Published in final edited form as:

Brain Res. 2009 June 1; 1273: 114–128. doi:10.1016/j.brainres.2009.02.070.

A lack of default network suppression is linked to increased distractibility in ADHD

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Abstract

Heightened distractibility in participants with ADHD as indexed by increased reaction time (RT) variability has been hypothesized to be due to a failure to sufficiently suppress activation in the default attention network during cognitively demanding situations. The present study utilized fMRI to examine the relationship between intra-individual variability (IIV) in task RT and suppression of BOLD response in regions of the default network, using a working memory paradigm and two levels of control tasks. IIV was calculated separately for thirteen healthy control and twelve children with ADHD, Combined Type. Children with ADHD displayed significantly more RT variability than controls. Neural measures showed that although both groups displayed a pattern of increasing deactivation of the medial prefrontal cortex (PFC) with increasing task difficulty, the ADHD group was significantly less deactive than controls. Correlations between IIV and brain activation suggested that greater variability was associated with a failure to deactivate ventromedial PFC with increasing task difficulty. T-tests on brain activation between participants with ADHD with low versus high IIV implicated a similar region so that high variability was associated with greater activity in this region. These data provide support for the theory that increased distractibility in at least some participants with ADHD may be due to an inability to sufficiently suppress activity in the default attention network in response to increasing task difficulty.

Keywords

ADHD; fMRI; medial prefrontal cortex; variability; default attention network

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The authors report no competing interests.

1. INTRODUCTION¹

Attention Deficit Hyperactivity Disorder is a common childhood disorder characterized by inattention, hyperactivity and impulsivity (Barkley, 2006). Although it is a widely studied disorder, the underlying pathophysiology is still much debated. A number of theoretical frameworks have been proposed as mechanisms for the disorder including a weakness in executive functioning (Barkley, 1997), difficulties with reward processing (Sagvolden et al., 1998), and energetic dysfunctions as described by the cognitive energetic model (Sergeant, 2000; 2005). ADHD is a disorder typically characterized by high degrees of intra-individual variability (IIV) in reaction time (RT) (e.g., (Castellanos et al., 2005; Leth-Steensen et al., 2000)). This characteristic high RT variability has been argued to be an important endophenotype for the disorder (Band and Scheres, 2005; Castellanos et al., 2005; Castellanos and Tannock, 2002; Douglas, 1999; Kuntsi et al., 2001; Kuntsi and Stevenson, 2001; Nigg et al., 2004). Increased RT variability has been associated with fluctuations in attention or arousal (Bellgrove et al., 2004; Cao et al., 2008; Stuss et al., 2003) or response control (Suskauer et al., 2008). Greater RT variability has been noted in ADHD compared to healthy control (HC) participants utilizing a variety of different paradigms including inhibition and sustained attention tasks (Alderson et al., 2007; Bellgrove et al., 2005; Cao et al., 2008; de Zeeuw et al., 2008; Epstein et al., 2006; Heiser et al., 2004; Hervey et al., 2006; Johnson et al., 2007; Klein et al., 2006; Kuntsi et al., 2005; Lijffijt et al., 2005; Shallice et al., 2002), choice reaction time tasks (Geurts et al., 2008; Leth-Steensen et al., 2000), flanker paradigm (Castellanos et al., 2005) and working memory tasks (Buzy et al., 2009; Karatekin, 2004; Klein et al., 2006; Piek et al., 2004) and has been associated, in particular, with DAT-1 dopamine transporter genotype (Bellgrove et al., 2005). However, many studies of IIV in ADHD utilize the standard deviation of RT across the entire task, a summary statistic that gives an estimate of variability around the mean and assumes that RTs fall on a normal Gaussian distribution. Recent findings, suggest, that RT distributions of ADHD participants are not necessarily best characterized by fitting the normal distribution because they are usually positively skewed (Douglas, 1999; Epstein et al., 2006; Leth-Steensen et al., 2000) and research suggests that parametric studies of the shape of the RT would provide more information than standard summaries such as the mean and standard deviation (Leth-Steensen et al., 2000).

The ex-Gaussian model is a right-tailed distribution which is commonly used to estimate the distribution of RT (Heathcote, 1996). It can be decomposed into the summation of two independent components: a symmetric Gaussian component and an exponential component (which captures the extremely slow RTs displayed by ADHD participants) which can dramatically influence the mean and standard deviation. A small number of studies have utilized the ex-Gaussian model to examine IIV in ADHD (Buzy et al., 2009; Epstein et al., 2006; Geurts et al., 2008; Hervey et al., 2006; Leth-Steensen et al., 2000) and have all found differences in IIV between ADHD and HC volunteers, with the exception of Geurts et al. (2008). The latter authors suggest that their choice reaction time task of three minutes length may have been too brief to reveal differences in IIV.

¹Abbreviations: ACC: anterior cingulate cortex; HC: healthy control; IIV: intra-individual variability; PFC: prefrontal cortex; RT: reaction time

Variable RT is associated with both weak positive activation of task relevant regions and insufficient suppression of the “default mode network” (Weissman et al., 2006). With regard to task positive activations, slow and variable RT has been linked to altered activation in dorsolateral PFC in HC participants (Bellgrove et al., 2004; Stuss et al., 2003). In a recent study comparing IIV in HC and ADHD participants, increased IIV in controls was associated with a decrease in activity in pre-supplementary motor area and increased activity in prefrontal cortex, whereas the ADHD participants displayed exactly the opposite pattern (Suskauer et al., 2008).

The ‘default-mode’ attention network is a set of brain regions, primarily located along the medial wall of the brain, associated with task-irrelevant mental processes that are putatively *suppressed* in order to perform optimally in cognitively demanding situations (Raichle et al., 2001). That is, these regions are commonly deactive during cognitively demanding paradigms. Deactivation in this network is thought to be due to an interruption of ongoing processes that occur during rest and non-demanding situations (Binder et al., 1999; Gusnard et al., 2001b; Shulman et al., 1997). These processes are thought to include monitoring of the environment, body state or emotional state (Gusnard et al., 2001b; Shulman et al., 1997), ongoing internal thought processes or mind wandering (Binder et al., 1999; Shulman et al., 1997). An inability to sufficiently suppress activation in this network has been linked to distraction or momentary attention lapses and errors in performance (Eichele et al., 2008; Weissman et al., 2006), whereas successful performance has been linked to increased deactivation in these regions in HC participants (Daselaar et al., 2004; Hahn et al., 2007; Hester et al., 2004; Polli et al., 2005). Raichle et al. (2001) proposed that these regions are tonically active, monitoring the surroundings of an organism and must be inhibited in situations that require concentrated attention. In HC subjects, the degree of suppression in these default network regions appears to be related to task difficulty, with greater deactivation associated with increasing difficulty (McKiernan et al., 2003).

Inspired by the Weissman et al. (2006) finding that variable RT is linked to a failure to suppress the default network, Sonuga-Barke, Castellanos and colleagues proposed the “default-mode interference” hypothesis (Castellanos et al., 2008; Sonuga-Barke and Castellanos, 2007). They suggest that variability in performance in ADHD may be due to a dysfunctional synchronization in the default network or interactions between this network and “task-active” regions. Castellanos et al. (2008) examined functional connectivity between active regions usually implicated in cognitive control processes and default network regions during a resting state in ADHD and HC adults. The ADHD subjects evidenced decreases in connectivity between the posterior cingulate/precuneus and task-active regions such as dorsal ACC but also other default network regions such as ventro- PFC. Recent evidence from this group suggests that slow or variable RTs are associated with a weak correlation between task positive regions and task negative regions (Kelly et al., 2004). Finally, a reduction in power in very low frequency oscillations electrodes consistent with default network regions was found in young adults with greater numbers of ADHD symptoms, particularly symptoms relating to inattention (Helps et al., 2008). Low frequency oscillations in resting state fMRI data have previously been found to reflect interactions in the default attention network (De Luca et al., 2006).

This study sought to explore how IIV, calculated using the ex-Gaussian distribution, was associated with deactivation in the default network among children with ADHD, Combined Type in comparison to HC children and whether IIV changed with different levels of task difficulty. Sonuga-Barke and Castellanos (2007) suggest that the default-mode interference hypothesis might be most pertinent for the primarily inattentive ADHD subtype. We sought to examine whether there was support for their theory in our Combined Type sample, considering that these subjects also exhibit inattentive symptoms.

We utilized data from a previous working memory study (Schweitzer et al., under review) to examine how task difficulty level, that is, working memory load, affected patterns of deactivation in the default network in ADHD compared to HC children. Previous research utilizing a working memory task with parametrically-increasing working memory load in HC children suggested an active suppression of default network regions with increasing task difficulty (Thomason et al., 2008). The authors utilized a correlation method to confirm that areas which showed increased suppression with increasing task difficulty overlapped with regions of the default network which were defined by being functionally connected during rest. Castellanos and colleagues address how inattention in ADHD may be related to default network activity interfering with current engagement in active task performance. Hence we sought to examine how default network activity is attenuated in children with ADHD during a cognitively demanding paradigm and with increasing task difficulty. This contrasts with other studies which have examined activity in the default network in ADHD during resting states only.

Based on our previous work (Buzy et al., 2009) we hypothesized that children with ADHD would display greater levels of IIV than controls during the working memory paradigm. We also predicted that IIV would increase with task difficulty in all children (McKiernan et al., 2003; Thomason et al., 2008). Furthermore, we expected that participants with ADHD would fail to sufficiently suppress activity in the default attention network with increasing cognitive load and that this would be paired with increased IIV in comparison to their healthy control peers. Finally, we hypothesized that ADHD children who displayed the least amount of suppression of the default network would also have greater levels of intra-individual RT variability.

2. RESULTS

The following results represent a subset of participants from our previous working memory study (Schweitzer et al., under review). We excluded one ADHD female from this analysis as her data for the present study lay almost 3 standard deviations outside her peers'. Groups did not differ across age, SES, or IQ (Table 1). There were no differences in accuracy or mean RT between the ADHD and HC groups on the Visual Serial Attention Task (VSAT), Addition Task (AT) or Match to Sample Task (MST). Accuracy was defined as the percent correct responses of all attempted responses, that is, excluding omission trials. In other words, including trials on which ADHD participants attempted to respond, there were no differences in performance between groups. The ADHD group did produce significantly more omission errors on both the VSAT and AT paradigms, suggesting greater inattention or distractibility as task difficulty increased (Table 2).

Two-tailed independent t-tests revealed no significant differences in movement between groups in any of the six directions measured (x, y, z, pitch, roll and yaw), although there was a non-significant trend for ADHD participants to move more in the x direction ($t(23) = 1.87$, $p < 0.09$).

2.1 IIV during working memory and control tasks

2.1.1. sigma—Figure 1a presents a graph of IIV, represented by sigma, for the ADHD and HC groups across the tasks. The figure suggests greater variability for the ADHD children than HCs, but with some outliers and modest sample sizes. A Mann-Whitney test of variability confirmed significantly greater RT variability for ADHD children only for the VSAT ($p = 0.01$). Examination of IIV across tasks via further Mann-Whitney tests revealed that for all subjects there was a significant increase in variability with increasing task difficulty from MST to AT ($p < 0.001$) but not from AT to VSAT. Testing each group separately revealed a significant increase in variability with increasing task difficulty from MST to AT ($p < 0.001$) in controls but no significant change from AT to VSAT. Participants with ADHD showed a significant increase in IIV from MST to AT ($p < 0.001$) and AT to VSAT ($p = 0.01$).

2.1.2 tau—Figure 1b presents a graph of tau for the ADHD and HC groups across the tasks. The figure suggests larger tau for the ADHD children than HCs. A Mann-Whitney test of variability confirmed a significantly greater tau for ADHD children only for the VSAT ($p = 0.01$), with a trend in that direction for the AT ($p = 0.08$). Examination across tasks via further Mann-Whitney tests revealed that for all subjects there was a significant increase in tau with increasing task difficulty from AT to VSAT ($p = 0.001$) but not from MST to AT. Testing each group separately revealed a significant increase in tau with increasing task difficulty from AT to VSAT ($p < 0.001$) in participants with ADHD only.

2.1.3 sigma plus tau—Figure 1c presents a graph of IIV, represented by sigma plus tau for the ADHD and HC groups across the tasks. The figure suggests greater variability for the ADHD children than HCs. A Mann-Whitney test of variability confirmed a significantly greater RT variability for ADHD children only for the VSAT ($p = 0.02$), but with trends for the ADHD group to be more variable than the HC group on the AT and MST (AT: $p = 0.08$; MST: $p = 0.09$). Examination of IIV across tasks via further Mann-Whitney tests revealed that for all subjects there was a significant increase in variability with increasing task difficulty from MST to AT ($p < 0.001$) and from AT to VSAT ($p < 0.001$). These results remained significant when we conducted these tests on each group separately.

2.2 Within-group activation within default attention network regions

The within-group OR map resulted in four regions, the posterior cingulate extending into precuneus, medial PFC and ACC (see Table 3 and Figure 2). Repeated-measures ANOVA of the degree of increased deactivation in AT and VSAT tasks compared to MST baseline revealed main effects of both group and task in ACC ($F(1,23) = 31.83$, $p < 0.001$; $F(1,23) = 4.96$, $p = 0.03$, respectively) and PFC ($F(1,23) = 6.80$, $p = 0.01$; $F(1,23) = 6.52$, $p = 0.01$, respectively) and a main effect of group in ventromedial PFC ($F(1,23) = 11.87$, $p < 0.001$). As Figure 2 reveals, in all three medial PFC regions, there was significantly overall greater

deactivation for HCs than for ADHD participants, a finding that was consistent across both tasks (no significant interaction, $p > 0.10$ for all.) Moreover, the ACC and PFC showed a greater deactivation in the VSAT than in the AT task, consistently for both participant groups (no significant interaction). There was no significant main effect of group or task in the posterior cingulate cortex. T-tests revealed that both groups significantly deactivated this region during all tasks.

The main effect of task in medial PFC combined with the main effect of group suggests that although both groups may have suppressed activation more for the VSAT, the ADHD group suppressed activation in these regions significantly less than the HC group compared to the MST baseline.

2.2.1 Correlations between IIV and brain activation in functionally defined default network regions

—In order to determine if increased RT variability during the task was associated with an inability to suppress activity in the default attention network, we tested correlations between IIV and brain activation during the VSAT (see Figures 3 and 4 for scatter plots). As correlations for sigma alone, tau alone and the combination of sigma and tau all gave similar results (with one exception detailed below), thus we report only the results for the combined sigma + tau IIV. Correlations across all subjects revealed a positive correlation between RT variability and activity in ventromedial PFC ($r(25) = 0.53$, $p = 0.007$), consistent with the hypothesis that greater variability is associated with greater activation (or less deactivation). When we examined each group individually, children with ADHD displayed a strong positive correlation between IIV and activity in ventromedial PFC ($r(12) = 0.73$, $p < 0.008$) whereas the HC group did not show a significant correlation suggesting that the correlation across all subjects was driven by the ADHD group. A negative correlation was revealed for the ADHD group only in the more superior region of medial PFC ($r(12) = -0.59$, $p = 0.05$, see area 1 in Fig 2). Thus those children with ADHD displaying greater IIV were those who deactivated the superior medial PFC more.

We also examined correlations between change in variability and change in brain activity from AT to VSAT to examine whether a large increase in variability from AT to VSAT was associated with a failure to sufficiently suppress activity from AT to VSAT. This revealed a positive correlation in the same ventromedial area for the whole group ($r(25) = 0.52$, $p = 0.008$) and for the ADHD group alone ($r(12) = 0.59$, $p = 0.05$). This is consistent with the hypothesis that participants with a greater increase in variability from AT to VSAT show a smaller activation difference between VSAT and AT (greater suppression in VSAT compared to the AT would be reflected by a larger negative number). When examining whether an increase in tau from AT to VSAT was associated with a failure to suppress activation from AT to VSAT, we found no significant correlation in any region in either group.

We found one negative correlation between IIV in the group as a whole and activity in posterior cingulate ($r(25) = -0.42$, $p = 0.04$) suggesting that children with greater IIV were those who deactivated the posterior cingulate more.

2.2.2 Correlations between ADHD symptoms and IIV and brain activation in default network regions

We examined whether inattentive symptoms alone were correlated with IIV and brain activity in default network regions. Neither DSM-IV inattentive or hyperactive/impulsive scores correlated significantly with brain activation in the ADHD group.

2.3 Between-group activation within default attention network regions

The between-group contrast revealed two regions within the medial PFC/ ACC that were significantly more active in the ADHD as compared to the HC group; that is, the HC group deactivated these regions more than ADHD participants. As Figure 5 reveals, these regions partially overlapped with the HC prefrontal regions from the within-group analysis.

2.4 Independent t-tests on brain activity during the VSAT between participants with low vs high IIV

An independent t-test revealed a small cluster of activation (110 μ l, $x = 3$, $y = 36$, $z = 3$) within our ventro-medial PFC ROI alone when examining the ADHD group solely (see Figure 5), with participants in the high IIV group showing greater activity in this region than participants in the low IIV group. Again, this is consistent with the hypothesis that ADHD participants with the greatest degree of IIV are those who are least able to suppress activity in ventro-medial PFC within the default attention network during a cognitively demanding task.

T-tests between children with low versus high IIV in the group as a whole and in the HC group alone did not result in any activation within our ROIs.

3. DISCUSSION

The default attention network is a group of regions located along the brain's medial wall, which are active during non-cognitively demanding paradigms and have been associated with task-irrelevant thought processes, mind wandering, and attention to the outside environment or one's own mental state (Gusnard et al., 2001b; Shulman et al., 1997). Using tasks with increasing levels of cognitive demand, we isolated a number of regions -- principally in medial PFC and ACC, and consistent with the default attention network -- in which HC participants demonstrated increasing levels of deactivation as task difficulty increased. The pattern of increasing levels of deactivation with escalating cognitive demand was less apparent in our matched sample of ADHD participants. This lack of deactivation was accompanied by larger degrees of IIV in ADHD as compared to HC participants. Furthermore, subjects who displayed the greatest amounts of IIV also failed to sufficiently suppress activity in ventromedial PFC/ ACC.

Greater IIV is generally thought to indicate a lack of attention control (Bellgrove et al., 2004; Stuss et al., 2003). It is a construct frequently associated with ADHD and thought to represent an important endophenotype of the disorder (Band and Scheres, 2005; Castellanos et al., 2005; Castellanos and Tannock, 2002; Douglas, 1999; Kuntsi et al., 2001; Kuntsi and Stevenson, 2001; Nigg et al., 2004). A number of recent studies have used the ex-Gaussian distribution to characterize the pattern of RT responding displayed by individuals with

ADHD (Buzy et al., 2009; Epstein et al., 2006; Geurts et al., 2008; Hervey et al., 2006; Leth-Steensen et al., 2000).

The ex-Gaussian procedure may be superior in capturing multiple components of variability associated with ADHD. Differences emerge between ADHD and control participants in the exponential component of the ex-Gaussian curve which reflects a greater number of particularly slow RTs, represented by the right tail of the distribution (Buzy et al., 2009; Epstein et al., 2006; Hervey et al., 2006; Leth-Steensen et al., 2000). The standard deviation of the normal component of the ex-Gaussian curve also differs between groups (Epstein et al., 2006; Hervey et al., 2006). We previously examined IIV behaviorally in a larger group of children, including some of the children in this study, using the ex-Gaussian distribution model (Buzy et al., 2009) and found an increase in IIV in children with ADHD consistent with previous studies utilizing the ex-Gaussian distribution. IIV was also correlated with ADHD symptom ratings in this study. The present study utilized a quasi-parametric design in that the active working memory task was presented with two control tasks, each less cognitively demanding than the working memory paradigm. Here, we found that RT variability increased among all participants with increasing task difficulty and children with ADHD displayed elevated levels of IIV in comparison to their HC peers.

There are three parameters that describe the ex-Gaussian distribution; the mean and standard deviation of the normal component are μ and σ respectively and the mean and standard deviation of the exponential component are represented by τ . Previous studies of IIV in ADHD have found group differences in both σ and τ (Buzy et al., 2009; Epstein et al., 2006; Hervey et al., 2006) with one study finding differences in τ only (Leth-Steensen et al., 2000). Examination of group and task differences between σ and τ in the present study produced similar results. Participants with ADHD displayed significantly greater σ and τ than their control peers on the VSAT. The HC group displayed a significant increase in σ from MST to AT only whereas the ADHD group's σ value increased across all three tasks. With regard to τ , the ADHD group alone displayed a significant increase from AT to VSAT only. As σ and τ results did not dramatically differ, we deemed it appropriate to use the combined value as a measure of IIV.

Deactivation in the default network, located primarily in posterior cingulate extending into precuneus and the medial PFC, during goal-directed behavior was posited by Raichle and colleagues (Gusnard et al., 2001b; Raichle et al., 2001) to reflect a suspension of ongoing baseline activity. The authors suggested that posterior cingulate extending into precuneus may be involved in general awareness of the environment which is suppressed during demanding mental activities (Raichle et al., 2001; Shulman et al., 1997). They propose that medial PFC is engaged in the interplay between cognitive and emotional information or states (Simpson, et al., 2001b; 2001a). Previous studies of error-related activation have revealed that an insufficient degree of suppression of default network regions predicted an error (Eichele et al., 2008; Polli et al., 2005). The default network has also been associated with non-task related, self-referential mental processes (Gusnard et al., 2001b) and mind wandering (Gilbert et al., 2006; 2007). Inability to sufficiently suppress activity in the default network during a cognitively demanding paradigm may lead to less focus on the task

at hand and more vulnerability to distraction from the external environment or one's own internal non-task-related thoughts (Weissman et al., 2006).

Sonuga-Barke and Castellanos' "default-mode interference hypothesis" (2007) suggests that the characteristic increase in RT variability in ADHD may be due to intrusions by the default attention network into goal-directed activity. They posit that the normally adaptive state of periodically attending to potential novel events in the environment (subserved by the default attention network) can become maladaptive and interfere with ongoing task-related processes. They propose that if activation in the default network surpasses a particular threshold, there is a potential for competition with task-specific attention processes, leaving the individual open to attention lapses and decrements in performance. Castellanos and colleagues (Sonuga-Barke and Castellanos, 2002; Castellanos et al., 2008) purport this as a model for attention deficits in ADHD with inattention stemming from an imbalance between suppressing the default network and activating task-appropriate regions.

In this study we found a number of deactive regions consistent with the default attention network in HC and ADHD children during two tasks of increasing levels of cognitive demand. However, contrary to Castellanos and colleagues' (Castellanos et al., 2008; Uddin et al., 2008) finding of dysfunction in the posterior cingulate in ADHD, we found no differences in patterns of deactivation in this region between ADHD and HC children in either the simpler AT task or the more cognitively demanding VSAT. This held true for both the posterior cingulate region defined by the HC group and that defined by the ADHD group. Group differences were only found in medial PFC. As can be seen in Figure 2, although both groups tended to increase deactivation from AT to VSAT in three regions in medial PFC/ACC, the ADHD group failed to suppress activity in these regions to the same degree as their HC peers.

Given the increased variability in the ADHD group paired with an inability to sufficiently suppress activity in the default network during more difficult tasks, we examined whether children in this group displaying increased IIV would be prone to suppression failure in areas of the default network. The medial prefrontal region that extended into ventral ACC was the only region to display a significant positive correlation between brain activity and IIV. A region in superior medial PFC displayed a negative correlation between IIV and activity. Examining all children as a whole, those with greater RT variability during the VSAT also tended to display less deactivation in the ventro-medial PFC during the working memory task. We also examined correlations between the change in variability and brain activation from AT to VSAT and found that overall, children who showed the greatest increase in IIV from AT to VSAT were also the children who failed to successfully suppress activity from AT to VSAT tasks. The same pattern was found for the ADHD group only, perhaps due to greater variability in that group compared to the HC group. Finally, an independent t-test between children in the ADHD group with low versus high IIV revealed a significant relationship between IIV and brain activity within the functionally-defined area in the default network in the ventro-medial PFC (see Fig 6).

These data support the theory that increased RT variability in the ADHD group was associated with an inability to suppress activity in the default attention network (specifically

in medial PFC) during a working memory paradigm. As mentioned previously, medial PFC/rostral ACC is thought to be involved in self-referential activity (see (Castelli et al., 2000) for a review), monitoring one's own or others' emotional state (Frith and Frith, 2006; 2003; Lane et al., 1997;1998) or a task-dependent dynamic interplay between cognitive and emotional states (Simpson, et al., 2001b; 2001a). Increased deactivation in medial PFC, in particular, has been noted in performing cognitively demanding tasks (Gusnard et al., 2001a; 2001b; Lawrence et al., 2003; Shulman et al., 1997) and has been linked with successful performance in healthy controls (Hahn et al., 2007; Hester et al., 2004).

A number of authors suggested that suppression in medial PFC during cognitively demanding situations may reflect a redirecting of resources from internal monitoring during less demanding situations in favor of attention to an external source (Gusnard et al., 2001a; 2001b; Hester et al., 2004; Polli et al., 2005; Raichle et al., 2001). It is possible, therefore, that HC children in this task were more adept than their ADHD peers at suppressing task independent, self-directed thought during the more cognitively demanding portion of the task. An alternate possibility is that the baseline task was more demanding for ADHD than HC participants, resulting in lower baseline levels of task independent thought in these subjects. A recent study examining default network activity revealed attenuated levels of activation in medial PFC, ACC and posterior cingulate in children compared to adults (Marsh et al., 2006). This finding was interpreted as being due to greater automaticity of performance on the baseline task in adults leading to an increase in task-irrelevant thoughts compared to children. However, we believe that the first possibility is more likely, as there were no significant performance differences between groups on the MST task and the ability to suppress activity in the medial PFC was associated with better performance (in the form of less IIV) during the working memory task. Therefore we suggest that an inability to suppress task-independent thought may have led to an increase in IIV in the ADHD group. However, we cannot rule out the possibility that ADHD children are less able to engage in task-independent thought during the MST, as they displayed a non-significant trend to greater IIV during the MST condition.

Although Castellanos and colleagues (2008) suggest that the region of the default network incorporating posterior cingulate extending into precuneus may be a core of dysfunction in ADHD participants responsible for increased variability, we found no suggestion of any difference between ADHD and HC participants in this region. Furthermore, we found that in the group as a whole, increased IIV was associated with increased suppression of posterior cingulate, whereas we might have expected a correlation in the opposite direction. However, Castellanos et al. (2008) examined default network activity in a group of adults at rest. Significant differences between the adult and child default network have previously been noted (Fair et al., 2007; 2008), with regions being "sparsely functionally connected" (page 4028) (Fair et al., 2008) in children from 7 to 9 years of age. In children, proximal regions tend to be interconnected more than in adults, whereas distal regions, such as medial PFC/rostral ACC and posterior cingulate, tend to be less interconnected (Fair et al., 2007). Default network structure in adolescents is thought to lie somewhere between that of children and adults, with shorter range connections being progressively broken and longer range connections being formed (Fair et al., 2007). Our sample included children in the

range of childhood to young adolescence, precisely the period during which these changes are taking place.

Furthermore, we examined active suppression of the default network during a cognitive paradigm involving a parametric manipulation of task difficulty rather than during rest. Previous research has suggested that examination of regions that show task-related decreases in activation and regions that are highly correlated during rest are both effective methods of defining default attention regions in children (Thomason et al., 2008). To the best of our knowledge, we are the first group to examine the default attention network during situations of increasing cognitive demand in a group of ADHD participants.

It is compelling that we found the hypothesized pattern of increased variability associated with an inability to sufficiently suppress activity in a region of the default network in a relatively small group of children. However, due to the small group of children it is also difficult to draw strong conclusions about the population as a whole. When examining the patterns of correlation between IIV and brain activity (see Figures 3 and 4), it could be argued that only five of the children with ADHD are driving our results. We examined the data to determine whether these children differed in age or severity of symptoms from the rest of the ADHD group and found that they did not. It may be that the default network hypothesis is applicable to at least a large subgroup of individuals with ADHD. Furthermore, we failed to find a correlation between IIV, brain activity and ADHD symptoms in the ADHD group, possibly due to the small number of subjects in this study. Thus, future work may benefit from utilizing larger sample sizes of children with ADHD to further explore the relationship between IIV, ADHD symptoms and default network activity.

Further limitations of our study include our failure to incorporate a rest or fixation point condition between active runs of the task in addition to including a block of fixation-only in order to examine the default network at rest. However, our experience suggested that this would have made the task overly long for our ADHD participants, leading to increased movement and hence a decline in data quality. The participants in our study possessed above-average IQs possibly limiting the generalizability of our results. Finally, varying degrees of exposure to stimulant medication in ADHD participants may have altered brain activation in certain participants. However, recent studies comparing stimulant-naïve and stimulant-exposed pediatric participants (Pliszka et al., 2006) challenge the extent to which these effects exist.

CONCLUSION

Using tasks of increasing parametric difficulty we found elevated IIV in the ADHD group accompanied by a failure to suppress regions of the default attention network to the same degree as their healthy control peers. Furthermore, participants who displayed increased levels of IIV were also those that showed the least suppression in ventromedial PFC. These findings are consistent with the Sonuga-Barke and Castellanos (2007) default-mode interference hypothesis that increased performance variability in at least a subset of individuals with ADHD is due to problems with suppression of the default attention network, given that this group of children with ADHD also displayed greater inattention via

omission errors on the tasks and rating scale data. Future studies should explore the relationship between these findings and neurochemical functioning in individuals with ADHD.

4. EXPERIMENTAL PROCEDURES

4.1. Participants

Through recruitment strategies that included newspaper advertisements, pediatric and ADHD clinics, support groups and websites 17 ADHD and 22 HC children between the ages of 8 and 14 years were recruited. The final group of participants included 12 ADHD (11 male) and 13 HC (8 male) children selected to match the age, IQ, and SES of the ADHD group (see Table 1). Six (four ADHD) children were excluded for excessive amounts of movement or asking to discontinue the fMRI session. One ADHD female also had data that lay almost 3 standard deviations outside her peers' and thus was excluded from further analysis. Those taking stimulant medication (n=9) did not take it for 48 hours before the fMRI session. The HC group included one and the ADHD group included two left-handed volunteers. Participants received a \$50 gift certificate and parents received \$15/hour for their involvement. Volunteers were recruited through newspaper advertising, pediatric and ADHD clinics, support groups and websites. Parents gave written informed consent; participants 13 and older gave written assent, whereas younger participants gave verbal assent for a protocol approved by the University of Maryland School of Medicine IRB.

ADHD participants met DSM-IV-TR criteria for ADHD, Combined Type based on the Diagnostic Interview for Children and Adolescents (DICA, (Reich,2000), follow-up interviews (Barkley,1998) and parent rating scales (Conners, 1997); (see Table 1). The absence of psychopathology and learning disabilities was confirmed in all healthy controls using the same components (i.e., clinical interview, ratings, IQ & achievement testing) of the screening process. All volunteers participated in all phases of the screening process.

Participants with co-existing Axis I or II diagnoses (except for ADHD in the ADHD group), metal or prosthesis in the body or major medical conditions were excluded. Volunteers with first-degree family members with a history of severe mental illness and controls with first-degree family members with ADHD were excluded. Only assistants with a master's level degree in psychology or higher conducted the clinical interviews and psychological testing. A licensed, Ph.D. level psychologist (J.B.S.) then reviewed all evaluations to determine whether participants were appropriate for the study.

4.2. Experimental Task

The results from the working memory component of this study are reported elsewhere (Schweitzer et al., under review). The VSAT working memory condition presents single-digit random numbers with participants adding each number to the one on the preceding screen and comparing the sum to an "answer" in parentheses (see Figure 7). An easier paradigm, a simple addition task (AT), required participants to add two numbers presented on the same screen and compare the sum to an answer in parentheses. The easiest control task, a match to sample task (MST) required participants to report whether two

simultaneously presented numbers matched. Minimal working memory was involved in either control task, as stimuli and answers were presented on-screen simultaneously. Only participants who performed a minimum of 85% correct on all tasks in previous training outside the scanner were selected to participate in the imaging session. This minimized the potential for disproportionate numbers of incorrect responses between groups contaminating or biasing group difference activation maps (Murphy and Garavan, 2004).

Task stimuli were presented for 1 sec with an ISI of 2.8 sec. Each condition consisted of 10 events (an additional 4 MST events were included in the first block to allow for T1 equilibration effects) and alternated as follows: MST, AT, VSAT, MST, AT, VSAT, MST, AT, VSAT, MST. Each participant completed three runs of the task.

4.3 Behavioral data analysis

We considered any RT of less than 150 msec as either an accidental press or a very late response to the prior trial and excluded these trials from any further analyses (see Buzy et al., 2009). We then fit the ex-Gaussian model to estimate the model parameters and used these to estimate intra-individual variation (IIV) in RT. When this model is a good fit to the data, it should give more stable estimates of the IIV, especially with small samples with outliers compared to a standard normal distribution. Model validation indicated a good fit and that the primary source of between-person differences in IIV was variation difference (both from the normal and exponential components), not shifts in the normal component's mean (results not shown).

The numerical algorithm *Quantile Maximum Probability Estimator (QMPE)* (Heathcote et al., 2004) was used to estimate the ex-Gaussian parameters. IIV was estimated within each condition (MST, AT and VSAT), for all 25 subjects (13 HC and 12 ADHD). In addition to examining the variability of Gaussian component (σ) and the exponential component (τ) separately we used a combination of the two as our estimate of the intra-individual RT variability as expressed by the following equation:

$$IIV = \sigma + \tau$$

Mann-Whitney U tests compared IIV between groups and also across conditions (MST to AT to VSAT). A non-parametric test was chosen as we are assuming non-normality or lack of equality of variance of the IIV data. IIV across conditions was compared examining all participants as a whole and also within each group (HC and ADHD).

4.4 fMRI data acquisition and analysis

A 1.5T Philips Eclipse scanner (Philips Medical Systems, Cleveland) equipped with high performance gradients acquired 88 high resolution T1-weighted axial slices (TR = 25 msec; TE = 4 msec; matrix size = 256×256; 1.5mm slice thickness; FOV=230 mm). High resolution anatomical scans were not collected for five (three ADHD) participants due to the child's request to end the scanning session. Each functional run acquired 223 volumes (22 axial, 5 mm slices, 1 mm gap) using single-shot, T2* weighted, echo-planar imaging

sequences (TR = 2000 msec, TE = 35 msec, matrix size=128×128, FOV = 230 mm). Vision 2000 goggles from Resonance Technologies (Northridge, CA) presented the stimuli.

Data were preprocessed and analyzed using AFNI software (Cox, 1996) (<http://afni.nimh.nih.gov/afni>). Volumes were 3D motion corrected and aligned to the eighth volume in the run immediately preceding the structural scan. The first seven volumes as well as volumes displaying excessive motion (more than one voxel size or 5mm) were excluded from further analysis. Data were smoothed (4mm Gaussian FWHM) and converted to percent change scores using MST as baseline and any activation outside the brain was set to zero.

For each participant, data from all runs were concatenated together. Due to excessive movement, the final run was not included for five ADHD children. In the interest of maintaining equal power between groups, we randomly selected five HC subjects, removed their final run and conducted all analyses with matched and unmatched group. We found no differences in the location of functionally-defined regions between matched and unmatched analyses. Ideal waveforms were created for AT and VSAT conditions by multiplying a square-wave function with a hemodynamic response function. Multiple regression analyses generated percent signal change for AT and VSAT above MST baseline. Motion parameters were modeled as variables of no interest. Images corresponding to estimates of the parameters of interest were then warped into the standard Talairach space (Talairach and Tournoux, 1988) ($1 \times 1 \times 1 \text{ mm}^3$).

4.4.1 Within- and between-group activation maps—One sample t-tests against the null hypothesis of no signal change from MST baseline were conducted for each group and each condition separately. Independent t-tests were also carried out between HC and ADHD groups on VSAT activation maps. All activation maps were thresholded at a voxel-wise threshold of $p = 0.001$, paired with a minimum cluster-size criterion of 136 μl , determined by Monte Carlo simulations, resulting in an overall 5% probability of a significant cluster surviving by chance. Thus activation maps were corrected at $p = 0.05$, corrected for multiple comparisons. Within-group VSAT and AT regions from both groups were combined into one “OR” activation map whereby any active voxel in any map survives in the combined map, resulting in one HC and ADHD AT plus VSAT map. Based on our hypothesis that increased performance variability would be linked to activation in regions in the default attention network, only functionally defined regions of deactivation in areas consistent with this network were selected for further analysis. For working memory associated activations see (Schweitzer et al., under review).

Average activation, per region, from the OR default network map, was determined for each participant. Repeated measures 2 (Group) $\times$ 2 (Condition) ANOVA were carried out in each region to examine any main effects of condition, group or any significant interaction between them. One-sample t-tests, against the null hypothesis of no activation change, were also performed in each region for each condition and each group to ascertain whether or not de/activation was significantly different from MST baseline. Correlations between average activation in each functionally-derived default region and IIV were carried for all participants and for each group separately (HC and ADHD). To test the hypothesis that

inattention, in particular, is associated with default network activity and IIV, we correlated DSM-IV inattentive and hyperactive/ impulsive scores with VSAT IIV, and VSAT – AT IIV scores, VSAT activation and VSAT – AT activation in each functionally-derived default region.

4.4.2 Brain activation resulting from t-tests between individuals with high and low IIV in functionally defined regions of interest—To examine what brain regions were associated with high and low IIV, we carried out split-half analyses, dividing ADHD subjects into either low or high variability groups and performing an independent t-test analysis between high IIV and low IIV groups. We also performed this analysis for the HC group alone and for all subjects pooled together. Activation maps were thresholded at $p < 0.005$ paired with a cluster criterion of 100 μl . We limited activations to regions of interest (ROI), defined by the centers of mass of our functionally defined regions from our activation maps. We created spheres of 5mm radius around these centers of mass which served as our ROIs. This afforded us additional power as we were not examining every voxel in the brain but merely any active voxels within our ROIs (this resulted in four regions defined by the OR map). Thus, independent t-test analyses were conducted examining 1) All subjects together and 2) Within-group (HC and ADHD separately).

4.4.3 Tests for handedness and gender effects—We conducted a number of t-tests in order to determine whether handedness or gender inequality between groups may have affected our activation maps. Statistical tests excluding left-handed participants and the extra females in the control group did not change the activation maps beyond differences that were explicable by the extra power of greater numbers of participants. Therefore we deemed it appropriate to include the left-handed children and the extra numbers of females in the HC group.

Acknowledgements

The authors thank the participants and their parents; Mark Cochran, Ph.D., Rao Gullapalli, Ph.D., Malle Tagamets, Ph.D., Caitlin Dunning, Psy.D., Barbara McGee, J. Daniel Ragland, Ph.D., Gloria Reeves, M.D., T. Andrew Windsor and Jiachen Zhuo for their assistance. Funding for this study was provided by the National Institutes of Mental Health, National Institute of Health (R01 MH066310) and University of Maryland School of Medicine Intramural Award to J.B.S. Additional support was partially funded by Grant Number UL1 RR024146 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

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Figure 1.

Graphs of IIV (represented by sigma in panel A, tau in panel B, and the sum of sigma and tau in panel C) for the ADHD and HC groups across MST, AT and VSAT tasks. Individual results for RT variability are displayed by the dot plot and mean and standard deviation are represented by the vertical line.

Figure 2.

Regions in default mode attention network resulting from the HC and ADHD “OR” within-group activation map.

Bar plots illustrate the signal change associated with each group (HC and ADHD) during AT and VSAT tasks in each functionally defined region from the OR within-group contrast map.

Medial PFC [bar plots: 1) superior medial PFC, 2) ACC and 3) ventromedial PFC].

HC children displayed significant deactivation in medial PFC during AT and VSAT tasks, with a tendency to increase deactivation for the VSAT working memory task (1, 2 and 3). Activation in medial PFC in ADHD children did not significantly differ from MST baseline in any region except in a superior region of medial PFC (1), which they significantly deactivated during the VSAT, although not to HC levels. In fact, examination of the bar plot

reveals that children with ADHD deactivated the ACC during the VSAT to a similar degree as HC children during the simpler AT condition. Repeated measures ANOVA revealed a main effect of group for all medial PFC regions (1, 2 and 3) and a main effect of condition for a superior region of medial PFC (1) and ACC (2). Thus the HC group tended to deactivate medial PFC more than the ADHD group in general and deactivation was significantly boosted with increasing task difficulty.

Posterior cingulate/ precuneus (bar plot 4): The bar plot reveals that both HC and ADHD participants significantly deactivated posterior cingulate/ precuneus during AT and VSAT tasks (4). Therefore both groups deactivated posterior cingulate extending into the precuneus equally for the AT and VSAT conditions.

Figure 3.

Scatter plots illustrating the relationship between IIV and brain activation in all participants combined (on the left) and ADHD participants alone (on the right).

Figure 4.

Scatter plots illustrating the relationship between change in IIV from AT to VSAT tasks and change in activation between AT and VSAT tasks in all participants combined (on the left) and ADHD participants alone (on the right).

Figure 5.

HC versus ADHD between-group VSAT activation map combined with the HC within-group activation map.

Regions in orange are those regions from the HC within-group map. Regions in green were derived from the between-groups map and the yellow regions represent areas that these two maps overlap. Significant between-group differences were seen in medial PFC only, with overlap between maps in rostral ACC.

Figure 6.

Low versus high IIV between-group VSAT activation map.

Between-group activation was examined in ROIs based on the centers of mass of within-group regions from the HC and ADHD maps. One small cluster of activation was noted in the ventromedial PFC ROI only. ADHD participants with high levels of IIV showed greater levels of activity (that is, less deactivation) in this region. The ROI is represented in range and the cluster in yellow in this figure.

Figure 7.**Experimental Paradigm**

The paradigm used included three levels of task difficulty: A) the MST (Match-to-Sample Task) required participants to respond "yes" by a right-hand button press if the number on the top of a screen matched one presented on the bottom or "no" by a left-hand button press if the numbers displayed were different; B) the AT (Addition Task) required participants to respond "yes" by a right-hand button press if the sum of the top two numbers equaled the number in parentheses and "no" by a left-hand button press if the sum differed from the

number in parentheses; C) the VSAT (Visual Serial Addition Task) was the most difficult level of task. Each number on the top of the screen is added to the top number from the previous trial, and the sum was compared to the number on the bottom in parentheses. Again participants responded “yes” if the sum was correct by right hand button press and “no” the sum was incorrect by left hand response.

Table 1

Demographics and Characteristics

Variable	Control Group		ADHD Group		p
	Mean	Std. Dev.	Mean	Std. Dev.	
Age	10.6	1.8	10.94	4.22	0.80
WISC-III Full Scale IQ	117.62	12.15	115.58	9.28	0.65
WJ-III					
Calculation	113.77	10.97	110.42	10.07	0.44
Passage Comprehension	106.69	7.56	108.17	13.31	0.73
Word Attack [†]	109.17	9.19	110.18	10.13	0.80
CPRS-R:L Scales					
Cognitive Problems/ Inattention	44.46	4.08	69.83	8.04	0.0001*
Hyperactivity	44.62	2.29	69.33	6.92	0.0001*
ADHD Index	43	2.58	72.25	6.21	0.0001*
DSM IV Inattentive	43.15	2.79	72.83	6.53	0.0001*
DSM IV Hyperactive	44.54	3.82	70.75	8.57	0.0001*
DSM IV Total	43.69	3.84	73.75	5.99	0.0001*
CTRS-R:S Scales:					
Cognitive Problems/ Inattention	48.64	5.56	54.8	6.91	0.03*
Hyperactivity	45.3	1.57	59.4	14.09	0.01*
ADHD Index	48.82	3.22	62.8	14.07	0.007*

Note: WISC: Wechsler Intelligence Scale for Children III Edition;

WJ-III: Woodcock Johnson III Edition;

CPRS-R:L: Conners' Parent Rating Scale-Revised: Long Version;

CTRS-R:S: Conners' Teacher Rating Scale-Revised: Short Version. CTS-R:S scores may have been acquired from teachers during periods of time they observed the subjects with ADHD when they were medicated, resulting in lower than expected scores.

[†] df = 21 due to missing data from one HC and one ADHD participant

Table 2

Behavioral Performance

Variable	Control Group		ADHD Group		t(23)	p
	Mean	Std. Dev.	Mean	Std. Dev.		
VSAT						
MST						
% Accuracy	95.94	2.38	94.71	4.29	0.91	0.38
Correct Response RT (msec)	747.46	151.53	759.74	121.41	0.22	0.83
% Incorrect Responses	4.03	2.35	5.66	4.12	1.23	0.23
% Omissions	0.53	0.22	1.32	0.4	1.71	0.1
AT						
% Accuracy	85.9	10.06	85.32	9.36	0.15	0.88
Correct Response RT (msec)	1027.74	273.94	1027.74	424.74	0.73	0.48
% Incorrect Responses	14.02	10	14.95	9.16	0.24	0.81
% Omissions	0.67	0.36	2.7	0.85	2.21	0.05*
VSAT						
% Accuracy	87.6	6.66	83.26	8.89	1.41	0.17
Correct Response RT (msec)	1053.59	330.54	1186.44	391.87	0.92	0.37
% Incorrect Responses	12.21	6.7	16.34	8.53	1.36	0.19
% Omissions	1.24	0.77	5.89	1.81	2.29	0.04*

VSAT: Visual Serial Addition Task; AT: Addition Task; MST: Matching-to-Sample Task

Table 3

Default Attention Network Within-group Activations

Region	Brodmann Area	Volume (μl)	Talairach coords. (center of mass)		
			x (RL)	y (AP)	z (IS)
post. Cing/precuneus	23/31/7/6/5	5121	2	-31	49
ACC	24	653	0	27	19
medial PFC	9/10	393	0	53	19
medial PFC/ ACC	24/32	220	-2	42	1

Note: For x, y, z coordinates, R, A & S are positive coords., coordinates; post. Cing, posterior cingulate; ACC, anterior cingulate cortex, PFC, prefrontal cortex corrected for multiple comparisons