40)	961	36	-51	38	N/A	0.38	(0.16)	0.39	(0.29)	17	0.10 0.92 0.04
(8) L Inferior Parietal Lobe (BA 40)	438	-31	-48	38	N/A	0.44	(0.24)	0.48	(0.30)	20	0.36 0.72 0.15
No-Go & Go^{***} (No-Go trials)											
<i>Frontal</i>											
(1) R FEF (BA 6)	456	32	-2	51	N/A	0.25	(0.32)	0.76	(0.30)	21	4.03 <0.01* 1.64
(2) R Pre-SMA (BA 6)	1,429	4	9	46	N/A	0.50	(0.55)	0.88	(0.36)	18	2.00 0.05* 0.82
(4) R IFG [†] (BA 44)	722	45	3	28	N/A	0.68	(0.40)	0.83	(0.30)	20	1.04 0.31 0.43
<i>Parietal</i>											
(7) R Inferior Parietal Lobe (BA 40)	961	36	-51	38	N/A	0.47	(0.37)	0.72	(0.27)	20	1.89 0.07 0.77
(8) L Inferior Parietal Lobe (BA 40)	438	-31	-48	38	N/A	0.41	(0.44)	0.60	(0.22)	16	1.34 0.20 0.55

Note. Brain regions are defined by direct contrast of trial types (No-Go > Go) and by conjunction analyses (No-Go & Go). Regions of interest are numbered, and are based on activation demonstrated by either group (“OR” map). Regions are labeled and numbered as in Fig. 2 and Fig. 3 and follow the convention of the Talairach atlas (Talairach and Tournoux, 1988), $p^1 = \alpha$ per cluster as estimated by AlphaSim (i.e., corrected α). Coordinates represent distance in mm from anterior commissure: x right (+)/left(-); y anterior (+)/posterior (-); z superior (+)/inferior (-). Abbreviations used in tables are as follows: R = right; L = Left, BA = Brodmann areas; FEF = Frontal Eye Fields; SMA = Supplementary Motor Area; IFG = Inferior Frontal Gyrus; ACC = Anterior Cingulate Cortex; CTRL = control group. Average parameter estimates of magnitude of hemodynamic response ($\pm$ SD) during both trial types are listed by each experimental group in each functional region of interest (fROI). Summary statistics (i.e., t , p , and Cohen's d) describe the result of direct comparisons of the magnitude of hemodynamic response between groups (i.e., ADHD vs. CTRL) within each fROI while each group performed each trial type. Positive t and d values represent ADHD < CTRL. $p^2 = \alpha$ related to comparison of average magnitude of response within an fROI (ADHD vs CTRL);

* $p < .05$;

** $p < .005$ (uncorrected), 200 μ l cluster size threshold;

p < .0005 (uncorrected), 350 μ l cluster size threshold;
† pars opercularis

Table 3
Brain Regions Exhibiting Change in Activation During Correct “No-Go” Trials of the Go/No-Go Task

Brain Region	Vol (μl)	x	y	z	p^I	ADHD (SD)	CTRL (SD)	df	t	p^2	d
<i>No-Go > 0</i> ***											
<i>Frontal</i>											
(1) R FEF (BA 6)	1,888	34	0	48	0.001*	0.23 (0.22)	0.71 (0.19)	21	5.72	<0.01*	2.34
(2) R Pre-SMA (BA 6)	1,692	6	9	47	0.001*	0.46 (0.50)	0.83 (0.32)	18	2.16	0.04*	0.88
(3) L Precentral Gyrus (BA 4)	858	-41	-2	31	0.02*	0.42 (0.41)	0.84 (0.39)	21	2.57	0.02*	1.05
(4) R IFG [†] (BA 44)	1,340	46	5	28	0.001*	0.64 (0.28)	0.80 (0.33)	21	1.28	0.21	0.52
(5) R Anterior Insula (BA 13)	1,130	34	14	2	0.003*	0.51 (0.24)	0.75 (0.36)	19	1.92	0.07	0.78
<i>Parietal</i>											
(7) R Inferior Parietal Lobe (BA 40)	2,419	36	-53	38	0.001*	0.44 (0.32)	0.69 (0.25)	20	2.13	0.04*	0.87
(8) L Inferior Parietal Lobe (BA 40)	1,003	-32	-48	37	0.01*	0.37 (0.32)	0.59 (0.18)	17	2.08	0.05*	0.85
(9) L Precuneus (BA 39)	509	-27	-69	34	0.19	0.34 (0.28)	0.70 (0.26)	21	3.26	<0.01*	1.33
<i>Occipital</i>											
(11) R Inferior Occipital Gyrus (BA 18)	470	30	-89	-5	0.23	0.58 (0.50)	0.56 (0.26)	16	-0.12	0.90	-0.05
<i>No-Go < 0</i> ***											
<i>Frontal</i>											
(6) L Anterior Cingulate (BA 32)	753	-2	39	-6	0.05*	-0.89 (0.62)	-0.83 (0.60)	21	0.24	0.81	0.10
(12) L Superior Frontal Gyrus (BA 9)	602	-10	52	22	0.12	-0.81 (0.37)	-0.80 (0.79)	15	0.04	0.97	0.02
<i>Parietal</i>											
(10) Precuneus (BA 31)	4,706	0	-68	18	0.001*	-0.66 (0.20)	-0.48 (0.46)	15	1.24	0.23	0.51

Note. Regions are labeled and numbered as in Table 2, Figure 2, and Figure 3. Coordinates and abbreviations follow the same convention as in Table 2. $p^I = \alpha$ per cluster as estimated by AlphaSim (i.e., corrected α). Average parameter estimates of magnitude of hemodynamic response ($\pm$ SD) during correct No-Go trials are listed for each experimental group in each fROI. Summary statistics (i.e., t , p , and Cohen's d) describe the result of direct comparisons of magnitude of hemodynamic response between groups (i.e., ADHD vs. Control) within each fROI while each group performed correct No-Go trials. Positive t and d values represent ADHD < CTRL. $p^2 = \alpha$ related to comparison of average magnitude of response within an fROI (ADHD vs Control);

* $p < .05$;

** $p < .005$ (uncorrected), 200 μ l cluster size threshold;

*** $p < .0005$ (uncorrected), 350 μ l cluster size threshold;

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