Published in final edited form as:

Psychiatry Res. 2014 August 30; 223(2): 121–128. doi:10.1016/j.psychres.2014.05.012.

Brain activity in predominantly-inattentive subtype attention-deficit/hyperactivity disorder during an auditory oddball attention task

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Abstract

Previous functional neuroimaging studies have found brain activity abnormalities in attention-deficit/hyperactivity disorder (ADHD) on numerous cognitive tasks. However, little is known about brain dysfunction unique to the predominantly-inattentive subtype of ADHD (ADHD-I), despite debate as to whether DSM-IV-defined ADHD subtypes differ in etiology. This study compared brain activity of 18 ADHD-I adolescents (ages 12–18) and 20 non-psychiatric age-matched control participants on a functional magnetic resonance image (fMRI) auditory oddball attention task. ADHD-I participants had significant activation deficits to infrequent target stimuli in bilateral superior temporal gyri, bilateral insula, several midline cingulate/medial frontal gyrus regions, right posterior parietal cortex, thalamus, cerebellum, and brainstem. To novel stimuli, ADHD-I participants had reduced activation in bilateral lateral temporal lobe structures. There were no brain regions where ADHD-I participants had greater hemodynamic activity to targets or novels than controls. Brain activity deficits in ADHD-I participants were found in several regions important to attentional orienting and working memory-related cognitive processes involved in target identification. These results differ from those in previously studied adolescents with combined-subtype ADHD, who had a lesser magnitude of activation abnormalities in frontoparietal regions and relatively more discrete regional deficits to novel stimuli. The divergent findings suggest different etiological factors might underlie attention deficits in different DSM-IV-defined ADHD subtypes, and they have important implications for the DSM-V reconceptualization of subtypes as varying clinical presentations of the same core disorder.

Keywords

ADHD; Inattentive; attention; oddball; fMRI

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1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is characterized by symptoms of inattention, hyperactivity, and impulsivity that cause impairment in social, academic, or occupational functioning (American Psychiatric Association, 1994). Since 1968, when this disorder was added to the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II; American Psychiatric Association, 1968) as hyperkinetic reaction disorder, the criteria and name have changed with every DSM revision (Baeyens et al., 2006). These revisions have in part resulted from uncertainty about core deficits in ADHD, particularly questions regarding primacy of attentional or behavioral control dysfunction. DSM-IV (American Psychiatric Association, 1994) specifies three ADHD subtypes: predominantly inattentive (ADHD-I), predominantly hyperactive-impulsive (ADHD-H), and combined (ADHD-C). These subtypes have been the topic of considerable debate as to whether they represent different dimensions of the same disorder, or different disorders altogether.

There is convincing evidence for these DSM-IV clinical subtypes based on latent group analysis of symptom profiles (Lahey et al., 1998; Woo and Rey, 2005). The subtypes also have different patterns of psychiatric comorbidity, psychosocial function, and treatment response (see review by Baeyens et al., 2006). For instance, children with ADHD-I tend to have later age of onset (Applegate et al., 1997), have less comorbidity with oppositional defiant disorder (ODD) and conduct disorder (CD) (Barkley et al., 1990), and are less assertive and knowledgeable about appropriate social skills than children with ADHD-C (Maedgen and Carlson, 2000). Based on this evidence, some researchers have concluded ADHD-I and ADHD-C (the two most frequently studied and most prevalent (Woo and Rey, 2005) subtypes found after first grade) are clinically distinct disorders (Milich et al., 2001; Diamond, 2005). Both subtypes have generally the same neuropsychological deficits (Willcutt et al., 2012), differing primarily in severity (Nikolas and Nigg, 2013), hindering conclusions about different neural abnormalities. Summaries of the literature comparing ADHD-I and ADHD-C subtypes over the past decade continually have concluded that there is as yet insufficient evidence to differentiate them neurobiologically (Hinshaw, 2001; Lahey, 2001; Baeyens et al., 2006). This conclusion and a call for further, subtype-specific neurobiological research was recently echoed following a rigorous meta-analysis of ADHD empirical data (Willcutt et al., 2012).

Studies of genetic liability suggest both shared and unique heritable pathways to each subtype exist (Stawicki et al., 2006; Misener and Barr, 2009; Nikolas and Burt, 2010). Moreover, some evidence indicates that inattention and hyperactivity symptoms themselves have separable genetic influences (Nikolas and Burt, 2010). However, these genetic differences have yet to be tied to differences in the brain, as few structural magnetic resonance imaging (MRI) or functional MRI (fMRI) studies exist that seek to identify neuroanatomical or neurofunctional differences between the ADHD clinical subtypes. Indeed, few studies of brain structure or function to date have specifically examined ADHD-I. Solanto and colleagues compared brain activation between children with either ADHD-I or ADHD-C during an fMRI Go/No-Go test of inhibitory control (Solanto et al., 2009).

Despite similar behavioral performance and overall brain activity patterns, ADHD-I children had greater amplitude of hemodynamic response in right superior temporal lobe, left inferior parietal lobe, and bilateral middle frontal gyri compared with ADHD-C children. Conversely, brain activation was greater for children with ADHD-C in bilateral medial occipital lobes. Though suggestive of different underlying pathophysiologies, this study had no non-ADHD control group, making it difficult to say whether the subtype differences represented abnormalities. Another study found numerous cortical and subcortical regional activation levels were associated with ADHD inattentive symptoms during Stroop fMRI task performance; furthermore, these regions' activity was not linked to hyperactivity symptoms (Depue et al., 2010). However, none of these brain regions were abnormal relative to controls. Most recently, Edell and colleagues compared medication-naïve ADHD-C and ADHD-I adults' brain activity during a Monetary Incentive Delay fMRI task, finding subtype differences in ventral striatum and orbitofrontal cortex activation levels – important areas involved in reward processing (Edell et al., 2013). Nearly all other published fMRI studies either have not differentiated between ADHD-C and ADHD-I subtypes when sampling, or restricted their focus to the ADHD-C subtype (Bush et al., 2005).

Therefore, there is as yet a poor and incomplete understanding of whether there might be ADHD-I specific brain function deficits, particularly for relevant cognitive domains most often found to be abnormal in ADHD such as attention, working memory, or cognitive control. Some evidence for distinct neural subtype profiles related to attention has come from a growing body of EEG research comparing electrophysiological activity in the ADHD-I and ADHD-C subtypes. A frequently used paradigm in these studies is the “oddball” task, in which participants respond deliberately to infrequent target stimuli, ignoring frequent standards or rare novel stimuli. This paradigm primarily assesses attentional orienting and updating of contextual information in working memory (Donchin and Coles, 1988). A review of ADHD auditory oddball studies indicates that in addition to ADHD-I differing from non-ADHD controls in N1, P2, and P3 amplitudes to infrequent stimuli (Brown et al., 2005), ADHD-I and ADHD-C children differ in amplitude, latency, or topography for early N1, P2, and N2 event-related potentials (ERPs), widely thought to index “pre-attentive” and early neural responses to stimuli (Barry et al., 2003). Deficits in the later P3 ERPs thought to index working memory updating have been reported for both clinical subtypes, but with mixed evidence across studies (Barry et al., 2003), particularly in older ADHD youth. Proponents of a two-component model for ADHD based on EEG research suggest that maturation interacts with ADHD deficits, where a hyperactive/impulsive component matures with age and a distinct inattentive component remains more stable over time (Clarke et al., 2001). Therefore, electrophysiological evidence suggests that ADHD-I might be a less complicated form of ADHD that has only a single type of clinical impairment (and by extension, less complex pathophysiology might show abnormal function in fewer neural systems).

The purpose of this study was to use fMRI to characterize regional ADHD-I brain dysfunction related to well-characterized ADHD deficits in EEG auditory oddball tasks. FMRI oddball studies have found numerous cortical and subcortical activity deficits in ADHD-C (Rubia et al., 2007; Stevens et al., 2007; Tamm et al., 2006), including the left middle frontal gyrus, bilateral superior temporal gyrus, bilateral parietal lobes (including the

superior parietal gyrus and supramarginal and angular gyri of the inferior parietal lobe), right precuneus, thalamus, basal ganglia, and posterior cingulate. However, oddball task-elicited brain function in ADHD-I relative to controls has not yet been explored. Because there have been so few neuroimaging studies in the ADHD-I subtype, neurobiological theories of ADHD-I are less developed than those for ADHD as a whole. Although some have proposed specific frontoparietal abnormalities in ADHD-I (Diamond, 2005), the sparseness of theoretical literature in this area made it difficult to make precise predictions where ADHD-I would have abnormal brain function. Therefore, we performed a whole brain analysis at stringent statistical thresholds so that any evidence obtained would provide clear support for ADHD-I functional abnormality. Our broad hypothesis was ADHD-I would show deficits in brain regions linked to attentional orienting on oddball tasks, such as bilateral temporal cortex and frontoparietal systems. Supplemental analyses were conducted to examine the possible relationship between regional brain dysfunction and inattentive symptom severity. A secondary goal was to compare evidence for regional brain activity abnormalities in ADHD-I to ADHD data from Stevens et al. (Stevens et al., 2007). Using the same three-stimulus auditory oddball fMRI task, that study reported widespread brain activity deficits in a sample of mixed ADHD-C and ADHD-H youth. To provide a preliminary examination of possible clinical subtype differences, we compared the ADHD-I adolescents with ADHD-C participants in brain regions found to function abnormally in ADHD-I relative to controls.

2. Methods

2.1. Participants

Participants included 18 adolescents (14 males; 4 females, ages 12–18) who were diagnosed with DSM-IV ADHD-predominantly inattentive subtype (ADHD-I) and 20 healthy control participants matched on age, sex, and ethnicity. These participants were recruited via physician referral and community advertisements. Five participants in the ADHD-I group also met criteria for CD and one met criteria for ODD. The healthy control sample was free of any Axis I DSM-IV disorders, medical problems, or learning disabilities. Diagnoses were confirmed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (Kaufman et al., 1997) administered by experienced staff. Because two participants with ADHD were left-handed by self-report, a similar number of left-handed participants (matched by age) were included in the control group. Table 1 presents study group characteristics and results of *t*-test comparisons. At the time of fMRI, all ADHD-I participants who were prescribed psychostimulant treatment had not taken medication for at least 24 h.

Study procedures were explained in detail to potential participants and a parent or legal guardian during an informed consent/assent protocol approved by Hartford Hospital's Institutional Review Board. Research procedures adhered to ethical standards. Participants received monetary compensation for their time.

2.2. fMRI task and procedure

The task was a three-stimulus auditory oddball task used in previous fMRI studies (Stevens et al., 2007), using custom software (VAPP; <http://www.nrc-iol.org/vapp/>) for presentation. The standard stimulus was a 1000-Hz tone (probability=0.80), the target stimulus was a 1500-Hz tone (probability=0.10), and the novel stimuli (probability=0.10) consisted of non-repeating random digital noises (e.g., tone sweeps, whistles). In each of the two runs, there were 24 target tone stimuli, 24 novel sound stimuli, and 196 nontarget tone stimuli. Stimuli were presented for 200 ms with a pseudorandom stimulus onset asynchrony ranging from 1,000 to 2,000 ms (mean=1,500). Participants were instructed to respond as quickly and as accurately as possible with a right index finger button press for every target tone, and not for other stimuli. Before beginning the task, each participant performed a 20-s practice trial to ensure understanding of the instructions. During scanning, all participants reported that they could hear the stimuli and discriminate them from the background scanner noise. Stimulus events and behavioral responses (hits or false alarms within 1,250 ms) were recorded and monitored online on a separate computer.

2.3. Imaging parameters

Imaging was done on a Siemens Allegra 3T system at the Olin Neuropsychiatry Research Center of the Institute of Living/Hartford Hospital in Hartford, Connecticut. Functional image volumes were collected in axial orientation to the anterior commissure-posterior commissure line using a gradient-echo sequence sensitive to the blood-oxygen-level-dependent (BOLD) signal (repetition time=1,500 ms, echo time=28 ms, flip angle=65°, field of view=24×24 cm, 64×64 matrix, 3.4×3.4 mm in plane resolution, 5 mm slice thickness, 30 slices) effectively covering the entire brain (150 mm) in 1.5 s. The two runs each consisted of 255 time points, including a 9-s rest session at the beginning that was collected to allow T₁ effects to stabilize. These initial six images were not included in subsequent analyses.

2.4. Image processing

Functional images were reconstructed offline, and each run was separately realigned using INRIAlign (Freire et al., 2002) as implemented in Statistical Parametric Mapping (SPM5). All participants had head motion <1 voxel length in any x,y,z plane. In addition, absolute average movement for the two groups did not statistically differ when tested by *t*-test in x- (2 run average HC 0.25 vs. ADHD 0.42 mm), y- (0.15 vs. 0.77 mm) or z-planes (0.18 vs. 1.07 mm). A mean functional image volume was constructed for each participant for each session from the realigned image volumes and was used to determine parameters for spatial normalization into standardized Montreal Neurological Institute (MNI) space. These normalization parameters were then applied to the corresponding functional image volumes. Normalized images were smoothed with a 12-mm³ full-width-at-half-maximum Gaussian filter.

2.5. fMRI statistics

The regressors for each participant's fMRI model were derived by extracting stimulus onset timing for correct target, novel, and standard stimuli and modeled using a synthetic hemodynamic response function and temporal derivative. Six motion-correction parameter

estimates (x , y , and z displacement and roll, pitch, and yaw rotations) were included as covariates of no interest to statistically control signal change related to motion. A high-pass filter (cutoff period=128 s) was incorporated into the model to remove low-frequency signals. For each condition of interest, SPM5 wrote an image in which each voxel represented the estimated amplitude of hemodynamic response.

2.6. Behavioral performance analysis

Two-sample t -tests were used to evaluate mean reaction time for correct target responses and false alarm rates for novel and standard stimuli.

2.7. fMRI data analysis

Using the same approach taken in our previous ADHD fMRI oddball study (Stevens et al., 2007), we examined GLM contrasts from individual subject-level fMRI models that represented BOLD signal change to targets or novels relative to an implicit (i.e., unmodeled) baseline. These target and novel activation maps were contrasted by two separate SPM5 two-sample t -tests, using stringent statistical corrections ($p < 0.05$ family-wise error; FWE) for searching the whole brain. Results of group analyses are displayed using cortical surface renderings with hemodynamic activity overlays. Although both target and novel stimuli engage an automatic attentional orienting process, target stimuli also elicit other cognitive processes related to behavioral relevance, i.e., those needed to identify, consciously compare the stimulus to the target working memory template, and update working memory contents in preparation for subsequent trials (Donchin and Coles, 1988). We also performed a whole brain ($p < 0.05$ FWE) analysis of this contrast.

A supplemental multiple regression analysis was conducted to determine the linear association of ADHD inattentive symptom counts from the Schedule for Affective Disorders and Schizophrenia for School-Age Children with ADHD-I brain activity. These analyses were done only in regions-of-interest (ROIs) identified to differ between ADHD-I participants and healthy controls during either target or novel two-group contrasts. ROIs were defined as 6-mm radius spheres centered on coordinates of peak ADHD-I versus control differences from the primary study analyses. Twenty-one target ROIs were identified. To account for multiple comparisons across ROIs, an α -adjusted critical threshold of $p < 0.002$ small volume correction (SVC) FWE was used for targets to evaluate statistical significance. The α -level was adjusted for the four novel ROIs to $p < 0.0125$ SVC FWE.

2.8. Comparison with previously published ADHD-C results

A secondary analysis was conducted to compare the amplitude of hemodynamic response to target and novel stimuli between ADHD-I and control participants in this study with data from a sample of ADHD-C participants that was earlier described in detail (Stevens et al., 2005). This analysis used the ROIs based on findings of the initial whole brain analysis comparing ADHD-I and healthy controls (listed in Table 2). Those peak activation coordinates were used as the center of 6-mm radius spherical ROIs. Because there were multiple ROIs to search, an α -adjusted critical threshold of $p < 0.001$ FWE (SVC, corrected for searching the ROI volume) was used. Finally, a whole brain analysis using a rigorous

statistical threshold ($p < 0.05$ FWE) was done to ensure no undetected ADHD-I vs. ADHD-C difference existed outside of the *a priori* search focus.

3. Results

3.1. Behavioral performance

There were no statistically significant differences between ADHD-I and healthy control participants in the number of hits or false alarms to novel or standard stimuli (Table 1). A two-sample *t*-test showed that the ADHD-I target reaction time was not significantly different from that of healthy controls, though this was a “trend” level of significance ($t_{38} = 1.66$, $p = 0.10$). The ~45-ms reaction time difference between the groups represented a Cohen’s *d* effect size (Cohen, 1990) of 0.55, which is a medium effect size.

3.2 Between-groups comparisons of hemodynamic response to target and novel stimuli

Results for the comparison of ADHD-I and control groups on response to target stimuli are shown in Table 2 and illustrated in Fig. 1. Consistent with our hypotheses, ADHD-I participants had less target-elicited hemodynamic activity than healthy controls in several brain regions. These included the right middle frontal gyrus, pre-supplementary motor area (SMA), SMA, bilateral cingulate cortex, bilateral insula, left sensorimotor cortex, right inferior parietal lobule/supramarginal gyrus, bilateral superior temporal gyrus, thalamus, cerebellum, and brainstem (all $p < 0.05$ FWE).

Results for the comparison of ADHD-I and control groups on response to novel stimuli are shown in Table 2 and illustrated in Fig. 2. ADHD-I participants had less hemodynamic activity than healthy controls to novel stimuli in the left and right superior temporal gyrus (all $p < 0.05$ FWE).

In no brain region did ADHD-I participants show a greater amplitude of hemodynamic response relative to control subjects for either target or novel stimuli.

These analyses were re-done, omitting the five ADHD-I participants with comorbid CD. With a less stringent statistical threshold appropriate to the reduced sample size and pre-knowledge of where to look ($p < 0.05$ small volume-corrected FWE for each ROI without α -adjustment searching multiple ROIs), we replicated ADHD-I target deficits in nearly all regions. When ADHD-I adolescents comorbid for CD were omitted, evidence was no longer found for deficits in the pre-SMA, bilateral insula, right posterior parietal cortex, and anterior thalamus (though the anterior thalamus was different at a trend level, $p < 0.077$ SVC FWE). For novel stimuli, ADHD-I without CD still showed bilateral temporal lobe activation deficits.

3.3. Between-group comparison of target versus novel activation

Table 3 describes brain regions where ADHD-I participants had a lower amplitude of the target minus novel response relative to controls. These regions were very consistent with the ADHD-I deficits to targets. Only the ADHD-I abnormalities in bilateral temporal lobe and thalamus were not detected in this contrast. Bilateral globus pallidus ADHD-I abnormalities were found. There were no brain regions where ADHD-I participants had a greater

amplitude than controls. Fig. 3 depicts these group differences and the estimated amplitude of response to each task condition for the peak x,y,z coordinates reported in Table 3. Not only was the difference between target and novel activation greater in non-ADHD compared with ADHD-I participants, ADHD-I adolescents actually deactivated regions to novel stimuli that in controls were either associated with activation (midline cingulate) or no response (SMA, right IPL, left globus pallidus, and cerebellum).

3.4. Supplemental analysis of symptom severity

There was no relationship between Inattentive ADHD symptom severity and brain function to either target- or novel-elicited brain activity. The lack association might have been due to the restricted range of the covariate, due to the criteria for diagnosis of ADHD-I (i.e., Inattentive symptoms ranged only from 6 to 9; mean 7.33, SD 1.02).

3.5. Secondary analysis comparing ADHD-I to ADHD-C

All ADHD-I deficit-ROIs were found to have less hemodynamic activity in ADHD-C compared with controls, but most ROIs also had a significantly decreased response in ADHD-I relative to ADHD-C. Specifically, all regions tested had significantly lower response in ADHD-I relative to ADHD-C at $p < 0.01$ SVC FWE, but 6 of these 24 regions did not survive α -correction for multiple comparisons. The supplemental whole brain analysis found several additional regions where ADHD-I had lower activation to target stimuli: left postcentral gyrus ($x,y,z = -36, -21, 63, t=7.08$), left posterior insula ($x,y,z = -48, 0, 3, t=7.69$), right mid-insular cortex ($x,y,z = 42, 12, 3, t=7.75$), and bilateral putamen/globus pallidus (left $x,y,z = -18, 6, -3, t=6.19$; right $x,y,z = 21, 12, -3, t=6.06$). There were no additional ADHD-C > ADHD-I regions for novel stimuli, and no additional regions where ADHD-I showed greater activity than ADHD-C.

4. Discussion

This study compared fMRI-measured hemodynamic activity elicited during infrequent target and novel oddball stimulus processing between ADHD-I adolescents and healthy controls. ADHD-I adolescents had significant activity deficits in brain regions associated with attentional orienting and working-memory cognitive processes (Donchin and Coles, 1988; Baudena et al., 1995; Halgren et al., 1998). During target processing, ADHD-I participants had less hemodynamic activity than controls in right middle frontal gyrus, supplementary motor area, bilateral cingulate cortex, bilateral insula, left sensorimotor cortex, right inferior parietal lobule/supramarginal gyrus, bilateral superior temporal gyri, thalamus, cerebellum, and brainstem. To novel stimuli, there were ADHD-I hemodynamic deficits in bilateral superior temporal gyri. Only bilateral temporal lobe response was commonly affected in target and novel processing. Without a concurrent examination of EEG and fMRI data (e.g., Calhoun et al., 2006), it is not possible to conclusively link these activation deficits directly to specific ERPs previously reported to differ between the ADHD-I and ADHD-C subtypes (Barry et al., 2003). However, fMRI/EEG “fusion” work using this exact paradigm has indicated bilateral temporal lobe and right parietal lobe deficits reflect either N1 or N2 ERPs, while supplementary motor area activity likely reflect either N2- or P3-related cognitive processes (Calhoun et al., 2006). The brainstem ADHD-I abnormalities were

previously linked to a post-P3 “slow wave”-like process. These results are consistent with previous EEG ADHD-I research that found N1, P2, and P3 deficits (Brown et al., 2005).

In all of these brain regions, adolescents with ADHD-I displayed less brain activation than adolescents with ADHD-C (Stevens et al., 2007). This cannot be explained simply by the degree of inattentive symptom severity, because it was uncorrelated with brain activation (though the symptom range was restricted, so additional studies are needed). When the overall profile of brain function abnormalities for ADHD-I adolescents was contrasted with the ADHD-C deficits observed in previous work (Stevens et al., 2007), clearly different patterns of brain dysfunction for each ADHD clinical subtype were found. For target stimuli, ADHD-C adolescents had many additional brain regions with activation deficits compared with healthy controls. These included areas of the frontal gyri, precentral and postcentral gyri, superior parietal lobules, middle temporal gyri, amygdala/parahippocampal gyri, lingual gyri, and putamen/globus pallidus (Stevens et al., 2007). Conversely, in the current study, there also were ADHD-I oddball task activation deficits not previously observed in adolescents with ADHD-C. These included impaired midline SMA and left sensorimotor cortex activation. Midline pre-SMA also appears to be uniquely abnormal in ADHD-I, but our *post hoc* analyses raised the possibility that this functional deficit might be linked to CD comorbidity, along with evidence for lower target-related activity deficits in insular cortex and thalamus. Moreover, these regions are somewhat consistent with known gray matter volume deficits in CD (Rubia, 2011). For novel stimuli, the adolescents with ADHD-I only had deficits in activation in the superior temporal gyri bilaterally, whereas adolescents with ADHD-C had substantially more regional deficits to novel stimuli. The ADHD-I temporal lobe deficit finding is the only major discrepancy with the sole previous fMRI-based comparison of ADHD-C and ADHD-I, probably due to the different paradigms used (i.e., the current task emphasized attentional orienting while Solanto et al. used a response-inhibition task).

In sum, ADHD-I adolescents seem to have generally fewer, more pronounced (in the regions examined), but also different brain-activation deficits on oddball attention tasks than ADHD-C adolescents. These results support the general conclusion of previous ADHD oddball EEG findings (Johnstone et al., 2001) that different etiological factors might underlie simple attentional orienting deficits in different DSM-IV-defined ADHD subtypes. It remains unclear, however, whether this is a difference in degree of abnormality, type of neural systems implicated, or both. Inattention has been somewhat neglected in current neurobiological theories of ADHD, which alternatively propose impairments of response inhibition (Barkley, 1997; Aron and Poldrack, 2005), motivation or effort (Sergeant, 2005; Sonuga-Barke, 2005), or executive functions (Willcutt et al., 2005). In general, our study found little evidence for frontostriatal abnormalities in ADHD-I adolescents when simple activation was examined, but caudate and lateral prefrontal oddball activation deficits previously were seen in ADHD-C adolescents on this task (Stevens et al., 2007). This suggests that frontostriatal deficits could be specific to hyperactive/impulsive ADHD symptoms, as many would predict. However, our direct contrast of target versus novel conditions suggests that ADHD-I adolescents actually abnormally disengage some aspects of frontostriatal and cerebellar systems (midline cingulate, SMA, right IPL, putamen/globus

pallidus, and cerebellum) to novel stimuli in addition to showing deficits in target processing – all of which were associated with lower activation in ADHD-I compared with ADHD-C in both ROI analyses and supplemental whole brain analyses. This suggests a qualitative difference in what neural systems are called upon to filter out unimportant information in ADHD-I, which might underlie some inattentive ADHD symptoms. The results also support proposed frontoparietal deficits in ADHD-I (Diamond, 2005), a finding that is consistent with targets of norepinephrine pathways implicated in ADHD (Arnsten, 2006) and oddball-elicited ERPs (Nieuwenhuis et al., 2005). However, both ADHD-I and ADHD-C adolescents (Stevens et al., 2007) showed some evidence for frontoparietal deficits, suggesting a shared impairment. It is noteworthy, however, that the parietal lobe, insular and cingulate abnormalities were of greater magnitude in ADHD-I than ADHD-C adolescents during oddball-elicited attentional function, raising the possibility that patients with the ADHD-I subtype might be more impaired in this neural system. In this report, we found no significant symptom-brain activation relationships. However, Depue and colleagues found in ADHD-C adults that degree of inattention was linked to over a dozen regions throughout frontal, temporal, parietal lobes, as well as the basal ganglia, thalamus, and cerebellum (Depue et al., 2010). It seems clear that direct comparison of the relationships between symptom severity and brain-activation levels between ADHD-C and ADHD-I samples will be needed across several meaningful task contexts in order to shed further light on the question of unique versus shared etiological influence. Such a dimensional approach to analyses is consistent with recent thinking in psychiatry (Swanson et al., 2009), as well as the emphasis placed in DSM-V on clinical “presentations” of ADHD symptom domains, rather than diagnostic subtypes.

This study has an advantage over many previous ADHD neuroimaging studies in that there was relatively careful control over ADHD subtype inclusion (DSM-IV ADHD 314.00, predominantly inattentive type) and most psychiatric comorbidity. Although several CD-comorbid participants were included, the results were not substantially different when the analyses were redone without those subjects. Another strength is the use of “whole brain” fMRI methods, though it is noted that the stringent statistical thresholds needed might have led to failure to detect lesser but nevertheless meaningful ADHD-I abnormalities. Previous research has found differences in oddball-elicited brain activity between males and females with ADHD (Barry et al., 2006) that could not be explored in the present study, with its uneven gender distribution. Therefore, although gender was matched across groups in the present study, future research should examine the impact of gender of neural activity in ADHD-I.

In conclusion, this was the first study to compare ADHD-I directly with non-ADHD controls to characterize attention-related brain activity abnormalities, and was only the second fMRI study that contrasted ADHD-I to ADHD-C youth. We identified numerous brain regions in adolescents with ADHD-I with abnormal neural activity during performance on the auditory oddball attention task, most consistent with dysfunction in early sensory processing/orienting cognitive processes. The overall profile of ADHD-I deficits varied notably from that previously found in adolescents with ADHD-C, both in their relative magnitude (greater deficits in ADHD-I) and in which specific brain regions that were found to be abnormal in each ADHD clinical subtype, suggesting that specific and distinct brain

regions are abnormal in each DSM-IV ADHD subtype. These results support the proposal that attention dysfunction in ADHD-I could result from different underlying pathophysiology than in ADHD-C. Far greater evidence needs to be accumulated before the ADHD-I and ADHD-C subtypes can be considered neurobiologically distinct disorders, including additional direct comparison of the two subtypes, along with careful dissection of shared versus unique subtype brain function abnormalities across a wide range of ADHD-relevant neurocognitive probes. Future ADHD-I fMRI studies also might profit by a systematic examination of the relationship between brain dysfunction and each type of Inattention symptom (e.g., disorganization, distractibility, sluggish cognitive tempo). Such an analysis might find clear differences between the DSM-IV-defined ADHD subtypes in the relationship of specific symptoms or associated neurocognitive impairments (Nigg et al., 2005) to brain dysfunction.

Acknowledgments

This project was supported in part by NIH grants MH070036 and MH080956.

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- Brain activity of 18 ADHD-Inattentive adolescents and 20 controls was compared
- ADHD-I deficits were in regions linked to attentional orienting and working memory
- These results differ from previously studied adolescents with Combined-subtype ADHD
- The divergent findings suggest different etiological factors for ADHD subtypes

Fig. 1. Cortical surface renderings showing the results of the comparison between ADHD-I and control study groups for hemodynamic response to infrequent oddball target stimuli ($p < 0.05$ FWE corrected for searching the whole brain).

Fig. 2.
Cortical surface renderings showing the results of the comparison between ADHD-I and control study groups for hemodynamic response to infrequent oddball novel stimuli ($p < 0.05$ FWE corrected for searching the whole brain).

Fig. 3.

(A) Axial slices showing ADHD-I and control study group differences in the comparison between infrequent target and novel stimuli activation ($p < 0.05$ FWE corrected for searching the whole brain). (B) Amplitude of estimated target and novel BOLD response for selected brain regions.

Characteristics and behavioral performance on a three-stimulus auditory oddball task in participants with ADHD-I and a demographically-matched control group

Table 1

	ADHD-I Group (N=18)		Control Group (N=20)		Analysis <i>t</i>
	Mean	SD	Mean	SD	
Demographic and clinical characteristics					
Age (Years)	15.20	1.72	14.91	1.80	0.50
KSADS-PL					
ADHD hyperactive/impulsive symptoms	2.0	1.31	0.0	0.00	6.90 [*]
ADHD inattentive symptoms	8.0	1.08	0.0	0.00	30.24 [*]
fMRI task behavioral performance					
Target stimulus reaction time (msec)	456.7	95.33	410.6	98.6	1.66 [†]
Target stimulus hit percentage	94.9%	11.21	98.6%	2.51	1.45
Novel stimulus false alarm percentage	1.6%	2.23	1.3%	1.73	0.57
Standard stimulus false alarm percentage	1.1%	1.68	1.4%	2.17	0.46

* $p < .05$

[†] $p < .10$ (trend level of significance)

Table 2

Brain regions with significantly greater hemodynamic response amplitude for control participants compared to ADHD-I. Brain activity group differences for both targets and novels compared to the unmolded implicit baseline are shown. All brain regions survive correction for searching the whole brain, $p < .05$ FWE. There were no brain regions where ADHD-I had a greater hemodynamic response than controls.

Targets vs. Implicit Baseline				
Brain Region	Voxel of Peak Intergroup Difference in t			Peak t score
	x	y	z	
Frontal lobes				
Right middle frontal gyrus (BA 10)	33	39	24	5.99
Midline pre-supplementary motor area	−3	3	51	8.37
Midline supplementary motor area	3	−3	63	8.46
Left cingulate cortex (rostral cingulate zone)	6	21	33	8.56
Right cingulate cortex (rostral cingulate zone)	−12	27	24	6.87
Mid-cingulate cortex	0	−6	39	7.56
Left anterior insula	−42	9	−3	8.51
Right anterior insula	36	15	−12	7.87
Parietal lobes				
Left sensorimotor cortex	−36	−36	51	7.19
Right inferior parietal lobule/supramarginal gyrus	48	−39	48	6.26
Temporal lobes				
Left superior temporal gyrus	−54	0	−6	8.78
	−48	−12	0	9.69
	−63	−30	−3	5.92
Right superior temporal gyrus	63	−27	−3	10.64
	60	−39	15	9.12
Deep gray matter				
Thalamus (anterior)	−3	−6	6	6.84
Thalamus (posterior)	−3	−24	6	7.07
Other				
Cerebellum	0	−75	−18	8.09
	3	−78	−36	8.39
Left Brainstem	−12	−24	−15	6.87
Right Brainstem	12	−27	−12	6.80

<i>Novels vs. Implicit Baseline</i>				
Brain Region	Voxel of Peak Intergroup Difference in t			Peak <i>t</i> score
	x	y	z	
Temporal lobes				
Left superior temporal gyrus	−60	−24	6	8.84
	−42	−33	9	8.51
Right superior temporal gyrus	63	−27	3	9.30

<i>Novels vs. Implicit Baseline</i>				
Brain Region	Voxel of Peak Intergroup Difference in t			Peak <i>t</i> score
	x	y	z	
	66	-18	3	8.92

Table 3

Brain regions where control participants had significantly different amplitude of response to target stimuli compared to novel stimuli relative to ADHD-I participants. All brain regions survive correction for searching the whole brain, $p < .05$ FWE.

Brain Region	Voxel of Peak Intergroup Difference in t			Peak t score
	x	y	z	
Frontal lobes				
Midline supplementary motor area	-6	-3	72	10.16
Midline cingulate gyrus	0	-6	39	6.96
Midline cingulate cortex (rostral cingulate zone)	3	18	33	8.41
Left anterior insula	-39	6	3	7.40
Right anterior insula	45	15	-3	7.56
Parietal lobes				
Left sensorimotor cortex	-42	-27	60	9.53
Left inferior parietal lobule	-66	-27	24	6.95
Right inferior parietal lobule	45	-42	45	5.42
Deep gray matter				
Left globus pallidus	-12	0	0	6.31
Right globus pallidus	12	0	-6	6.03
Left thalamus (posterior)	-9	-24	3	6.24
Other				
Cerebellum	0	-42	-3	8.10
	21	-54	-27	7.35
	3	-69	-18	6.54
Left brainstem	-12	-24	-15	7.84
Right brainstem	12	-24	-12	6.40

Table 4

Secondary analysis comparing amplitude of hemodynamic response to target and novel stimuli among Predominantly Inattentive ADHD and control participants in this study to a sample similar to the Combined-subtype ADHD data previously published in Stevens et al. 2007. The analysis used a region-of-interest (ROI) approach based on peak activation coordinates listed in Table 2 as the center of 6mm radius spherical ROIs. An α -adjusted critical p -level threshold of $p < .001$ FWE (corrected for searching the ROI volume) was employed. All ROIs were found to have less activity in ADHD-C compared to controls, but most ROIs also had significantly lower response in ADHD-I relative to ADHD-C. Columns list ROI brain region labels, ROI center coordinates, t scores from the group contrast and significance levels.

<i>Targets vs. Implicit Baseline</i>			Inattentive ADHD vs. Combined ADHD		Healthy Controls vs. Combined ADHD	
Brain Region	Region of Interest Center			ADHD-I > ADHD-C t score	ADHD-I < ADHD-C t score	HC < ADHD-C t score
	x	y	z			
Frontal lobes						
Right middle frontal gyrus (BA 10)	3	3	2	ns	4.56*	6.23***
	3	9	4			ns
Midline pre- supplementary motor area	-3	3	5	ns	6.62**	8.86***
			1			ns
Midline supplementary motor area	3	-3	6	ns	4.33*	8.14***
			3			ns
Left cingulate cortex (rostral cingulate zone)	6	2	3	ns	7.05**	8.93***
Right cingulate cortex (rostral cingulate zone)	-	2	2	ns	6.04**	6.72**
	1	7	4			ns
	2					
Mid-cingulate cortex	0	-6	3	ns	3.72 [†]	7.65***
			9			ns
Left anterior insula	-	9	-	ns	5.19*	7.60**
	4		3			
	2					
Right anterior insula	3	1	-	ns	3.61*	6.22**
	6	5	1			ns
			2			

<i>Targets vs. Implicit Baseline</i>		Inattentive ADHD vs. Combined ADHD			Healthy Controls vs. Combined ADHD		
Brain Region	Region of Interest Center	ADHD-I > ADHD-C <i>t</i> score	ADHD-I < ADHD-C <i>t</i> score	ADHD-I < ADHD-C <i>t</i> score	HC > ADHD-C <i>t</i> score	HC < ADHD-C <i>t</i> score	HC < ADHD-C <i>t</i> score
	x	y	z				
Parietal lobes							
Left sensorimotor cortex	-	-	5	<i>ns</i>	3.14 [†]	7.13 ^{***}	<i>ns</i>
	3	3	1				
Right inferior parietal lobule/supramarginal gyrus	6	6					
	4	-	4	<i>ns</i>	3.85 [†]	5.72 ^{***}	<i>ns</i>
	8	3	8				
		9					
Temporal lobes							
Left superior temporal gyrus	-	0	-	<i>ns</i>	5.49 ^{**}	7.55 ^{***}	<i>ns</i>
	5		6				
	4						
	-	-	0	<i>ns</i>	5.40 ^{**}	9.72 ^{***}	<i>ns</i>
	4	1					
	8	2					
	-	-	-	<i>ns</i>	2.32 [†]	5.90 ^{**}	<i>ns</i>
	6	3	3				
	3	0					
Right superior temporal gyrus	6	-	-	<i>ns</i>	5.47 ^{**}	9.78 ^{***}	<i>ns</i>
	3	2	3				
		7					
	6	-	1	<i>ns</i>	4.47 [*]	7.18 ^{***}	<i>ns</i>
	0	3	5				
		9					
Deep gray matter							
Thalamus (anterior)	-3	-6	6	<i>ns</i>	5.14 [*]	5.22 [*]	<i>ns</i>
Thalamus (posterior)	-3	-	6	<i>ns</i>	4.55 [*]	4.85 ^{***}	<i>ns</i>
		2					

<i>Targets vs. Implicit Baseline</i>			Inattentive ADHD vs. Combined ADHD		Healthy Controls vs. Combined ADHD	
Brain Region	Region of Interest Center			ADHD-I < ADHD-C <i>t</i> score	ADHD-I > ADHD-C <i>t</i> score	HC < ADHD-C <i>t</i> score
	x	y	z			
Other						
Cerebellum	0	-	-	<i>ns</i>	5.03 [*]	8.95 ^{***}
		7	1			
		5	8			
	3	-	-	<i>ns</i>	3.91 [†]	7.84 ^{***}
		7	3			
		8	6			
Left Brainstem	-	-	-	<i>ns</i>	4.60 [*]	6.68 ^{***}
	1	2	1			
	2	4	5			
Right Brainstem	1	-	-	<i>ns</i>	3.56 [*]	7.04 ^{***}
	2	2	1			
		7	2			

<i>Novels vs. Implicit Baseline</i>			Inattentive ADHD vs. Combined ADHD		Healthy Controls vs. Combined ADHD	
Brain Region	Region of Interest			ADHD-I < ADHD-C <i>t</i> score	ADHD-I > ADHD-C <i>t</i> score	HC < ADHD-C <i>t</i> score
	x	y	z			
Temporal lobes						
Left superior temporal gyrus	-	-	6	<i>ns</i>	4.61 [*]	10.20 ^{***}
	6	2				
	0	4				
	-	-	9	<i>ns</i>	3.30 [†]	7.47 ^{***}
	4	3				
	2	3				
Right superior temporal gyrus	6	-	3	<i>ns</i>	4.80 [*]	9.46 ^{***}
	3	2				

<i>Novels vs. Implicit Baseline</i>		Inattentive ADHD vs. Combined ADHD		Healthy Controls vs. Combined ADHD	
Brain Region	Region of Interest	ADHD-I > ADHD-C <i>t</i> score	ADHD-I < ADHD-C <i>t</i> score	HC > ADHD-C <i>t</i> score	HC < ADHD-C <i>t</i> score
7					
	6 - 3	<i>ns</i>	6.03**	9.26***	<i>ns</i>
8					
	6 1				

* $p < .001$,
** $p < .00001$,
*** $p < .0000001$ FWE (using small volume correction)
† $p < .01$ FWE, but does not survive corrections for multiple comparisons (using small volume correction)