Default mode network abnormalities during state switching in attention-deficit/hyperactivity disorder

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Abstract

Background. Individuals with ADHD display excess levels of default mode network (DMN) activity during goal-directed tasks, which are associated with attentional disturbances and performance decrements. One hypothesis is that this is due to attenuated downregulation of this network during rest-to-task switching. A second related hypothesis is that it may be associated with right anterior insula (rAI) dysfunction – a region thought to control the actual state-switching process.

Method. These hypotheses were tested in the current fMRI study in which 19 adults with ADHD and 21 typically developing controls undertook a novel state-to-state switching paradigm. Advance cues signalled upcoming switches between rest and task periods and switch-related anticipatory modulation of DMN and rAI was measured. To examine whether rest-to-task switching impairments may be a specific example of a more general state regulation deficit, activity upon task-to-rest cues was also analysed.

Results. Against our hypotheses, we found that the process of down-regulating the DMN when preparing to switch from rest to task was unimpaired in ADHD and that there was no switch specific deficit in rAI modulation. However, individuals with ADHD showed difficulties upregulating the DMN when switching from task to rest.

Conclusions. Rest-to-task DMN attenuation seems to be intact in adults with ADHD and thus appears unrelated to excess DMN activity observed during tasks. Instead, individuals with ADHD exhibit attenuated upregulation of the DMN, hence suggesting disturbed re-initiation of a rest state.

Key words: Attention-deficit/hyperactivity disorder, default mode network, insula, state switching.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) has a complex pathophysiology related to dysfunctions in multiple brain regions (Coghill et al. 2013; Cortese et al. 2012; E. Sonuga-Barke et al. 2010). Traditional accounts have primarily emphasized the hypoactivation of task-related regions known to mediate effective engagement of attention during goal directed tasks (Aron & Poldrack 2005; Bush et al. 1999; Ernst 2003). However, in recent years, the new focus on the resting brain and the discovery of the default mode network (DMN) has provided a different perspective on deficient attentional engagement during task performance in ADHD (Konrad & Eickhoff 2010; Paloyelis et al. 2007; Raichle et al. 2001). The DMN – encompassing anterior and posterior midline brain structures (medial prefrontal cortex (mPFC) and posterior cingulate cortex (PCC)/ precuneus) – is active during rest or when individuals are engaged in internally-oriented self-referential cognitive processes (Buckner et al. 2008; Gerlach et al. 2011; Spreng & Grady 2010). DMN activity attenuates following engagement with tasks requiring externally orientated, goal directed attention. The degree of attenuation (i) varies as a function of cognitive load (Fransson 2006; Greicius et al. 2003; Greicius & Menon 2004; McKiernan et al. 2003; Pyka et al. 2009; Singh & Fawcett 2008) and (ii) is predictive of performance deficits linked to residual task-related DMN activity (Li et al. 2007; Sonuga-Barke & Castellanos 2007; Weissman et al. 2006). Consistent with the default mode interference hypothesis (Sonuga-Barke & Castellanos 2007) there is evidence of DMN hyperactivation during task performance in individuals with ADHD (Fassbender et al. 2009; Helps et al. 2010; Liddle et al. 2011; Peterson et al. 2009). This is postulated to cause lapses of attention and increased reaction time variability (Karalunas et al. 2014; Weissman et al. 2006).

The exact mechanism leading to DMN interference during tasks in ADHD is currently unknown. One hypothesis is that it is caused by deficient switching from resting to active goal directed task states. More specifically, anticipatory preparation for, and implementation of,

rest-to-task state switching may be impaired in ADHD, reflecting problems in "switching off" the DMN. However, to date, no study has directly investigated DMN modulation during rest-to-task switching as a potential predisposing factor for excess DMN activity during tasks and its interference with performance.

Consistent with its central role in recent models of between brain network switching, our investigation will also focus on the role of the salience network (SN) specifically its core node – right anterior insula (rAI). rAI is a multifunctional region, which gathers and integrates motivationally salient information and fosters effective neural modulation (Dove et al. 2000; Downar et al. 2000; Downar et al. 2001; Downar et al. 2013; Kurth et al. 2010). Being implicated in a wide range of cognitive processes and not only confined to salience processing, rAI has been postulated to play a critical role in state-to-state switching, controlling DMN disengagement and engagement of task-relevant brain networks during rest-to-task transitions (Menon & Uddin 2010; Seeley et al. 2007; Sidlauskaite et al. 2014; Sridharan et al. 2008). Failures of rest-to-task transitioning in ADHD might therefore be expected to implicate rAI. Indeed, although its role in state-to-state switching in ADHD has not been investigated directly, altered insula structure and function has been demonstrated in the condition in children and adults (Lemiere et al. 2012; Lopez-Larson et al. 2012; Spinelli et al. 2011; Sripada et al. 2014; Tian et al. 2006; Valera et al. 2010).

To study rest-to-task switching in ADHD, we used a recently developed task modelled on the classical cued task-switching paradigm (Sidlauskaite et al. 2014). This task includes advance cues signalling upcoming switches between rest and task periods. The use of these cues allows the investigation of anticipatory switch-related neural processes (Brass & Cramon 2002; Meiran et al. 2010). Sidlauskaite and colleagues (2014) applied this paradigm in healthy adults and found that cues signalling upcoming rest-to-task switches elicited downregulation of DMN. The obverse occurred upon cues signalling task-to-rest switches – the DMN was

upregulated. The core node of the SN – rAI appeared to be implicated when switching to tasks required active cognitive engagement.

For the current study, we predicted attenuated anticipatory downregulation of DMN in ADHD accompanied by decreased activation of rAI during rest-to-task switching, as a potential basis for excess DMN activity during tasks in ADHD. To examine whether rest-to-task switching impairments may be a specific example of a more general state-to-state switching deficit (e.g., state regulation deficit) (Metin et al. 2012; Sonuga-Barke et al. 2010; Wiersema et al. 2006), we also examined DMN and rAI activation to cues signaling upcoming task-to-rest switches. This allowed us to investigate whether individuals with ADHD also have problems in re-entering the resting state and re-activating the DMN.

Method

Participants

The study was approved by Ghent University Hospital ethics committee. Participants gave written informed consent and received a monetary compensation for participation. Nineteen individuals with a clinical diagnosis of ADHD (13 combined type; 6 inattentive type) and 21 typically developing controls (TD) participated in the study (the control sample in the current study highly overlaps (4 additional TD participants in the current study) with the subject sample from Sidlauskaite and colleagues (2014). Both individuals with and without ADHD diagnosis were recruited via advertising in local magazines, social websites, word of mouth or from the pool of individuals who have participated in earlier experiments and have agreed to be contacted for future research. Individuals with ADHD met the life span criteria for the disorder and had both an official clinical diagnosis obtained in a clinical setting and a research diagnosis of ADHD established and confirmed using the DSM-IV-based structured clinical Diagnostic Interview for Adult ADHD (DIVA 2.0; Kooij & Francken 2010). Moreover, all participants with ADHD scored above cut-offs on self-report measures of ADHD symptoms retrospectively in childhood (Wender Utah Rating Scale (WURS; M = 62.84, SD = 14.27); childhood ADHD criteria is met when the score is higher than 46; Ward et al. 1993) and in adulthood (Self-report questionnaire on problems of inattention and hyperactivity in adulthood and childhood; following the diagnostic guidelines adults with ADHD were required to exhibit at least 4 symptoms in the inattentinve and/or hyperactive/impulsive domain to meet the adulthood ADHD criteria; Kooij & Buitelaar 1997). None of the TD participants scored above the cut-offs on WURS (M = 26.95, SD = 12.70) and/or Self-report questionnaire on problems of inattention and hyperactivity in adulthood and childhood and nor met the criteria for childhood or adulthood ADHD. All participants had a full range IQ in the normal or above range (> 80) derived from a seven subtest version of the Wechsler Adult Intelligent Scale (Ryan & Ward

1999). Groups did not differ on IQ (TD: *M* = 117.95, *SD* = 11.20; ADHD: *M* = 112.05, *SD* = 13.60; *p* = .146), sex ratio (TD: 9 female; ADHD: 10 female) or age (TD: *M* = 26.80 years, *SD* = 8.62 ADHD: *M* = 29.78 years, *SD* = 9.61; *p* = .308). Nine ADHD group participants were taking psychostimulant medication (8 – methylphenidate and 1 – dextroamphetamine) from which they had to refrain for at least 24 h before the experiment. Four individuals with ADHD were also taking antidepressant medication (3 – selective serotonin reuptake inhibitors and 1 – buproprion chloride) which they could continue using. The overall exclusion criteria were neurological or psychiatric disease and history of brain damage. All participants had normal or corrected to normal vision, four were left-handed (1 ADHD).

Task Design

Presentation software package (Neurobehavioural Systems, www.neurobs.com) was used to program the task. It was presented in the scanner and had three trial types consisting of two different task trials, either a magnitude, where participants had to respond to numerical stimuli by deciding whether they were smaller or bigger than 5, or parity judgment, where participants had to respond to numerical stimuli by deciding whether they were odd or even, and rest trials. At the start of each trial a fixation cross appeared on the screen (500 ms) which was followed by a cue (500 ms) signalling the nature of the upcoming trial, (i.e. parity judgment task (task 1), magnitude judgment task (task 2) or rest). All stimuli were presented on a black screen and viewed via a mirror attached to the head-coil. During task trials, participants were instructed to respond as fast and accurate as possible. Depending on task rules, participants had to respond by pressing a button with their right or left index finger. During rest trials (minimum duration 6000 ms), in contrast to task trials, no stimuli followed the cue and participants were instructed to relax and rest. Trial types alternated in a pseudo-random fashion, so that the switch (task-to-rest, rest-to-task and task-to-task) and repeat (task repeat, rest repeat) trial ratios were kept at 1:3 to ensure a robust switch effect. The duration of inter-event intervals (i.e., the duration of

cue-target and response-fixation cross intervals) was pseudo-logarithmically jittered ranging from 200 ms to 6800 ms to reliably separate anticipatory cue-related activity from target-related activity (Figure 1; also see Sidlauskaite and colleagues (2014) for further details). All participants undertook four blocks of training before the experiment. The first three blocks were single-cue condition trials for learning the cue-trial associations. The last block mimicked the real task where the cues were intermixed and participants had to alternate between the two tasks and rest trials. There was a total of 300 trials in the experiment. These were divided into three runs (approximate duration of one run was 15 min) performed inside the scanner. At the beginning of each run instructions were displayed to remind the cue-trial associations.

Image Acquisition and Data Analysis

Images were acquired using a 3T Siemens Magnetom Trio MRI system (Siemens Medical Systems, Erlange, Germany) with a standard 32-channel head-coil. High-resolution $1mm^3$ anatomical images were taken with a T1-weighted 3D MPRAGE sequence (duration 6 min). Whole-brain functional images were acquired using T2*-weighted EPI sequence, which is sensitive to BOLD contrast (TR = 2000 ms, TE = 35 ms, acquisition matrix = 64 x 64, FoV = 224 mm, flip angle = 80^0, slice thickness = 3 mm, voxel size = 3.5 x 3.5 x 3.5 mm^3, 30 axial slices). To diminish T1 relaxation artifacts, the first four EPI images of every run were removed. Imaging data were pre-processed and further analyzed with Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). During data pre-processing, first, functional images were slice-time corrected and realigned to the first EPI. Second, functional-to-anatomic coregistration was conducted. Next, images were normalized to the Montreal Neurological Institute (MNI) template and smoothed using isotropic 8 mm full-width half-maximum (FWHM) Gaussian kernel and a high-pass temporal filter with a 128 s cut-off was applied. Event-related single-subject BOLD response was estimated using the

general linear model (GLM) in SPM8. The experimental conditions were used to compute event onset vectors. To study cue and switch type-related anticipatory BOLD response, onset-time regressors of interest were formed based on all cue and switch categories. This design enabled us to differentiate the cue-related BOLD response from all other events in the experiment (targets, responses, errors) which were modelled as regressors of no interest. Onset vectors formed the GLM matrix and were convolved with the canonical hemodynamic response function (HRF). Six subject-specific motion parameters were estimated during realignment (3 translational and 3 rotational). All subject-specific motion time-series were visually inspected and the whole data set was excluded from further analyses if motion exceeded 3 mm translationally and/or 3 degrees rotationally. To additionally account for head motion, realignment parameters were included as regressors into the GLM model. Moreover, a two-sample *t*-test analysis of the head motion parameters revealed no significant group differences in neither translational (ADHD: x = 0.173, SD = 0.090; y = 0.141, SD = 0.059; z = 0.429, SD = 0.300; TD: x = 0.183, SD = 0.100; y = 0.163, SD = 0.070); z = 0.382, SD = 0.186); p's respectively: 0.753; 0.296; 0.204), nor rotational (ADHD: roll = 0.0068, SD = 0.0044; pitch = 0.0039, SD = 0.0019; yaw = 0.0029, SD = 0.0012; TD: roll = 0.0054, SD = 0.0029; pitch = 0.0034, SD = 0.0019; yaw = 0.0026, SD = 0.0014; p's respectively: 0.237; 0.414; 0.560) motion.

Whole-brain analyses

Whole-brain analyses were used to define the regions of interest (ROIs) in an independent manner to avoid circularity in the analysis and "double dipping" (Kriegeskorte et al. 2009). First, we needed to establish whether rest cues elicited DMN activity (as was previously shown by Sidlauskaite and colleagues (2014)), thus the neural activity upon rest cues was compared to the activity elicited by task cues (i.e., rest cue vs. task cue contrast. Second, to identify

common switch-related activity, we contrasted all switch cues (irrespective of switch type, thus collapsing across state-to-state and task-to-task switches) with repeat cues (irrespective of repeat type, thus collapsing across rest and task repeat conditions). To confirm that the resulting activation maps from rest vs. task cue comparisons corresponded to the DMN, we masked it using a standard DMN mask, comprised of bilateral superior medial frontal gyrus and posterior cingulate/precuneus (Buckner et al. 2008; Franco et al. 2009). To ensure that the switch-related activation from switch vs. repeat cues corresponded to the SN, specifically rAI, we masked the activation maps using a standard SN mask comprised of bilateral insula and anterior cingulate cortex (ACC) (Kullmann et al. 2013; Seeley et al. 2007). Both DMN and SN masks were generated using the WFU Pickatlas automated anatomical labelling atlas (Tzourio-Mazoyer et al. 2002). All whole-brain single-subject contrasts were subjected to a second-level random effects analysis. To ensure that both groups of participants shared significant activations (i.e., that activations in both groups overlapped), we treated the single-subject contrasts from the two groups as belonging to one group (i.e., we merged ADHD and control group participants into one group) in the second level analysis and whole-brain activation maps were computed using a one sample *t* test to show significant increases in BOLD response. Activations were deemed significant if they survived a family-wise error (FWE) correction at a cluster level ($p < 0.05$), based on an auxiliary voxel-wise height threshold ($p < 0.001$ uncorrected).

ROI analyses

The DMN ROIs, derived from rest vs. task cue comparisons, included superior medial frontal gyrus (SmFG), MNI coordinates 13, 63, 20 and precuneus, MNI coordinates -12, -49, 41. rAI cluster, MNI coordinates 34, 28, 6, was derived from the switch collapsed vs. repeat collapsed comparison (whole-brain (masked) activation maps for the relevant comparisons are provided

in the supplementary material Tables 1-4; Figures 1-2). Experimental condition-related parameter estimates (beta values) were extracted from 10-mm radius spheres centred around the respective MNI coordinate for all ROIs. ROI parameter estimates were used as dependent measures in GLM repeated measures analysis of variance (rANOVA) using Statistical Package for Social Sciences (SPSS, v.19), and Bonferroni correction for multiple comparisons was applied (DMN ROI analyses – $p < 0.025$. Separate rANOVAs were computed to investigate the attenuation and upregulation DMN ROIs. To investigate the attenuation of DMN, rANOVAs for both DMN ROIs including a cue factor with 2 levels, i.e., rest-to-rest and rest-to-task, as a within-subject factor and group as a between-subject factor were computed. To examine the upregulation of the DMN, rANOVAs including a cue factor with 2 levels, i.e., task-to-task and task-to-rest, as a within-subject factor and group as a between-subject factor were performed.

rAI differential modulation by switch type was examined forming a rANOVA with cue type (5 levels to include all switch/repeat types) as a within-subject factor and group as between subject factor.

Results

Error rate did not differ between groups (controls > 97% correct, *SD* = 0.92; ADHD > 86%, *SD* = 13.70; $p = 0.09$). The ADHD group had significantly slower responses in all conditions ($F(1,38) = 9.57$, $p = 0.004$ controls: task-switch *M* = 897 ms, *SD* = 0.20; rest-to-task 826 ms, *SD* = 0.19; task-repeat *M* = 762 ms, *SD* = 0.16; ADHD: task-switch *M* = 1096 ms, *SD* = 0.27; rest-to-task *M* = 1069 ms, *SD* = 0.25; task-repeat *M* = 942 ms, *SD* = 0.21. There was a main effect of switch condition ($F(2,76) = 39.29$, $p < 0.001$), with slowest responses for task switch trials. The group x condition interaction was not significant ($F(2,76) = 1.91$, $p = 0.155$). The ADHD group had a significantly higher intraindividual response time variability irrespective of switch condition (intraindividual coefficient of variation (ICV) = (*SD* response time)/(*M* response time); $F(1,38) = 5.46$, $p = 0.025$). There was neither a main effect of condition ($F(1.6, 60.8) = 1.48$, $p = 0.234$) nor a group x condition interaction ($F(1.6, 60.8) = 1.68$, $p = 0.198$).

Rest-to-task switches: Anterior but not posterior DMN was downregulated (SmFG: $F(1,38) = 5.99$, $p = 0.019$; precuneus: $F(1,38) = 0.74$, $p = 0.393$). No main group effect was apparent (SmFG: $F(1,38) = 0.11$, $p = 0.734$; precuneus: $F(1, 38) = 0.352$, $p = 0.557$). The degree of DMN downregulation did also not differ between groups (group x condition interaction; SmFG: $F(1,38) = 0.005$, $p = 0.942$; precuneus: $F(1,38) = 0.032$, $p = 0.859$) (Figure 2).

Task-to-rest switches: DMN activity was upregulated to cues signalling task-to-rest switches (SmFG: $F(1,38) = 12.97$, $p = 0.001$; precuneus: $F(1,38) = 9.89$, $p = 0.003$). A trend toward a group effect was observed in SmFG ($F(1,38) = 4.53$, $p = 0.040$) with no group effect in precuneus ($F(1,38) = 0.88$, $p = 0.345$; Bonferroni correction $p < 0.025$). Upregulation of SmFG was greater in controls than participants with ADHD (group x condition interaction; $F(1,38) = 5.42$, $p = 0.025$; task-to-rest: $t(38) = 2.93$, $p = 0.006$; task-to-task repeat: $t(38) =$

0.025, p = 0.980), there was no difference between groups in terms of precuneus upregulation (group x condition interaction; $F(1,38) = 2.04$, $p = 0.161$) (Figure 3).

rAI: Switch type modulated rAI activation ($F(2.84, 108.06) = 36.62$, $p < 0.001$), with the strongest rAI response to rest-to-task cues. Groups did not differ with respect to this effect as indicated by the absence of a significant condition x group interaction ($F(2.84, 108.06) = 2.08$, $p = 0.110$). Instead, the ADHD group showed consistently less rAI activation irrespective of switch type ($F(1, 38) = 6.73$, $p = 0.013$) (Figure 4).

Discussion

The present study is the first to test the hypothesis that anticipatory rest-to-task switching is impaired in ADHD. Against our prediction, anticipatory DMN downregulation during rest-to-task switching was intact in adults with ADHD. However, we provide the first evidence for ADHD-related difficulties in DMN upregulation during switching from task-to-rest – as the individual reengages in the resting state. rAI activation was found to be reduced in ADHD, but this was irrespective of switch type.

First, we did not find support for our prediction that excessive DMN activity previously observed during goal directed tasks in ADHD may be due to impaired attenuation of DMN activity during rest-to-task switching. Adults with ADHD downregulated anterior DMN to the same degree as controls. Posterior DMN – precuneus was neither attenuated in controls nor in participants with ADHD. The heterogeneity of the DMN with regard to state switching replicates the findings of Sidlauskaite and colleagues (2014) and is in line with the literature implicating precuneus also in visuospatial processing, orientation within and interpretation of surroundings (Gusnard & Raichle 2001; Hahn et al. 2007). If DMN downregulation during rest-to-task switching is intact in individuals with ADHD, what might then explain DMN hyperactivation during tasks indicated in previous studies (Fassbender et al. 2009; Helps et al., 2010; Liddle et al. 2011; Peterson et al. 2009)? One possibility is that after a successful switch, individuals with ADHD may have difficulties maintaining the required level of effort or motivation to sustain suppression of DMN activity overtime, leading to DMN re-emergence during prolonged task intervals (Sonuga-Barke & Castellanos 2007). This increase in DMN activity over time during task performance has previously been shown in patients with traumatic brain injury (Bonnelle et al. 2011). However, this hypothesis still requires further investigation in ADHD with tasks incorporating longer trial blocks designed to test for sustained DMN suppression.

While the process of "switching off" the DMN appears intact, the results provide some evidence that adults with ADHD may have a problem "switching the DMN back on" when moving back to rest. Interestingly, for task-to-rest switches we found an attenuated anticipatory upregulation of the anterior DMN in ADHD and this novel finding of reduced DMN upregulation has several implications. First, it adds to the previously reported findings of reduced neural engagement during cued response time tasks in ADHD (Clerkin et al. 2013; Cubillo et al. 2012) and electroencephalographic studies reporting reduced CNVs, reflecting reduced preparatory and anticipatory attentional processes (Brunia & van Boxtel 2001; Nagai et al. 2004; Plichta et al. 2013; Poljac & Yeung 2014) in ADHD (Kenemans et al. 2005; Linssen et al. 2013). However, these studies were confined to cues signalling an upcoming task. Our findings suggest that anticipatory neural disturbances are not confined to task-related processing, but also encompass rest preparation, as reflected in attenuated upregulation of DMN. Hence, one possibility is that individuals with ADHD may suffer from altered anticipatory mechanism related to task and rest states or even a more generic one and this requires further investigation in future studies. Second, problems engaging DMN and initiating a resting or an idle state are consistent with the clinical idea that individuals with ADHD have problems calming down after a stimulating task and may also relate to commonly reported sleep initiation difficulties (Owens 2006; Owens 2009).

rAI was differentially modulated by the anticipation of different switch types and both groups exhibited the strongest rAI response during rest-to-task cues. This finding is in line with the model of rAI as a between large-scale brain network switching hub, controlling transitions disengaging the DMN and employing task-relevant brain regions (Menon & Uddin 2010; Sidlauskaite et al. 2014; Sridharan et al. 2008). rAI activation was found to be reduced in ADHD, however irrespective of switch type. rAI dysfunction is in accord with existing literature on insula function and activity alterations in ADHD, as well as evidence of structural

volumetric abnormalities of this region in ADHD (Lemiere et al. 2012; Lopez-Larson et al. 2012; Spinelli et al. 2011; Sripada et al. 2014; Valera et al. 2010). Since rAI is functionally multifaceted and sophisticated, one cannot strictly dissociate its specialized role in switching from DMN to task states, general saliency processing, and regulation of autonomic bodily functions (Medford & Critchley 2010; Seeley et al. 2007). Because rAI activation to cues appeared unrelated to abnormal switching patterns in ADHD, it may indicate general reduced saliency of cues in ADHD.

Limitations

The current experimental task included rest trials to investigate state-to-state transitions. However, on these trials the cued anticipatory phase could not be completely temporally separated from the actual rest period. While task anticipation and initiation were separated by the appearance of a target, rest was not. Nevertheless, our findings provide clear evidence of impaired early cue-related upregulation of DMN in ADHD. The temporal resolution of fMRI is inherently limited due to the BOLD hemodynamic response. Combining fMRI and EEG with its excellent temporal resolution in future studies, may increase our understanding about the timing of the processes involved in impaired anticipatory state switching in ADHD.

Conclusion

Anticipatory rest-to-task switching, in terms of cue-related DMN attenuation, seems to be intact in ADHD and cannot explain excess DMN activity observed during tasks. However, individuals with ADHD do exhibit attenuated DMN upregulation when anticipating switches back to rest, suggesting difficulties in initiating rest or idle states. Reduced rAI activation to cues irrespective of switch type potentially indicates general reduced cue salience in ADHD.

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Conflict of interest

Authors declare no potential conflict of interest.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Figure Legends

Figure 1. An outline of the cued state-to-state switching task. Each trial starts with a presentation of a fixation cross, followed by one of the three cues. The cue indicates the type of the trial. On task trials, after a jittered cue-target interval, a target appears on the screen and subjects have to respond by pressing a correct response button. The jittering interval ranges from 200ms to 6800ms; 50% of the trials has a cue-target interval ranging from 200ms to 2000ms. On 30% of the trials the cue-target interval ranges from 2600ms to 4400ms. The remaining trials have the cue-target interval in a range from 5000ms to 6800ms. The response-fixation cross interval is jittered in the same fashion. The minimum duration of a rest trial is 6000ms; no stimuli are presented and subjects are asked to relax and rest until the next fixation cross and trial indicating cue are presented.

Figure 2. Default mode network modulation anticipating rest-to-rest and rest-to-task switches in adults with ADHD and controls. The average parameter estimates (beta values ± standard deviation (SD)) for the ADHD and control group extracted from default mode network (DMN) regions. (A) Region of interest (ROI) analysis of the DMN – superior medial frontal gyrus (SmFG) during rest-to-rest and rest-to-task cues. (B) ROI analysis of the posterior DMN – precuneus during rest-to-rest and rest-to-task cues.

Figure 3. Default mode network modulation anticipating task-to-task (task repeat) and task-to-rest switches in adults with ADHD and controls. The average parameter estimates (beta values ± standard deviation (SD)) for the ADHD and control group extracted from default mode network (DMN) regions. (A) Region of interest (ROI) analysis of the DMN – superior medial frontal gyrus (SmFG) during task-to-task (task repeat) and task-to-rest cues. (B) ROI analysis of the posterior DMN – precuneus during task-to-task (task repeat) and task-to-rest cues.

Figure 4. Modulation of rAI during different types of switches in adults with ADHD and controls. The average parameter estimates (beta values ± standard deviation (SD)) for the ADHD and control group extracted form rAI per switch/repeat condition.

Figures

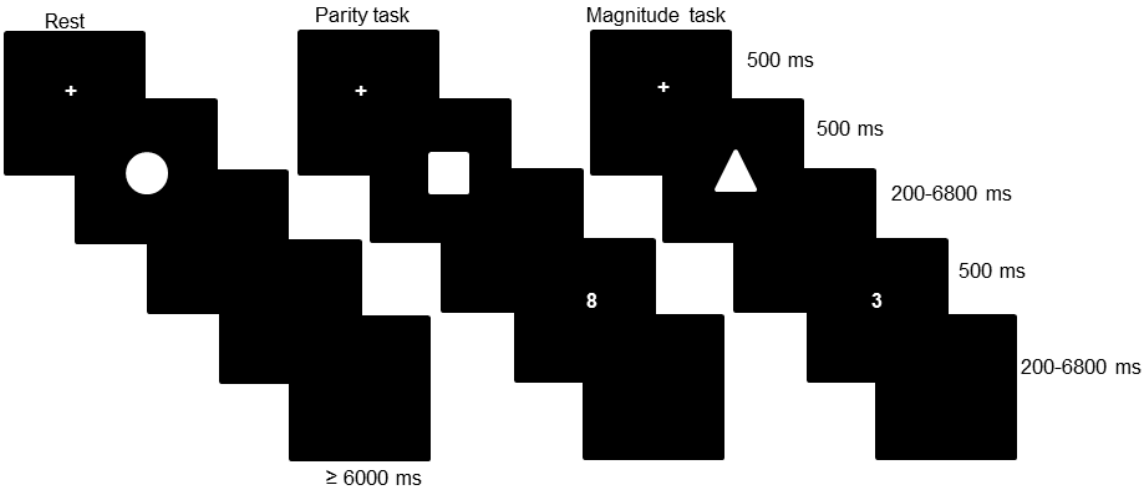

Figure 1.

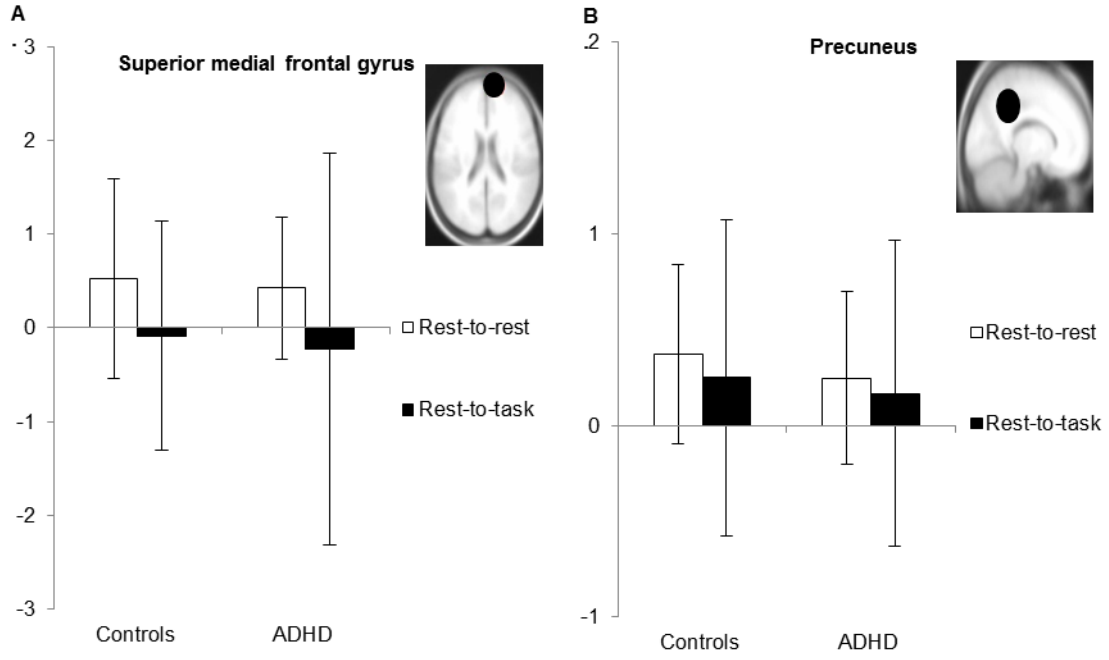
A
Superior medial frontal gyrus
3
2
1
0
-1
-2
-3
Rest-to-rest
Rest-to-task
Controls
ADHD
B
Precuneus
2
1
0
-1
Rest-to-rest
Rest-to-task
Controls
ADHD

Figure 2.

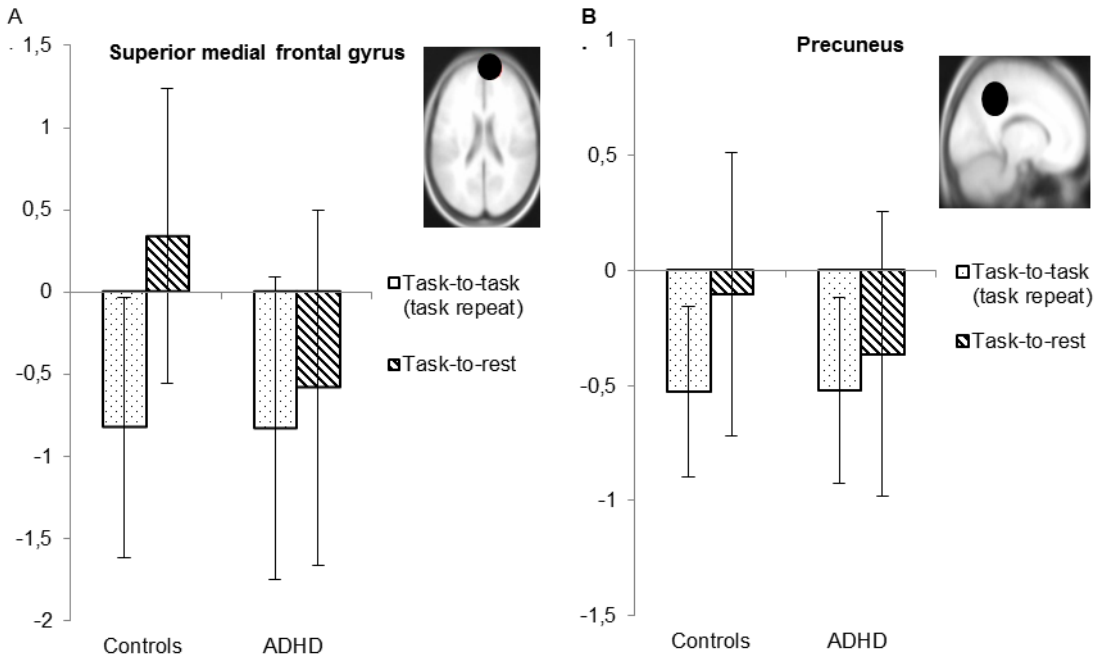
A
Superior medial frontal gyrus
1,5
1
0,5
0
-0,5
-1
-1,5
-2
Controls
ADHD
Task-to-task (task repeat)
Task-to-rest
B
Precuneus
1
0,5
0
-0,5
-1
-1,5
Controls
ADHD
Task-to-task (task repeat)
Task-to-rest

Figure 3.

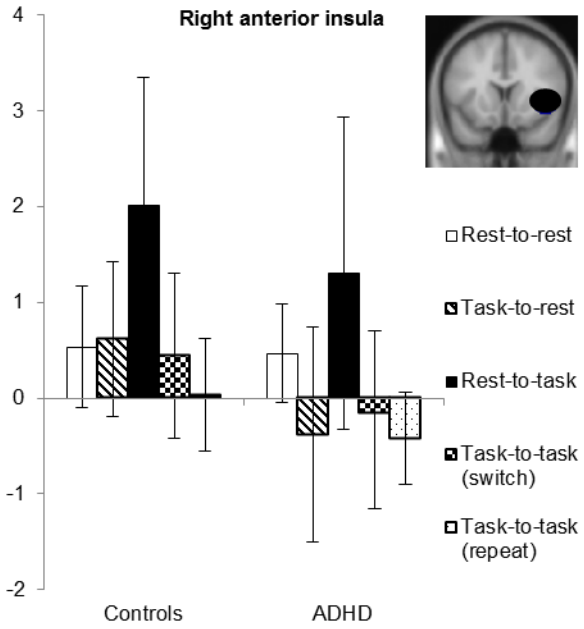
Right anterior insula
4
3
2
1
0
-1
-2
Controls
ADHD
Rest-to-rest
Task-to-rest
Rest-to-task
Task-to-task (switch)
Task-to-task (repeat)

Figure 4.

Supplementary material

Whole-brain (masked) analyses results for the merged ADHD and control group

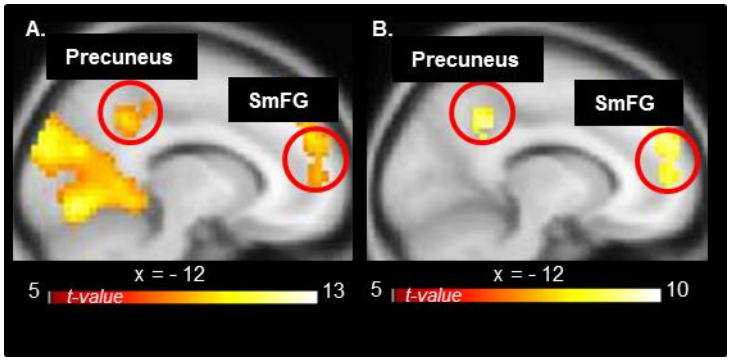

Figure 1. Brain activation map averaged over 19 ADHD and 21 control subjects depicting areas exhibiting activation increases upon rest cues (rest cue vs. task cue). A – whole brain unmasked contrast; B – whole-brain contrast inclusively masked by standard DMN mask; FWE-cluster level corrected $p < 0.05$.

Table 1. Overview of peak activation coordinates of areas for the rest cue vs. task cue contrast.

		MNI coordinates					
Region	Hemisphere	x	y	z	Cluster extent	*Z*-value	FWE-corrected cluster *p*-value
Cuneus	L	-18	-74	-12	2402	7.59	0.000
	L	-18	-88	30		7.58	
	L	-46	-77	20		7.50	
Middle temporal gyrus	L	-57	4	-12	276	7.00	0.000
	L	-57	-7	-4		6.98	
	L	-54	-7	-15		6.82	
Superior medial frontal gyrus	R	13	63	20	578	6.72	0.000
	R	16	42	44		6.31	
	L	-8	52	34		6.28	
Middle temporal gyrus	R	62	-14	-8	373	6.22	0.000
	R	55	0	-18		6.10	
	R	62	4	6		5.96	
Precuneus	L	-12	-49	41	159	618	0.000
	R	10	-42	52		5.91	
	L	-18	-35	48			

Table 2. Overview of peak activation coordinates of DMN areas for the rest cue vs. task cue contrast inclusively masked by the standard DMN mask.

		MNI coordinates					
Region	Hemisphere	x	y	z	Cluster extent	*Z*-value	FWE-corrected cluster *p*-value
Superior medial frontal gyrus	R	13	63	20	472	6.72	0.000
	R	16	42	44		6.31	
	L	-8	52	34		6.28	
Precuneus	L	-12	-49	41	75	6.18	0.000
	R	10	-42	52		5.91	
	R	10	-52	41		5.41	

Figure 2. Brain activation map averaged over 19 ADHD and 21 control subjects depicting areas exhibiting activation increases upon switch cues (switch cue vs. repeat cue). A – whole brain unmasked contrast; B – whole-brain contrast inclusively masked by standard SN mask; FWE-cluster level corrected $p < 0.05$.

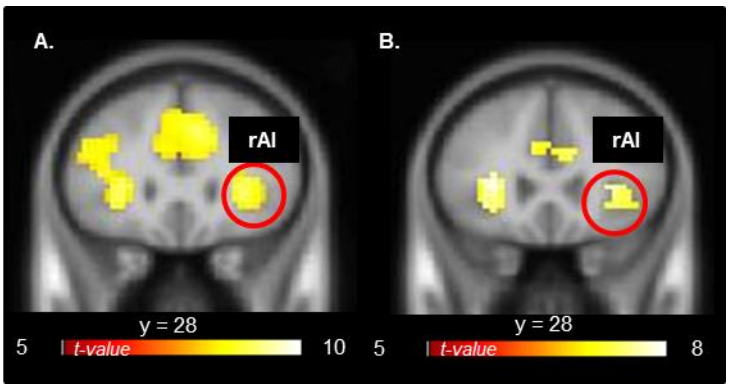

Table 3. Overview of peak activation coordinates of areas for the switch cue vs. repeat cue contrast.

		MNI coordinates					
Region	Hemisphere	x	y	z	Cluster extent	*Z*-value	FWE-corrected cluster *p*-value
Inferior parietal lobule	L	-39	-49	44	1183	6.84	0.000
	L	-12	-74	41		6.65	
	L	-50	-42	48		6.48	
Supplementary motor area	L	-8	10	58	1560	6.62	0.000
	L	-15	4	62		6.55	
	L	-29	24	10		6.34	
Cingulate gyrus	L	-4	-35	27	176	6.43	0.000
	L	-1	-18	30		5.79	
	L	-1	-7	34		5.01	
Right anterior insula	R	34	28	6	132	6.02	0.000
	R	24	21	-1		5.49	
Cerebellum	R	38	-56	-29	61	5.92	0.000
	R	24	-63	-29		5.32	
Fusiform gyrus	L	-54	-60	-15	96	5.75	0.000
	L	-43	-56	-29		5.72	
	L	-46	-63	-12		5.62	

Table 4. Overview of peak activation coordinates of SN areas for the switch cue vs. repeat cue contrast inclusively masked by the standard SN mask.

		MNI coordinates					
Region	Hemisphere	x	y	z	Cluster extent	*Z*-value	FWE-corrected cluster *p*-value
Left anterior insula	L	-29	24	10	79	6.34	0.000
Right anterior insula	R	34	28	6	46	6.02	0.000
Anterior cingulate	L	-8	32	27	79	5.72	0.000
	R	10	32	27		5.68	