Title: Dysfunctional Modulation of Default Mode Network Activity in Attention-Deficit/Hyperactivity Disorder

Running title: Default Mode Network in ADHD

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The study presented in this manuscript has been conducted at Ghent University, Faculties of Psychology and Medicine.

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Abstract

The state regulation deficit model posits that individuals with attention-deficit/hyperactivity disorder (ADHD) have difficulty applying mental effort effectively under suboptimal conditions such as very fast and very slow event rates (ERs). ADHD is also associated with diminished suppression of default mode network (DMN) activity and related performance deficits on tasks requiring effortful engagement. The current study builds on these two literatures to test the hypothesis that failure to modulate DMN activity in ADHD might be especially pronounced at ER extremes. Nineteen adults with ADHD and 20 individuals without any neuropsychiatric condition successfully completed a simple target detection task under three ER conditions (2, 4 and 8 sec inter-stimulus intervals) inside the scanner. Task related DMN deactivations were compared between two groups. There was a differential effect of ER on DMN activity for individuals with ADHD compared to controls. Individuals with ADHD displayed excessive DMN activity at the fast and slow, but not at the moderate ER. The results indicate that DMN attenuation in ADHD is disrupted in suboptimal energetic states where additional effort is required to optimize task engagement. DMN dysregulation may be an important element of the neurobiological underpinnings of state regulation deficits in ADHD.

Keywords: ADHD, state regulation deficit, event rate, fMRI, default mode network.
Introduction

Efficient performance depends on the ability to maintain an optimal energetic state despite changing environmental demands (Sanders, 1983). The performance of individuals with attention-deficit/hyperactivity disorder (ADHD) is hyper-sensitive to experimentally induced changes in certain aspects of the task context (see Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010 for a review). For instance, task performance in ADHD is disrupted at extreme event rates (ERs). A meta-analysis of ER effects on Go/No-Go tasks demonstrated that individuals with ADHD make more impulsive errors under fast ER conditions and respond slower under slow ER conditions (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012). The state regulation deficit (SRD) model applies the framework of Sanders (Sanders, 1983) to explain these effects in terms of deficient management of energetic resources to maintain optimal task engagement under non-optimal conditions (Sergeant, 2005). It has been hypothesized that individuals with ADHD have a problem in applying the required effort to actively modulate extreme ER-related changes in activation states through top down processes (Sergeant, 2005; van der Meere, Börger, & Wiersema, 2010).

Despite a considerable amount of supporting behavioral and psychophysiological evidence relating to the context dependent nature of ADHD deficits, little is currently known about the functional neuroanatomy of SRDs in ADHD. One interesting candidate brain network in this regard is the default mode network (DMN) - one of a number of resting state networks (Broyd et al., 2009; Damoiseaux et al., 2006; Raichle & Snyder, 2007). DMN is a set of brain regions, the activity of which varies as a function of task demands: It is active during “rest” or during less demanding tasks while its activity is attenuated as task-related attentional demands increase (Raichle & Snyder, 2007; Schulman et al., 1997). Recent studies suggest that the DMN in fact consists of a number of functionally distinct core components: In particular an anterior midline component (superior frontal gyrus and ventromedial prefrontal cortex) has
been segregated from posterior midline (precuneus/posterior cingulate cortex) and lateralised components (inferior parietal lobules) (Franco, Pritchard, Calhoun, & Mayer, 2009; Laird, Eickhoff, Li, Robin, Glahn, & Fox, 2009). These distinct components have been implicated in different ways in cognitive processes (Laird et al., 2009). The DMN represents a plausible neurobiological mediator of SRDs in ADHD for a number of reasons. First, it is state dependent - showing deactivations during effort-demanding tasks (Raichle & Snyder, 2007; Schulman et al., 1997). Second, failure to suppress activity within this network sufficiently during tasks is associated with attentional lapses and performance deficits of the sort observed at ER extremes in ADHD (Sonuga-Barke & Castellanos, 2007; Fassbender et al., 2009). Third, DMN modulation is affected by motivational and energetic factors (Liddle et al., 2011), suggesting a role for top down effort regulation. Fourth, it is ER sensitive - with more attenuation during fast compared to slow ER conditions in typically developing adults (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003). Finally, individuals with ADHD have difficulty suppressing DMN activity when required to perform attention-demanding tasks (Fassbender et al., 2009; Liddle et al., 2011) and show aberrant connectivity between DMN and task-positive areas (see Posner, Park, & Wang, 2014 for a review), which has been argued to both reflect a failure of neuro-modulation during rest-to-task transitions and periodic attentional lapses (i.e., DMN interference hypothesis) (Sonuga-Barke & Castellanos, 2007). Crucially, these effects can be ameliorated using medication or rewards (Liddle et al., 2011, Peterson et al., 2009) – both of which improve effort engagement during task performance (Volkow et al., 2004).

In the current paper we present the first data on ER-related modulation of the DMN during performance of an attention demanding task in adults with ADHD to examine the role of the DMN as a potential biological substrate of SRDs. We employed an oddball paradigm – a simple target detection paradigm in which individuals have to respond to rare targets and ignore
common standard stimuli - with trials presented at three different ERs to allow modeling quadratic trends (inter-stimulus intervals of 2 (fast), 4 (moderate) and 8 seconds (slow)). This task is particularly valuable as a way of isolating DMN components empirically because it contains both target stimuli that requires a response and standards which requires less effort.

On the basis of prior evidence that individuals with ADHD are less able to suppress DMN activity when required, we predicted that they would in general exhibit reduced deactivation in DMN than controls when presented with attention demanding oddball targets compared to standards. Further, on the basis of the SRD model we predicted a failure by ADHD individuals to modulate DMN activity as a function of ER - with excess activity being seen predominantly at slow and fast ERs where more effort is needed to modulate under- and over-activation respectively. In statistical terms we predicted a quadratic interaction between ER and group.

Method

The study was approved by the local ethics committee. After complete description of the study, written informed consent was obtained from all participants.

Participants

Twenty adults with ADHD and 20 sex- and age-matched controls (age range 18-38 years) without any known neuropsychiatric conditions took part in the study. One adult with ADHD was excluded because the responses were not recorded due to a computer error. All individuals were recruited from the community via advertising and word of mouth. Participants in the clinical group had a formal ADHD diagnosis provided by a trained physician, which was confirmed using a DSM-based structured interview [Diagnostic Interview for ADHD-DIVA (Kooij & Francken, 2010)] administered by an experienced clinical psychologist. The Social
Responsiveness Scale was used to screen out cases with high numbers of autism spectrum disorders symptoms (Constantino & Gruber, 2005). Controls were excluded if they met criteria on any of three ADHD standardized rating scales [ADHD Rating Scale (ARS; DuPaul, Power Anastopoulos, & Reid, 1998), Adult Self Report (ASR; Achenbach & Rescorla, 2003), Wender Utah Rating Scale (WURS; Ward, Wender, & Reimherr, 1993)]. Depression, anxiety and substance abuse were evaluated with the Adult Self Report Scale (Achenbach & Rescorla, 2003). The cutoff scores for these scales are as follows: ARS Adulthood: 4, ARS Childhood: 6, ASR: 70, WURS: 46. Individuals were excluded if they had an IQ below 85 based on the seven subtest short version of the Wechsler Adult Intelligence Scale-third edition (Ryan & Ward, 1999). There were no significant differences between groups in terms of age, gender composition or IQ (Table 1). Ten participants were using stimulants (nine participants were using methylphenidate and one was using dextroamphetamine sulfate) and three of the rest had a history of stimulant use. The participants using stimulants were instructed to stop the intake at least 48 hours before scanning. In addition two participants were using antidepressants (selective serotonin reuptake inhibitors) and one of these participants was taking carbamazepine as a mood stabilizer. These medications were allowed to be continued. None of the controls were using any neuropsychiatric medication or had a neuropsychiatric medication history.

Procedures and Task Design

We employed a simple target detection task likely to produce a high degree of accuracy in both groups in order to optimize the number of trials that could be used for the characterization of DMN and analysis. The task consisted of a series of targets (i.e., Q) and standards (i.e., O) presented for 100 msec in the middle of a blank computer screen. Participants were instructed to press a response pad button using the index finger of the right hand following each target as quickly and accurately as possible. The proportion of targets was
The inter-stimulus interval (during which time a fixation cross was presented) was varied across three randomized blocks (mean inter-stimulus intervals: 2 (fast), 4 (medium) and 8 sec (slow); see Figure 1 for task design). The inter-stimulus interval values were selected based on data from a previous meta-analysis (Metin et al., 2012) that explored the event rate effects on performance of individuals with ADHD.

The inter-stimulus interval was jittered and the intervals were sampled from a pseudo-exponential distribution for efficient analysis of BOLD response. In the fast ER condition the inter-stimulus interval was jittered between 1 and 4 sec; in the medium ER condition, between 3 and 6 sec; and in the slow ER condition, between 7 and 10 sec. The efficiency of accurately estimating the hemodynamic response for stimuli in rapid tasks (i.e., the fast condition) with a variable inter-stimulus interval has been confirmed previously (Dale, 1999). The fast, moderate and slow ER conditions consisted of 300, 150 and 76 trials respectively. In addition we included a 15 sec rest period in the middle of each condition to sample the baseline activity adequately. Each block took approximately 11 minutes and block order was randomized for each participant individually. Each participant received 35 euro compensation for their participation.

fMRI data acquisition and analysis

Data were acquired using a 3T Siemens Magnetom Trio MRI system (Siemens Medical Systems, Erlangen, Germany) with a standard 32-channel head coil. First, anatomical T1-weighted 3D MPRAGE images (TR = 2250 ms, TE = 4.18 ms, TI = 900 ms, acquisition matrix = 256 × 256, field of view = 256 mm, flip angle = 9°, voxel size = 1 × 1 × 1 mm) were acquired for co-registration and normalization. During the experimental task, T2-weighted echo planar images (EPIs) were acquired in 33 slices, in an interleaved scanning order (TR = 2000 ms, TE = 30 ms, acquisition matrix = 64 × 64, field of view = 192 mm, flip angle = 80°, voxel
size = 3 × 3 × 3 mm, distance factor = 0 %). The first four EPI volumes were discarded to restrict the analysis to data acquired during steady magnetization. Images were pre-processed and further analyzed using the Statistical Parametric Mapping software (SPM8; University College, London). Anatomical images were spatially normalized using the SPM segmentation procedure for parameter estimation and re-sliced to a voxel size of 1 × 1 × 1 mm. All functional EPIs were slice-time corrected, and realigned to the first acquired EPI and normalized based on the T1 segmentation parameters, re-sliced to a final voxel size of 3 × 3 × 3 mm, and smoothed with an isotropic full-width half-maximum Gaussian kernel of 8 mm. EPIs were also submitted to the ART toolbox for detection of movement related outliers in BOLD signal (http://www.nitrc.org/projects/artifact_detect/). Outliers were defined as 1 mm movement between two volumes or BOLD signal intensity change between two volumes exceeding three standard deviations of the global mean difference. No subject had more than 10% outliers and the ADHD and control groups did not differ in terms of number of outliers (p > 0.1).

For each trial, BOLD responses were modeled using delta functions at stimulus onset, which were then convolved with a standard hemodynamic response function. The resulting general linear model (Friston et al., 1995) consisted of six task regressors (target/standard crossed with three ER conditions). In addition, each condition included one regressor for rest block, one for error trials (omission and commission) and six realignment-derived movement parameters. Finally, a constant was added for each condition. Time series were corrected for slow drifts by applying a high-pass filter with a 128 second threshold.

Given the hypothesis-driven nature of the current study we adopted a region of interest (ROI) strategy to test our predictions. As the definition of DMN suggests that its activity should decrease as a function of cognitive demands (Raichle & Snyder, 2007), we defined DMN ROIs empirically by identifying regions where activity was significantly attenuated on oddball targets relative to standards using all trials and all participants. To establish this we employed a
repeated measures ANOVA as implemented in SPM with group as a between subject factor, ER and stimulus type (target and standard) as within subject factors. Clusters were retained in the mask if they were also consistent with DMN areas reported in previous studies (Franco et al., 2009, Laird et al., 2009). Three such clusters were identified at a false discovery rate-corrected p level of 0.05 (cluster forming threshold p<0.001) and included in the mask (see Figure 2 and Table 2): Two in the anterior component consisting of ventromedial prefrontal cortex (VMPFC) and a region in left superior frontal gyrus (LSFG) extending into middle frontal gyrus and one posterior component (left inferior parietal lobule (LIPL)). Left Inferior frontal gyrus (LIFG) was also significantly attenuated on target trials. This region was not included in the DMN mask in the current study because it is not typically associated with DMN (see Laird et al., 2009 for a review).

The beta values from the DMN mask for all regressors in the first level model were extracted using MARSBAR software (Brett, Anton, Valabregue, & Poline, 2002). These are the regression coefficients from the multiple regression model and represent the BOLD activity over and above the aggregated baseline associated with a specific experimental condition. As our primary hypothesis concerned task-related deactivations in DMN, we used beta values for target stimuli as the dependent variable. In order to test our predictions a two-way ANOVA was run with group (ADHD, controls) as the between-subject variable and ER (slow, moderate, fast) as within-subject variables.

Results

Reaction times longer than 2000 msec and those within the first 100msec of the trial onset were removed from the analysis. As expected given the choice of task, omission and commission errors were already very low for both groups with near 100% accuracy for all conditions and therefore they were not further analyzed. Reaction times and reaction time
variability increased linearly as ER slowed. Individuals with ADHD responded slower in general and had greater variability than controls. There was no significant interaction between group and ER for reaction time or variability (see Table 3 for descriptive statistics and ANOVA results).

fMRI results

Activity during target trials was greater overall for ADHD than control participants in the selected ROIs within the DMN (F(1.37)=4.49, p=0.04). The main effect of ER was not significant (F(1.85,68.58)=0.6, p=0.54). The two-way interaction of group by ER (F(1.85,68.58)=7.38, p=0.002) was significant, showing that groups were affected by ER manipulation differently (see Figure 3). This interaction followed a quadratic function (F(1,37)=12.94, p=0.001). Post-hoc analyses showed that participants with ADHD, compared to controls had greater activity within DMN regions on fast and slow ER trials (t(37)=2.25 and 2.99, p=0.03 and 0.005 respectively) but not on moderate ER trials (p=0.98). Moreover, while for controls DMN activity levels under these ER conditions were significantly below zero (t=4.03 and 3.36 and p= 0.001 and 0.003 respectively (indicating significant deactivation), for the ADHD group that was not the case. Inclusion of comorbidity (depression and anxiety) scores as covariates did not change the significance of interaction between group and ER.

As a supplementary analysis, we explored the effect of different ROIs on group by ER interaction by extracting the beta values separately for the three ROIs included in the DMN mask and LIFG. We then analyzed the results with a three way ANOVA with group as a between subject, ER and region (VMPFC, LIPL, LSFG, LIFG) as within subject variables. This analysis again showed a quadratic interaction between ER and group (F(1,37)=10.67, p=0.002). The three-way group by region by ER interaction was almost significant (F(5.62,207.9) =2.16,
p=0.052). Examining the ER x group plots for individual ROIs (see supplement) revealed that there was a quadratic interaction for the three regions included in the task but not for LIFG.

**Discussion**

We present the first evidence for a differential modulation of activity in specific DMN regions by ER in ADHD. Our predictions were based on the combined insights derived from the evidence of prior studies showing that individuals with ADHD have difficulty suppressing default mode activity on attention demanding tasks and the theoretical insights of the SRD model (Sergeant, 2005, van der Meere et al., 2010). According to the SRD model, DMN over-activity is predicted to occur primarily in conditions that require additional effort for regulating the behavioral state. Our findings showed that DMN over-activity in ADHD was observed only at ER extremes, while there were no group differences at moderate ER. Therefore, they confirm the predictions derived from the SRD model. This is not the first time that activation within the DMN of individuals with ADHD has been shown to be modulated by contextual or more specifically energetic factors. Using an inhibitory control task Liddle et al. (2011) have previously shown that DMN attenuation is normalized by the addition of performance-contingent reinforcement.

An alternative model, the default mode interference hypothesis, posits that default mode network activity characteristic of the resting brain gradually reemerges during performance on long and boring tasks in individuals with ADHD. In the current study this model would predict excess default mode network activity on slow trials but not on fast trials. Our finding of individuals with ADHD showing difficulties on both slow and fast trials encourages a reconciliation of the DMN interference and the SRD models, which can be formulated as follows. Individuals with ADHD are either unable or unwilling to expand the effort required under sub-optimal, energetically challenging task conditions (extreme ERs associated with under/over
activation or lack of motivation), to suppress DMN interference during response preparation to optimize performance. This refines the concept of DMN interference to highlight its context-dependent nature – only under non-optimal energetic conditions will the DMN attenuation fail in ADHD and lead to disruptions in information processing. At the same time, it provides a putative element relating to the historically underspecified neurobiological substrate of state-regulation mechanisms. This suggests that failure to regulate arousal/activation through effort allocation may be mediated by unattenuated activity within DMN regions. Previous neurobiological accounts of state regulation processes have focused on noradrenergic neurons whose activity is correlated with the changes in arousal level. Noradrenergic neurons originating in the locus coeruleus project widely throughout the entire cortex (Berridge & Waterhouse, 2003). These noradrenergic projections might be important in fine tuning of the balance between task-positive and task-negative networks.

Previously, Kooistra et al. (2010) conducted an fMRI study exploring the effects of ER in adults with and without ADHD. Using whole-brain analysis, this study mainly reported frontostriatal abnormalities in ADHD. However an interaction between group and ER for DMN similar to that in the current study was not found. This difference can be explained by two factors. First, the sample size was small in the previous study and employing a whole brain analysis method rather than a ROI analysis might have reduced the power to detect DMN changes. Second, only two ERs were used in that study which did not allow quadratic interactions to be tested.

While providing the first evidence for differential patterns of DMN modulation by ER in ADHD, the current study has a number of limitations that need to be mentioned. First, although the inclusion of three levels of ER allowed the modeling of the predicted quadratic effect, additional inter-stimulus interval conditions would have provided more information about ER effects on brain activity. Second, many of the adults with ADHD that participated in this
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study probably had a long history of stimulant medication. Although the participants stopped their medication at least 48 hours prior to testing, the stimulants may have a long-term effect on brain activation patterns (see Schweren, de Zeeuw, & Durston, 2013 for a review). Third, the fMRI task designed for the current experiment was not optimized to confirm ADHD-related behavioral effects seen in some previous ER studies. This is because we purposefully chose an easy to perform attentional oddball task with a large proportion of standard compared to target stimuli. This allowed us to (i) explore the impact of ER (i.e., state regulation load) rather than the effects due to computational load and (ii) to increase number of analyzable correct trials and so avoid error related BOLD signal differences between groups. This inevitably led to ceiling effects, especially for errors, and probably reduced the behavioral sensitivity of the task across all parameters. Fourth, in order to keep the block durations equivalent across ER conditions it was inevitable that each ER condition contained a different number of stimuli. This could reduce the power to detect significant effects on brain function in the 8 sec condition which had the fewest trials. However using equal number of stimuli would make slower conditions longer, which could create greater time-on-task effects for these conditions. As we aimed to measure state regulation deficits rather than time-on-task differences in ADHD, we chose to equalize the durations of the conditions.

Finally our approach to defining the DMN ROIs is worthy of discussion. We based these on an analysis of areas that are more active during standard baseline stimuli (where little attention is required) and that show deactivations during attention-demanding targets. While the resulting regions were consistent with previous DMN studies, they did not include all areas that have been previously associated with DMN (Laird et al., 2009). For instance, precuneus and posterior cingulate cortex (PCC), which are typically included in the DMN, were not identified by this method. Consistent with this, a large-scale study reported greater activation in precuneus and PCC during an oddball task for targets compared to standards (Kiehl et al., 2005).
supporting the view that the DMN is not a uniform network and that it harbors marked functional heterogeneity (see Laird et al., 2009 for a review). Therefore we conclude that task-related functional differences within DMN should be taken into account in future studies.

In summary, this study provides the first evidence for differential patterns of DMN modulation by ER as a function of ADHD. As predicted by the SRD model individuals with ADHD failed to effectively suppress activity within DMN regions on fast and slow but not moderate ER trials. Future studies should combine fMRI with psychophysiological measures of effort regulation such as event-related potentials (Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006) or pupil dilation (Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010) to directly test the hypothesis that individuals with ADHD have difficulty allocating effort to suppress DMN interference under sub-optimal and energetically challenging conditions and to explore the impact of effort allocation deficits on attentional lapses and mind wandering. Neurobiological interactions between DMN and the locus coeruleus and other brain regions previously postulated to be involved in state regulation are also ripe for future study.
References


Proceedings of the National Academy of Sciences of the United States of America, 103, 13848-13853. doi: 10.1073/pnas.0601417103


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Figure 1. Task blocks with mean inter-stimulus intervals (ISIs) and trial numbers. Trial types and ISI ranges are given under each block. Block order was randomized for each participant.
Figure 2. Regions of interest (ROIs) included in the default mode network (DMN) mask: a: ventromedial prefrontal cortex (VMPFC), b: left inferior parietal lobule (LIPL), c: left superior frontal gyrus (LSFG). ROIs are overlaid on the T1 template provided by the MRIfcron (Rorden, C., Karnath, H.-O., & Bonilha, L., 2007) software.
Figure 3. Beta values extracted from the DMN ROIs are plotted for each event rate separately for ADHD (N=19) and Control (N=20) groups.

$^a$ Significant between group difference (p<0.05). Error bars indicate standard errors.
Table 1. Demographic data of the participants, scores on screening questionnaires and between group differences.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ADHD (n=19)</th>
<th>Control (n=20)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>11:8</td>
<td>11:9</td>
<td>$\chi^2=0.03$</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td>t-value</td>
</tr>
<tr>
<td>Age</td>
<td>23.88 (4.63)</td>
<td>25.04 (4.82)</td>
<td>0.77</td>
</tr>
<tr>
<td>IQ</td>
<td>110.74 (14.45)</td>
<td>110.50 (7.41)</td>
<td>0.06</td>
</tr>
<tr>
<td>WURS</td>
<td>55.32 (14.43)</td>
<td>19.40 (10.06)</td>
<td>9.06$^a$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median (Min-Max)</th>
<th>Median (Min-Max)</th>
<th>Mann-Whitney U test, z value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASR-ADHD</td>
<td>73 (57-95)</td>
<td>53 (50-61)</td>
</tr>
<tr>
<td>ASR-Subs</td>
<td>52 (50-71)</td>
<td>52.5 (50-65)</td>
</tr>
<tr>
<td>ASR-Depression</td>
<td>58 (50-92)</td>
<td>51 (50-59)</td>
</tr>
<tr>
<td>ASR-Anxiety</td>
<td>52 (50-70)</td>
<td>51 (50-58)</td>
</tr>
<tr>
<td>ARS IA-Adulthood</td>
<td>7 (4-9)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td>ARS HI-Adulthood</td>
<td>5 (2-9)</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>ARS IA-Childhood</td>
<td>9 (4-9)</td>
<td>0 (0-4)</td>
</tr>
<tr>
<td>ARS HI-Childhood</td>
<td>8 (2-9)</td>
<td>1 (0-4)</td>
</tr>
</tbody>
</table>


$^a$ $p<0.0001$

$^b$ $p<0.05$
Table 2. Clusters showing significant attenuation in targets compared to standards.

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI coordinates for peak activations</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left inferior parietal lobule</td>
<td></td>
<td>-42</td>
<td>-76</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-48</td>
<td>-73</td>
<td>34</td>
</tr>
<tr>
<td>Left superior/middle frontal gyrus</td>
<td></td>
<td>-12</td>
<td>59</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-15</td>
<td>44</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-21</td>
<td>29</td>
<td>49</td>
</tr>
<tr>
<td>Ventromedial prefrontal cortex</td>
<td></td>
<td>0</td>
<td>32</td>
<td>-17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3</td>
<td>53</td>
<td>-8</td>
</tr>
<tr>
<td>Left inferior frontal gyrus</td>
<td></td>
<td>-54</td>
<td>29</td>
<td>10</td>
</tr>
</tbody>
</table>

MNI: Montreal Neurological Institute
Table 3. Summary statistics and ANOVA results for the behavioral data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Inter-stimulus interval</th>
<th>ANOVA results (F(1,37))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 sec Mean (SD)</td>
<td>4 sec Mean (SD)</td>
</tr>
<tr>
<td>MRT (msec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>482.26 (45.38)</td>
<td>508.53 (55.90)</td>
</tr>
<tr>
<td>Control</td>
<td>458.41 (52.91)</td>
<td>467.57 (48.08)</td>
</tr>
<tr>
<td>SDRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD</td>
<td>77.33 (18.46)</td>
<td>84.88 (36.43)</td>
</tr>
<tr>
<td>Control</td>
<td>56.58 (13.52)</td>
<td>62.60 (22.46)</td>
</tr>
<tr>
<td>Percentage of omission errors</td>
<td>Median (Min-Max)</td>
<td>Median (Min-Max)</td>
</tr>
<tr>
<td>ADHD</td>
<td>2 (0-23)</td>
<td>0 (0-27)</td>
</tr>
<tr>
<td>Control</td>
<td>1 (0-2)</td>
<td>0 (0-11)</td>
</tr>
</tbody>
</table>

MRT: Mean reaction time, SDRT: Standard deviation of reaction time

<sup>a</sup> ER and interaction effects were analyzed with linear contrasts

<sup>b</sup> p<0.05

<sup>c</sup> p<0.001