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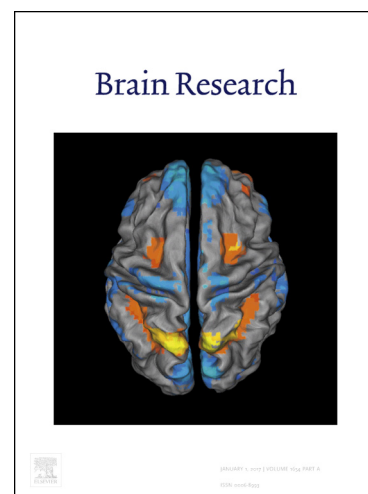
Title

Out of focus – brain attention control deficits in adult ADHD

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Abstract

Modern environments are full of information, and place high demands on the attention control mechanisms that allow the selection of information from one (focused attention) or multiple (divided attention) sources, react to changes in a given situation (stimulus-driven attention), and allocate effort according to demands (task-positive and task-negative activity). We aimed to reveal how attention deficit hyperactivity disorder (ADHD) affects the brain functions associated with these attention control processes in constantly demanding tasks. Sixteen adults with ADHD and 17 controls performed adaptive visual and auditory discrimination tasks during functional magnetic resonance imaging (fMRI). Overlapping brain activity in frontoparietal saliency and default-mode networks, as well as in the somato-motor, cerebellar, and striatal areas were observed in all participants. In the ADHD participants, we observed exclusive activity enhancement in the brain areas typically considered to be primarily involved in other attention control functions: During auditory-focused attention, we observed higher activation in the sensory cortical areas of irrelevant modality and the default-mode network (DMN). DMN activity also increased during divided attention in the ADHD group, in turn decreasing during a simple button-press task. Adding irrelevant stimulation resulted in enhanced activity in the salience network. Finally, the irrelevant distractors that capture attention in a stimulus-driven manner activated dorsal attention networks and the cerebellum. Our findings suggest that attention control deficits involve the activation of irrelevant sensory modality, problems in regulating the level of attention on demand, and may encumber top-down processing in cases of irrelevant information.

1. Introduction

Human attention control systems have evolved to ensure rapid reaction to sudden environmental changes and to help us focus on our goals and adapt them to different circumstances (Patel et al. 2015). The skills that support attention control have probably never been as important as they are in today's modern technology society, which is filled with potentially relevant information as well as distractors (Kovach 2010). Attention control allows us, on the one hand, to suppress irrelevant information and avoid triggering attention in a stimulus-driven manner; and on the other hand, to selectively focus our attention on one task at a time or divide our attention between multiple tasks simultaneously. Attentional control plays an increasing role in our hectic, everyday lives. This can severely impact the quality of life for individuals with attentional control deficits, such as the 5% of the population worldwide with attention deficit hyperactivity disorder (ADHD, Polanczyk et al. 2007).

1.1. Brain networks involved in ADHD

The control of attention, which is extensively studied in healthy humans, involves widespread networks in cerebro-cortical and subcortical brain structures (Petersen & Posner 2012, Duncan 2013). In recent years, it has been established that the pathophysiology of ADHD involves large-scale changes that cover most brain areas in the attention control networks (Castellanos & Proal 2012, Cao et al. 2014, Rubia et al. 2014). More specifically, several reviews and meta-analyses now agree that ADHD is associated with aberrant functioning of the dorsal (superior parietal lobule/intraparietal sulcus, SPL/IPS; frontal eye field, FEF) and ventral (temporoparietal junction/inferior frontal gyrus, TPJ/IFG) attention systems, the salience network (medial frontal cortex, MFC; anterior cingulate cortex, ACC; IFG, and anterior insula), the default-mode network (posterior cingulate cortex/ventromedial prefrontal cortex, PCC/VMPFC), the sensory-motor cortical areas, and the striatum and cerebellum (Dickstein et al. 2006, Cortese et al. 2012,

Castellanos & Proal 2012, Cao et al. 2014, Rubia et al. 2014). However, because the majority of recent brain imaging studies investigating the functioning of these networks in ADHD have utilized the resting-state approach, evidence of how the aberrant activity in these networks is linked to specific attention control deficits remains scarce.

1.2. Core functions of attention control Focused attention or sustained attention that refer to selectively maintaining the focus of attention on particular stimulus features is one of the key attention control functions (e.g., Mackworth 1968, Salmi et al. 2007). As attention is regulated by both the goal-directed or 'top-down', and stimulus-driven or 'bottom-up' function (Posner 1980, Salmi et al. 2009, Alho et al. 2015), focusing attention typically requires suppressing the processing of irrelevant information (Sarter et al. 2001, Salmi et al. 2009, Alho et al. 2015) such as transient ambient noises that may capture attention, or more sustained background noises that require higher selectivity during the primary focus task. Attention may also be divided among multiple targets to some extent (e.g., Spelke et al. 1976; Moisala et al. 2015, Salo et al. 2017), for instance when simultaneously driving a car and speaking on the phone.

A large extent of our attentional control relates to processing auditory and visual information. Although slightly different concepts have traditionally been used in the fields of auditory and visual attention research, auditory and visual attention have many similarities. In both modalities, attention influences sensory processing at a relatively early stage, already before awareness of the stimulus (Kastner et al. 2006, Rinne et al. 2008), and there is a considerable overlap between the higher-level attention control systems in the two modalities (Shomstein and Yantis 2006, Salmi et al. 2007, Salmi et al. 2009). Evidence spanning from neuronal pathways (Braga et al. 2017) to functional brain imaging (Salmi et al. 2007) suggests that the auditory system could be more sensitive to irrelevant information than the visual system, which in turn influence processing in a bottom-up manner (in the auditory system, bottom-up attention is often termed involuntary attention). In the

visual system, bottom-up effects are typically examined in the context of exogenous orienting of attention, where an exogenous cue may facilitate the attention shift to the target location (Posner 1980).

Although the roles of auditory and visual attention have not been examined in detail in ADHD research, each of the core attention control functions mentioned above are directly related to ADHD. Adults with ADHD have trouble maintaining sustained attention, are distracted by background noises, and have problems dividing attention among multiple tasks. This can manifest as typical inattention symptoms, such as lack of focus, absent-mindedness, and disorganized task structuring, which can hamper everyday work and academic tasks (see Barkley 1997, see also Gawrilow 2011). Developing sensitive experimental measures that capture these daily life symptoms has, however, turned out to be challenging, and it is still largely unclear which specific cognitive brain functions are affected when individuals with ADHD perform tasks requiring these subfunctions of attention control.

1.3. Functional characteristics of attention control networks

Controlled experiments on healthy humans suggest that sensory cortical areas and ventral attention networks mediate functions that can involuntarily capture our attention in a stimulus-driven manner in both visual (Serences et al. 2005, Serences et al. 2007, see also Corbetta et al. 2002) and auditory (Salmi et al. 2009, Alho et al. 2015) modalities, as well as cross-modally (Yang et al. 2014, Mayer et al. 2016). However, dividing attention under top-down control recruits the dorsal attention network (Johnson & Zatorre 2006, Moisala et al. 2015; Salo et al. 2015, Salo et al. 2017), which also overlaps with the two modalities (Shomstein & Yantis 2006, Salmi et al. 2007). Selectively focusing attention on a particular task content also activates the dorsal and ventral attention networks (e.g., Salmi et al. 2007, Serences et al. 2007), but not as prominently as conditions in which the focus of attention changes (e.g., Salmi et al. 2007, Salmi et al. 2009, Alho et al. 2015).

Activity in the posterior cerebellum (e.g., Salmi et al. 2007, Salmi et al. 2010, Stoodley 2012) is often observed together with activity in the cerebro-cortical attention control networks described above. Functional coupling of the cerebral and cerebellar areas of the attention control networks is based on prominent anatomical connections, and is proposed to help optimize the related cognitive, motor, or sensory functions (see Middleton & Strick 2000 for a review).

All complex situations involve constant dynamic interaction and competition between multiple attentional processes. Brain activation associated with different attention control functions has also been observed in largely overlapping networks (e.g., Serences et al. 2007, Salmi et al. 2009, Yang et al. 2014, Alho et al. 2015, Xuan et al. 2016). Hence, understanding the attention processes associated with observed brain activity requires simultaneous measurement of multiple core attention control functions and detailed cross-validation of several alternative hypotheses. Recent advances in brain imaging methods have enabled the investigation of multiple attention control processes and the relative roles of these networks within the same experiment (e.g., Salmela et al. 2016, Salo et al. 2017). This has opened up new opportunities to also study the deficits of attention control functions that manifest in widespread brain networks.

1.4. Research question and hypotheses

For the present study, we developed an experimental paradigm that allowed us to investigate the roles of focused, divided and stimulus-driven attention, as well as the effects of unimodal and bimodal visual and auditory inputs within the same experiment (Figure 1, see Salmela et al. 2016 and Salo et al. 2017). Our participants performed the auditory and visual discrimination tasks at a discrimination threshold of about 70%, i.e. at their individual performance limits. Our aim was to determine how adult ADHD affects the brain networks involved in multiple attention control functions. The included contrasts were selected on the basis of our previous studies (Salmela et al. 2016 and Salo et al. 2017) which validated this paradigm among healthy participants. Previous

ADHD studies have studied focused and stimulus-driven attention separately, and the neuronal correlates of divided attention have remained unclear. Our goal was, by measuring all these functions in the same study, to pursue a detailed functional characterization of the related attention deficits.

Based on previous studies on ADHD (for a meta-analysis, see Cortese et al. 2012), we expected ADHD participants to show altered activity in the dorsal and ventral attention systems, default-mode network, sensory-cortices, and subcortical areas during our demanding tasks. We tested two alternative hypotheses, aiming to resolve what happens when a specific attention function is called for: (1) Performing approximately equally demanding tasks may lead to group differences in task-relevant brain networks, and (2) Demands for a particular attention control function may reflect on other brain networks, and thus show enhanced activity, reflecting compensation by supporting attention networks or indicating difficulties in engaging in task-relevant functions. In the modulation of task-relevant functions, we expected to see effects of focused attention in sensory areas, possibly also in the dorsal attention system (e.g., Salmi et al. 2007, Serences et al. 2007). Group differences between the ADHD and control participants during focused attention tasks have previously been observed in the superior parietal cortex (e.g., Booth et al. 2005) and dorsolateral prefrontal cortex (Cubillo et al. 2011, Karch et al. 2014). Group differences in divided attention and stimulus-driven attention tasks, in turn, might be observed in the dorsal and ventral attention systems (cf. Corbetta & Shulman 2002, see also Johnson & Zatorre 2006, Moisala et al. 2015, Salo et al. 2015, Salo et al. 2017), respectively. Several studies of ADHD participants have reported activation changes, especially in the ventral attention system involved in stimulus-driven attention and response inhibition (see Cortese et al. 2012 for a meta-analysis). Compensatory activity could be observed in the opposite networks, in top-down systems for example, during the suppression of irrelevant information. Higher activity in the default-mode networks during task-relevant processing could be considered a potential index of difficulties in engaging attention (see Cortese et al. 2012).

Previous studies focusing on one task at a time and typically not controlling for individual differences in task demands have failed to differentiate between task-relevant and supporting brain functions.

2. Results

2.1. Behavioral results

As shown in Figure 2 (see also Supplementary Table 2), the reaction times (RTs) of the auditory and visual tasks differed (main effect of Target Modality, $F(1,17) = 47.34$, $p < 0.0001$). This modality difference was mainly caused by the visual targets having shorter RTs than the auditory targets in the focused attention tasks. The RTs were higher in the focused attention condition than in the simple button press task condition, and higher still in the divided attention condition (main effect of Condition, $F(2,17) = 185.4$, $p < 0.0001$). Moreover, distractors caused higher RTs than those in the trials with no distractor (main effect of Distractor $F(2,17) = 62.93$ $p < 0.0001$, ε 0.81). We observed significant interactions in Modality $\times$ Condition ($F(2,17) = 8.92$, $p < 0.01$), Modality $\times$ Distractor ($F(2,17) = 16.9$, $p < 0.0001$), Modality $\times$ Condition $\times$ Distractor ($F(2,17) = 3.51$, $p < 0.05$). There were no significant differences between the RTs of the ADHD participants and those of the neurotypical participants.

The mean auditory discrimination thresholds (see also Supplementary Table 2) of the ADHD group were 7.7% of the octaves (SEM 2.8) for the auditory focused attention tasks and 8.5% of the octaves (SEM 1.4) for the divided attention tasks. The mean visual discrimination thresholds were 12.3° of visual angle (SEM 3.9) for the visual focused attention tasks, and 22.7° (SEM 5.1) for the divided attention tasks (see also Supplementary Table 2). In the neurotypical group, the discrimination thresholds (DTs) were 6.8% (SEM 2) for the auditory focused attention tasks, 13.1% (SEM 2.2) for the auditory divided attention tasks. For the visual tasks, the DTs were 7.4° (SEM 2)

for focused attention, and 17.8° (SEM 4.4) for divided attention in the neurotypical group. The DTs were affected by the condition ($F_{(2,11)} = 21.57$ $p < 0.0001$, ε 0.858). That is, in the divided attention condition, the DTs were higher than in the unimodal or bimodal focused attention conditions. The DTs of the ADHD and neurotypical participants did not differ.

The hit rates (HRs) (see also Supplementary Table 2) were affected by Condition ($F_{(2,17)} = 15.5$ $p < 0.0001$). In both groups, this was mostly due to lower HRs in the divided attention conditions than in the focused attention. Unlike the RTs, the HRs did not show consistent distractor effects across different conditions. However, especially among the ADHD participants, the HRs tended to be lower for the auditory distractor trials, leading to a Modality $\times$ Group interaction ($F_{(2,17)} = 5,67$ $p < 0.05$). Condition $\times$ Distractor ($F_{(2,17)} = 6.37$ $p < 0.01$) and Modality $\times$ Distractor interactions ($F_{(2,17)} = 4.31$ $p < 0.05$) were also significant. These interactions were related to varying distractor effects in individual conditions. However, the patterns of distractor effects across the three conditions and two groups were rather complex. It should be noted that in several conditions, occurrence of distractors tended to also be associated with higher rather than lower HRs (e.g., auditory distractors during visual focused attention in the neurotypical group).

2.2. Activity in attention control networks across all participants

Compared with the simple button press task condition, all discrimination conditions showed larger activation in widespread attention networks, including the dorsal (SPL/IPS, FEF) and ventral (MFG/IFG, TPJ) frontoparietal systems, the pre-supplementary motor area (preSMA)/ACC, dorsal striatum, and posterior cerebellum across all participants (Figure 3a). We also observed activity across all conditions in the auditory and periauditory cortices (mainly in the superior temporal gyrus, STG), and lateral visual cortex (in the vicinity of V5). Whole brain regional analysis of the single conditions suggested that almost all these areas were activated during auditory and visual focused attention and during divided attention, and that the activity in several areas was further

enhanced when distractors occurred (Supplementary Figure 1). Compared with auditory focused attention, divided attention showed higher activity in widespread areas in the posterior parietal cortex, including the SPL/IPS (Supplementary Figure 1). Visual target trials with visual distractors were followed by activity that was clearly less distributed in the attention networks than in the visual target trials without distractors. No such effect was observed for auditory distractors. Yet even these tasks were associated with enhanced activity in the attention network areas outside the prefrontal cortex. As expected, in comparison with unimodal auditory and visual conditions, auditory and visual focused attention conditions with bimodal stimulation showed stimulus-dependent activations in the visual and auditory cortices, respectively, due to activity elicited by the stimuli of the unattended modality. Auditory stimulus-dependent activations were prominent in both groups, visual stimulus-dependent activations only reached the statistical threshold in the neurotypical control group.

2.3. ADHD-related task-specific changes in attention control networks

Comparisons between the whole brain regional brain activity of the ADHD and neurotypical participants revealed task-specific adaptations of the attention control networks (Figures 4 and 5, Supplementary Figure 2). Except for the simple button press test *vs.* rest comparison, we only show the comparisons in which the ADHD participants showed higher activity, as the opposite contrasts failed to reveal any areas in which brain activity was higher among the neurotypical participants. Among the ADHD participants, the repetitive stream of irrelevant auditory stimuli in the visual focused attention task, which enhanced the demands for selective attention, resulted in higher activity in the SMA/ACC than that in the visual unimodal task (Figure 4a). Irrelevant visual stimuli during the auditory focused attention task showed no group differences. When the visual focused attention task was compared with the simple button press condition, the ADHD participants showed higher activity than the neurotypical participants in the cuneus/precuneus and PCC (Figure 4b). During the auditory focused attention task with bimodal stimulation, the attention effects spread to

the medial and lateral visual cortices among the ADHD participants (Figure 4c). Direct comparison between auditory and visual focused attention tasks did not, however, reveal significant group differences.

During the divided attention task, we observed group differences in widespread networks including the main areas of the default mode network (PCC/SPL, MPFC, and superior areas of the lateral occipital cortex), spreading to frontoparietal attention networks (Figure 4d). Further analysis of the role of task modality in divided attention suggested that, in comparison to auditory focused attention with bimodal stimulation, divided attention in the ADHD group showed higher activity in the right superior and middle temporal cortex, right ventrolateral prefrontal cortex, right striatum, and both right and left thalamus (Supplementary Figure 2a). Comparison of divided attention and visual focused attention (with bimodal stimulation) contrast did not reveal significant group differences. In the simple button press condition, activity in largely overlapping default-mode network areas was observed in the opposite contrast (neurotypical > ADHD) between the two groups (Figure 4e).

Distractors showed higher activity in the SPL/IPS among the ADHD participants than among the neurotypical participants (Figure 5a). A specific analysis of the auditory distractors suggested group differences in more widely distributed areas, including, in addition to the parietal and cerebellar areas, also the medial prefrontal and cingulate cortex, bilateral visual cortices, and premotor/motor areas (Figure 5b). Visual distractors analyzed separately showed higher activity in the posterior cerebellum in ADHD participants (Figure 5c). Although the differential activations reached significance in the group comparisons of auditory and visual distractors, we found no modality-specific distractor effects. The specific analyses of distractors during the divided attention tasks suggested higher activity in the ADHD group in terms of default mode network (DMN), the right superior and middle temporal cortex, right ventrolateral and dorsolateral prefrontal cortex, right striatum, deep cerebellar nuclei, and both left and right thalamus (Supplementary Figure 2b).

3. Discussion

The present study was conducted to determine the neuronal underpinnings of multiple distinct attention control deficits among ADHD participants. The present experimental tasks required focusing and dividing attention in the presence of novel distracting stimuli in unimodal and bimodal blocks. The different attentional demands due to these manipulations were reflected by the RTs (Figure 2). Our adaptive design produced a relatively similar performance across the groups. In the reported behavioral analyses, we only found Modality × Group interaction, suggesting that ADHD participants found the auditory tasks more difficult than the visual tasks. Thus, attentional demands were constantly high, allowing reliable comparisons between the task conditions mostly unaffected by the performance differences among the participants. Overall, the task-related activations covered the key areas of the large-scale attention networks (Figure 3, see also Supplementary Figure 1).

Previous studies of adults with ADHD, which have typically not used adaptive tasks, often report hypoactivations among ADHD participants (for a meta-analysis, see Cortese et al. 2012). Our study with its adaptive design, in turn, exclusively revealed hyperactivity during attention control tasks performed under constantly high attentional demands (Figures 4 and 5). The striking observation was that difficulties managing situations that required attention control among individuals with ADHD appear to be related, not to the primary functions typically associated with these brain areas, but to the compensatory enhancement of activity in other brain systems (Figures 4 and 5). Based on the group differences in the main attention modes, that is, focused, divided and stimulus-driven attention, we propose three brain mechanisms that may cause a lack of focus on a given task when attention control demands are high: 1) Enhanced activity in the visual cortical areas during auditory focused attention 2) enhanced activity of the voluntary attention control network when irrelevant distractors (SPL/IPS and cerebellum) or irrelevant multimodal input (SMA/ACC) are presented, and 3) problems in regulating the level of attentional arousal on demand. The latter proposed

mechanism is also supported by our result that during the simple button press task, our control participants showed higher activity in the DMN. That is, during a highly demanding task increased DMN activity may reflect difficulties in engaging attention for the task, and in an easy and non-demanding task, lower DMN activity may reflect too much effort allocated to the task.

3.1. Impairment in selectively focusing attention on relevant stimulation

Both the unimodal/bimodal focused attention and divided attention tasks showed prominent activations across all participants, in addition to the higher-level attention control networks in the auditory and visual cortices discussed later (see Supplementary Figure 1c, 1d and 1e). These sensory cortical effects are likely to reflect enhancement of the sensory processing by attention, as numerous auditory (e.g., Petkov et al. 2004) and visual (e.g., Kastner et al. 1998) studies have observed. Whereas prior studies examining load-dependent responses of ADHD participants have mainly reported activation differences in brain areas primarily involved in the task (Booth et al. 2005, Cubillo et al. 2011, Karch et al. 2014), we observed differences in areas not primarily involved in the task (Figure 4b,c). During the auditory focused attention tasks, we found increased visual cortical activity, that is, in task-irrelevant sensory modality, among the ADHD participants. Studies of neurotypical participants have also sometimes reported spreading of activity across modalities (see Cate et al. 2009), especially when the auditory and visual stimuli are presented in synchrony (e.g., Busse et al. 2005, Degerman et al. 2007). Our findings further suggest that this could be one of the attentional mechanisms that is altered in ADHD.

In the visual focused attention task, we observed no enhanced activation in the irrelevant auditory modality, but instead the ADHD participants showed higher activation in PCC and cuneus than the controls. Although direct comparison between auditory and visual focused attention did not reveal group differences, different activation patterns in these two conditions may reflect some differences between the two modalities. Enhanced visual activity during auditory attention could either reflect increased suppression of irrelevant information or the spreading of attention to the irrelevant

modality (Busse et al. 2005, Degerman et al. 2007, Cate et al. 2009). DMN activity during the visual attention tasks could in turn reflect difficulties in engaging attention for the task. Due to the substantial differences between auditory and visual modalities (stimulus properties and sensory coding, organization of the sensory pathways, higher-level attention systems), it is difficult to reliably interpret where the possible modality differences in the present results stem from. Some evidence exists that auditory attention could be more sensitive to bottom-up influences than visual attention (see, e.g., Braga et al. 2017, Salmi et al. 2007). In the present study, we observed enhanced bottom-up intrusion during auditory focused attention among the ADHD participants, although slightly surprisingly, this occurred in the visual system. Even though this effect apparently relates to differences between the bottom-up processing of the two modalities, it remains unclear why cross-modal bottom-up driven intrusion of visual stimuli during auditory attention occurred. Perhaps top-down control of auditory attention was not able to efficiently suppress visual bottom-up input. Nevertheless, our results suggest that enhanced cross-modal distraction during auditory attention in the ADHD group relates to altered bimodal processing specifically in ADHD. More evidence of the modality-related bottom-up effects in ADHD is clearly needed.

Previous studies have demonstrated age differences in the influence of bimodal information on behavioral performance: Whereas in adults, coherent multisensory stimulation may improve performance (Bisch et al. 2016), in children even irrelevant noise may help in performing the task (Söderlund et al. 2007). As our participants performed the tasks at threshold, our study did not reveal any behavioral correlates of the irrelevant sensory stimulation. It does, however, suggest a possible neural mechanism for this phenomenon. Our results indicate that irrelevant information activates cross-modal pathways at a 'lower threshold'. In line with previous findings, our results suggest that auditory and visual stimulus environments should be considered together when planning support for ADHD individuals.

3.2. Enhanced voluntary attention control network activity when irrelevant information is presented

Frontoparietal networks are involved in voluntary (goal-directed) and involuntary (stimulus-driven) directing of attention to specific auditory (Shomstein & Yantis 2006, Salmi et al. 2007, Salmi et al. 2009, Alho et al. 2015) and visual (Vandenberghe et al. 2001, Yantis et al. 2002) sensory input, when switching between auditory and visual attention (Shomstein & Yantis 2004, Yang et al. 2014), and when dividing attention between auditory and visual tasks (Johnson & Zatorre 2006, Moisala et al. 2015, Salo et al. 2015, Salo et al. 2017). In addition, in these core attention networks, which consistently show altered brain activity in individuals with ADHD (see Cortese et al. 2012), the effects of higher attentional demands are not observed in the specific areas that are primarily required in a given situation. Instead, these attention deficits modulate activity in specific areas that are more closely involved in other attention control functions or that reflect difficulties in engaging attention control networks (see more details of these DMN activations below). We mainly observed altered processing of task-irrelevant distractors in the SPL/IPS and posterior cerebellum (Figure 5). The well-established role of these areas in voluntary top-down controlled attention (Corbetta & Shulman 2002) suggests that the modulation of SPL/IPS and posterior cerebellar function in ADHD participants is related to the compensation of the performance of other cognitive control functions. More specifically, enhanced SPL/IPS activity associated with stimulus-driven attention is likely to reflect extra effort in maintaining the focus of attention on a target, or in directing attention back to the task immediately after distraction (Salmi et al. 2009, Serences et al. 2007, Alho et al. 2015). The posterior cerebellum plays a key role in attentional anticipation (e.g., Allen et al. 1997) as well as in controlling the responses, especially when the demands are high (Salmi et al. 2010). In keeping with these findings, dysfunctions of the cerebello-thalamo-prefrontal circuits cause problems in inhibition, response control, and executive functions in individuals with ADHD (e.g., Berquin et al. 1998, see Stoodley 2016 for a review). The present study showed that modulated cerebellar activity during stimulus-driven attention may reflect related support functions, even though it should be

noted that we had no overt behavioral data that would allow us to conclude which specific compensatory processes are involved.

Auditory and visual distractors were associated with activations in different brain areas. More specifically, we observed activations associated with auditory distractors in widespread areas, whereas visual distractors only elicited significant activations in the posterior cerebellum. Even though we observed no statistically significant difference in the direct contrast between these two conditions, it is possible that the differential activation patterns were again due to the auditory system being more sensitive to bottom-up influences than the visual system. Increased sensitivity to bottom-up processing in the auditory system has already been observed in anatomical projections (Braga et al. 2017), as well as in brain activity (see Salmi et al. 2007). Moreover, comparison between divided attention and auditory focused attention showed significant group differences, whereas that between divided attention and visual attention did not. As the behavioral results suggested that focusing attention may protect against distraction, it appears that the higher activations in the focused auditory attention condition among the ADHD patients than among the controls could be due to ADHD patients' better ability to concentrate during focused attention than during divided attention. This is also in line with our results that suggest higher activity in these DMN and lateral prefrontal areas during divided attention than during focused attention.

We observed higher SMA/ACC activity among the ADHD participants when irrelevant auditory stimuli were presented during the visual focused attention task. Although the SMA/ACC was one of the areas activated across all conditions, in ADHD its function appeared to be specifically altered during the processing of irrelevant information. As part of the salience network, the SMA/ACC has been implicated in switching between the DMN and the task-positive network (Bressler & Menon 2010, Uddin et al. 2015). This area can also be defined as the 'executive system', one of the most commonly observed attention control areas, the disruption of which often leads to inhibition

problems (Petersen & Posner 2012). Furthermore, this area plays a key role in attentional lapses (Weissman et al. 2006), which may well happen when irrelevant information is presented.

3.3. Problems in regulating the level of attentional arousal on demand

Altered DMN activity, which occurs both during task performance and while the participants are at rest, is currently one of the most widely reported indices of ADHD-related brain function (for a review, see Castellanos & Proal 2012). Although evidence exists that DMN activity at rest is associated with ADHD symptoms (e.g., Cocchi et al. 2012) and mind wandering (e.g., Kajimura et al. 2016), the task-related attention control functions associated with atypical DMN activity in ADHD are not known in detail.

In the divided attention tasks compared to simple button press task, ADHD participants showed more DMN activity in PCC and VMPFC than the controls. In addition, the visual focused attention tasks elicited stronger DMN activity among the ADHD participants. The DMN activity in both of these conditions could reflect difficulty recruiting attention when the division of attention is required, even though it would be useful in such as situation. That is, as the DMN should be observed when focus of attention is lacking, we interpreted this activity as failing to regulate the level of attention on demand.

Activity in the PCC and VMPFC has been associated with absent-mindedness, problems in sustaining attention (e.g., Leech & Sharp 2014), and keeping attention away from the outside world during internally driven default mode operations (see Gilbert et al. 2012). Furthermore, in agreement with our findings on divided attention, patients with lesions in VMPFC have consistently been reported as having problems in multitasking (for a review, see Burgess 2000). Divided attention could be qualitatively different from focused or stimulus-driven attention, meaning that in addition to core attention control functions, it also involves higher-level functions such as working

memory. Therefore, one alternative interpretation of this activity is that it relates to enhanced demands, not in basic attention control function, but in higher-level cognitive function. In addition to these functions, it has been proposed that the PCC and VMPFC are involved in extremely diverse functions, ranging from social cognition (Schillbach et al. 2008) and controlling memory by responding to choices under uncertainty (Barron et al. 2016) to imagination (Agnati et al. 2013). As a simple mechanism, regulating the level of attention on demand may well also play a role in these more elaborated higher-level functions.

3.4. Conclusion

The findings of the present study strengthen the current knowledge regarding the role of the frontoparietal networks, default mode network, salience network, and cerebellum in the pathophysiology of ADHD. More specifically, we provide novel information on the context of these multifunctional regions when meeting typical everyday cognitive challenges by determining the relative contributions of these regions to focusing and sustaining attention on one stimulus stream, attending to multiple streams simultaneously, and in the ability to avoid distractors capturing attention in a stimulus-driven manner during a difficult task. The mechanisms of divided attention among ADHD participants had previously been largely unclear. According to the present findings, we propose three brain mechanisms that may cause a lack of focus on a given task when attention control demands are high: 1) Higher activation in the visual cortical areas during auditory attention 2) enhanced voluntary attention control network activity when irrelevant information is present, and 3) problems in regulating the level of attentional arousal on demand.

4. Material and methods

4.1 Participants

Sixteen volunteer ADHD patients (seven females, mean±SD age 38±9 years, age range 26–55

years) and 17 neurotypical controls (seven females, mean±SD age 38±8 years, age range 25–49 years) participated in our study. The majority of the ADHD (13) and control (10) participants were recruited on the basis of a previous project, Adult Dyslexia and Attention Deficit Disorder in Finland (DyADD, see Laasonen et al. 2009). Since we were unable to recruit a sufficient number of participants from the DyADD sample, SL recruited three additional ADHD participants from a private clinic in Helsinki. Additional neurotypical participants were recruited from the student e-mail list at the University of Helsinki. All the participants were right-handed, had normal or corrected to normal vision, no major hearing deficits, and Finnish was their native language. The participants in the neurotypical group were paid 15 €/h (total approximately 45 €). All participants gave written informed consent prior to participation. The study was approved by the Ethics Committee for Gynecology and Obstetrics, Pediatrics and Psychiatry of the Helsinki University Hospital.

ADHD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition (DSM-IV; American Psychiatric Association, 1994). For diagnostics, we used the Conners' Adult ADHD Diagnostic Interview for DSM-IV (Epstein et al. 2001). The patients had either only inattention (ADHD-PI, 314.00) or inattention and hyperactivity (ADHD-CT, 314.01). None of the participants had psychiatric or neurological disorders except for four ADHD participants who had symptoms of dyslexia. None of the participants used psychoactive medication during the experiment. Screening for depression symptoms was conducted using the DEPression Scale (DEPS, Salokangas et al. 1995), and for alcohol usage using the WHO Alcohol Use Disorder Identification Test (AUDIT-III). In addition, all participants filled questionnaires on attention and executive function deficits (ASRS, APQ, BRIEF), and participated in short neuropsychological testing (WAIS-III, matrix reasoning and vocabulary) in addition to prior extensive testing (see Supplementary Table 1). No significant group differences were observed in terms of DEPS (mean±SD, ADHD: 6.8±6.2, NT: 3.3±3.1) or AUDIT-III (ADHD: 4.9±2.8, NT: 3.9±1.8).

4.2. Experimental design

In all tasks, except the visual unimodal task, sine wave tones were presented at an intensity of 80 dB SPL for 300 ms, including 10 ms of linear onsets and offsets. The participants' auditory task was to indicate whether the pitch of the tone was higher or lower than the pitch of the previous tone. As we used the adaptive 2-1 staircase method, the change in pitch decreased after two consecutive correct responses and increased after an incorrect response. Tone frequency varied between 600 and 1800 Hz according to the participants' responses in the auditory focused attention task and divided attention task. The pitch change between consecutive trials was limited to a maximum of 0.5 octaves. Additional distractor sounds, that is, novel complex synthetic sounds (e.g., clicks and ringtones) were presented simultaneously with the sine wave tones in 1/6 of the trials, to involuntarily trigger attention in a stimulus-driven manner. Each distractor sound was presented only once to maximize distractibility and reduce adaptation (see Escera et al. 2000). The maximum intensity of the distractor sounds was 80 dB SPL, and they were low- and high-pass filtered, with cut-offs at 7000 Hz and 200 Hz, respectively. In addition, the distractor sounds were notch-filtered at 1000 Hz (filter width two octaves) to avoid acoustic masking of target tone frequencies. The presentation of distractor sounds was randomized; they did not occur at the beginning of the block (among the two first stimuli) and were never a subsequent pair.

All the bimodal tasks presented the visual stimuli in synchrony with the tones. Visual stimuli were grayscale sine wave gratings (see Figure 1). Each high-contrast grating was shown for 300 ms in a spatial Gaussian envelope (diameter 3°). The spatial frequency of grating was 2 c/° and the phase was randomly set in each trial. The participants' visual task was to indicate whether the orientation of the grating was rotated clock-wise or counter-clock-wise in relation to the orientation of the previous grating. We used an adaptive 2-1 staircase method, and thus the amount of orientation change decreased after two consecutive correct responses and increased after an incorrect response.

The grating orientation was varied according to the task performance in the visual focused attention task and divided attention task. We limited the maximum change between the consecutive trials to 90°. As in the tone sequences, novel distractors were presented simultaneously with gratings in 1/6 of the trials (only one distractor could occur at a time). The visual distractors were colored textures (size 16 x 24°, see Figure 1). The root mean squared contrast of the textures was 0.3. To avoid spatial masking and to keep gratings identical across conditions, a circular area (diameter 6°) was cut out of the center of the distractor textures. Each visual distractor occurred only once during the experiment. The tones and gratings were presented a constant onset-to-onset intervals of 1.8 s. Stimuli were created, and we controlled their timing using Presentation® software (Neurobehavioral Systems, Berkeley, CA, USA, www.neurobs.com).

In the unimodal auditory/visual and bimodal selective focused attention conditions, the participants performed either tone discrimination or grating discrimination tasks (see Figure 1). In the divided attention condition, they performed both tone and grating discrimination tasks simultaneously, knowing that on each trial the stimulus was changed in only one modality. The focused attention conditions also contained sham trials in which the stimulus also changed in the non-attended modality. These trials were discarded from the analysis in order to keep the bimodal focused attention conditions similar to those of the divided attention condition in which the stimuli varied in both modalities. In addition, we gave participants a simple button press task condition in which they had to press a button whenever the tone-grating pair occurred. In total, there were six different experimental conditions: 1) An auditory unimodal focused attention condition, 2) an auditory bimodal focused attention condition, 3) a visual unimodal focused attention condition, 4) a visual bimodal focused attention condition, 5) a divided attention condition (bimodal), and 6) a simple button press task condition (bimodal). Moreover, each bimodal condition contained six different types of trials: 1) An auditory target without a distractor, 2) an auditory target with an auditory distractor, 3) an auditory target with a visual distractor, 4) a visual target without a distractor, 5) a visual target with an auditory distractor, and 6) a visual target with a visual distractor. The auditory

and visual unimodal conditions only had targets with no distractor and targets with an intramodal distractor. In the simple button press task condition, all tone-grating pairs were targets that had to be responded to with the same button press when they occurred either without a distractor, with an auditory distractor or with a visual distractor. In each contrast related to the attention effects, similar stimuli were presented (see, however, Supplementary Figure 1a–b for stimulus-dependent activations). That is, only bimodal conditions were included for examining the effects of focused attention. We also used similar experimental variables in our earlier studies, confirming the efficiency of the design in fMRI data analysis (Salmela et al. 2016, Salo et al. 2017).

In the bimodal conditions, each task consisted of 60 trials occurring in a random order (see also Figure 1): 40 trials without distractors, 10 trials with an auditory distractor, and 10 trials with a visual distractor. Each bimodal task consisted of 20 tones and 20 gratings with no distractor and 5 intramodal and 5 intermodal distractors. In the unimodal conditions, only intramodal distractors were presented, but the amount of distractors was the same. Thus, they consisted of 20 tones or gratings and 10 intramodal distractors. The specific tasks were performed in different blocks, and the order of blocks was randomized within each run. The participants performed three runs, except for two ADHD participants, who performed only two runs, and one neurotypical participant, who performed only one run. Each task was presented once during one run. Between task conditions, there was a four-second resting period and in the middle of the run a 40-second resting period during which the participants were instructed to fixate on a fixation cross. For further details of the experimental design, see Salmela et al. (2016).

4.3. MRI acquisition

We collected fMRI data using a Siemens MAGNETOM Skyra 3 T scanner (Siemens Healthcare, Erlangen, Germany) with a 30-channel head coil. We measured three functional runs using a gradient-echo echo planar imaging sequence (TR 1.9 s, voxel matrix 64×64, slice thickness 3.0

mm, in-plane resolution 3.1 mm × 3.1 mm × 3.0 mm). Each run in the functional measurements consisted of 360 volumes. The first four volumes were discarded to stabilize magnetization. A structural MR image with a T1-weighted MPRAGE sequence (1 mm slice thickness) was acquired before the third functional run for registration purposes. The timing of the scanning was random in relation to the presentation of the stimulus.

4.4. Analysis of fMRI data

The fMRI data were analyzed using FSL tools (Smith et al. 2010). We performed the general linear model data-analysis using fMRI Expert Analysis Tool software (FEAT, v6.00), Functional Magnetic Resonance Imaging of the Brain Centre (FMRIB) software library (FSL, release 5.0.9). Motion correction was performed using FMRIB's Linear Image Registration Tool (MCFLIRT). DVARS (D referring to temporal derivative of timecourses, VARS referring to root mean square variance over voxels, see Power et al. 2010) were regressed from the data to avoid the involvement of motion during scanning on statistical testing. We also confirmed that there were no group differences in relative or absolute movements. We used the Brain Extraction Tool (BET) for T1 as well as functional images to isolate the brain tissue from the non-brain tissue. The functional data were high-pass filtered using a 100-second cutoff. The linear registration of the functional image via the anatomical image to standard space (MNI152 template, Montreal Neurological Institute) was performed using FMRIB's Linear Image Registration Tool (FLIRT). The registration of the functional image to the anatomical image was performed using six rigid body transformations. In the linear transformation from anatomical to functional image, we used 12 degrees of freedom. We preformed spatial smoothing separately on each volume of the data by setting a 10 mm Gaussian kernel to the signal. We selected a relatively large smoothing kernel to account for the individual variance of the functional loci in widespread attention networks. FILM (FMRIB's Improved Linear Model) was used in the first level analysis. We defined the explanatory variables on the basis of the stimulus onsets and durations. Double gamma function was used in the convolution of the

hemodynamic response function (HRF). We used the same high-pass filter for the model as we did for the time series data.

We analyzed the fMRI data using FSL tools (Smith et al. 2010). A standard general linear model (GLM) analysis (FEAT) was run using 22 task regressors, and nuisance regressors for instructions (1) and motion (6). We used FLAME (FMRIB's Local Analysis of Mixed Effects) in the fMRI group analysis. Cluster-based thresholding ($Z > 3.0$ $p < 0.05$ for the across-groups effects and $Z > 2.0$ $p > 0.05$ for the group comparisons) was used to account for multiple comparisons. This threshold was considered reasonably high for the group comparisons, considering that our experimental control was extremely stringent in relation to previous brain imaging studies of ADHD. This correction method has shown to be sensitive in finding the true signal in large scale activation clusters (Woo et al. 2014). The reliability of FLAME was tested by Eklund et al. (2016) and this specific method provided reliable statistical inferences in all analyses concerning event-related designs. In addition, we used DVARS as a covariate in the model.

4.5. Analysis of behavioral data

The effect of Target Modality (auditory, visual) × Condition (simple button press task, focused attention, divided attention) × Distractor (no distractor, auditory distractor, visual distractor) × Group (neurotypical, ADHD) on the behavioral data was tested using analysis of variance (ANOVA), with Group as fixed factor and Modality, Condition, and Distractor as random-effect factors. A separate ANOVA was conducted for reaction times (RTs), discrimination thresholds (DTs), and hit rates (HRs), and unimodal *vs.* focused attention tasks. When the group variances were not equal, we used Greenhouse-Geisser correction as indicated by correction factor ε, given together with the *p* value. However, even in these cases, the original degrees of freedom were reported for the F value. For each participant, the average of the reversal points of the staircase series in a given condition was used as the DT. For DTs, the Distractor factor, and for HRs the

simple button press task condition were excluded from the ANOVAs since they provided no data on discrimination accuracy. We calculated reaction times for correct trials.

5. Acknowledgements

6. Author contributions

VS, ES, KA and JS designed the experiment, JS, KM, VS, and ES collected the data, JS, VS and KM analyzed the data. SL, LH, ML, and PT selected, recruited, and diagnosed the patients. JN examined the structural MRI images and excluded participants if required, on the basis of related criteria. JS wrote the manuscript, which was commented, expanded, or agreed on by all the authors.

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8. Figure legends

Figure 1. Experimental setup. a) The participants were presented with synchronous streams of tones with varying pitches, gratings with a varying orientation, and a constant onset-to-onset interval of 1.8 seconds. In 1/6 of the trials, an auditory novel distractor (spectrally complex novel sounds) and in the 1/6 of trials, a visual novel distractor (complex colored novel textures) concurred together with the tone-grating pair. b) The participants performed a discrimination task in which they were instructed to indicate the direction to which the stimulus changed in relation to the previous stimulus (rotation to the left or right, left and right buttons; pitch up or down, top and bottom buttons). During the focused attention tasks they selectively attended to either visual or auditory input and during the divided attention tasks they performed auditory and visual tasks simultaneously. Novel distractors that captured attention in a stimulus-driven manner were presented in each condition. c) In each bimodal block, we presented 20 sounds and gratings with no distractor (ND), five intramodal distractors (IMDs) and five cross-modal distractors (CMDs). During unimodal conditions, only IMDs were presented. Tasks were presented in runs in which each task was presented once. Each participant had a total of three runs.

Figure 2. Reaction times (RTs) for targets with and without irrelevant distractors in the simple button press task, and during the unimodal and bimodal focused attention tasks, and bimodal divided attention tasks. Task performance in auditory conditions is presented at the top and in visual conditions at the bottom. In both modalities, RTs were increased from the simple button press task to the unimodal and bimodal focused attention tasks, then further to the bimodal divided attention tasks. In each condition, the RTs were higher for distractors, indicating that they indeed captured attention in a stimulus-driven manner. Error bars indicate the mean standard error.

Figure 3. Brain activity across all attention control conditions among the ADHD and neurotypical participants was observed in the dorsal and ventral frontoparietal networks, and auditory and visual areas (Z > 4.0, corrected $p < 0.01$). In addition to these surface-rendered cerebro-cortical areas, activity was also observed in the posterior cerebellum and the dorsal striatum. Frontal eye field/middle frontal gyrus, FEF/MFG; intraparietal sulcus, IPS; motor cortex, MC; superior parietal lobule, SPL; inferior frontal gyrus, IFG; auditory cortex, AC; supplementary motor area/anterior cingulate cortex, SMA/ACC; visual area 5, V5.
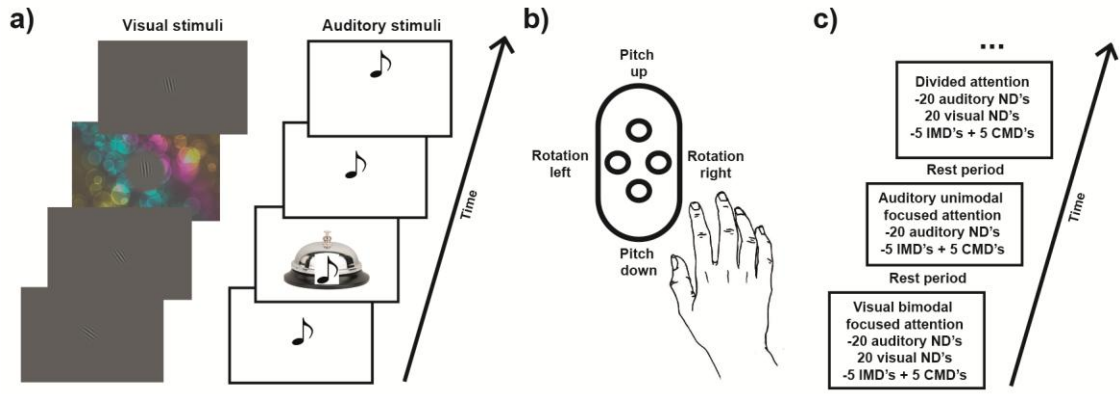
Figure 4. Contrasts showing significant group differences in bimodal *vs.* unimodal focused attention, auditory focused attention, visual focused attention, divided attention, and the simple button-press task (Z > 2.0, corrected $p < 0.05$). In other contrasts, excluding the button press task, brain activity was higher among the ADHD participants than among the neurotypical participants. Supplementary motor area/anterior cingulate cortex, SMA/ACC; motor cortex, MC; default mode network, DMN; visual cortex, VC.
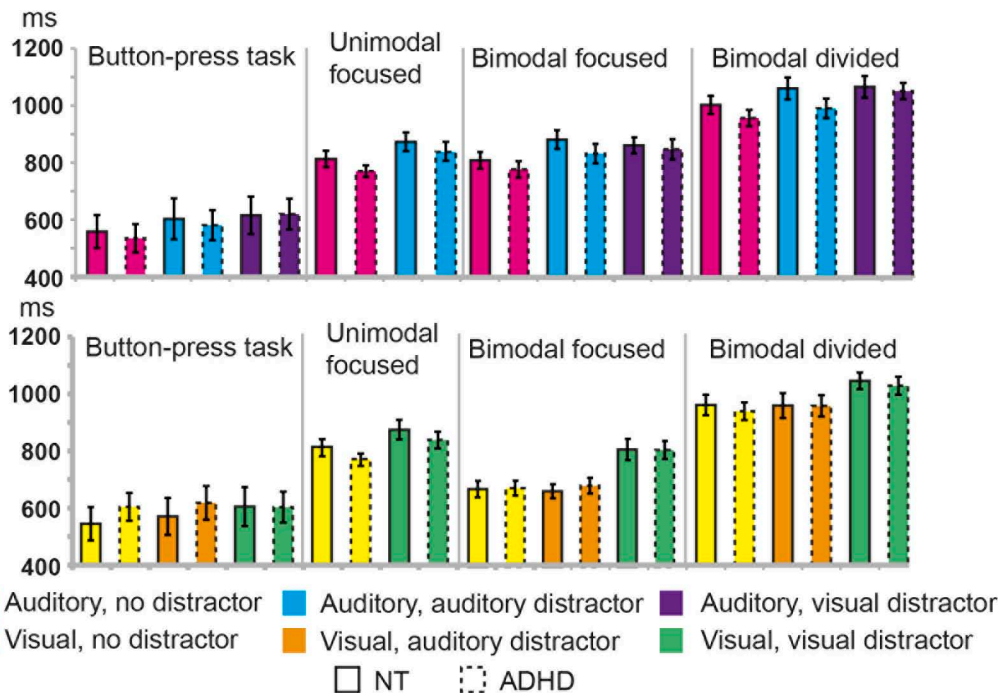
Figure 5. Group differences (ADHD > neurotypical, NT) in processing irrelevant distractor stimuli triggering stimulus-driven attention in audition and vision or across the two modalities (Z > 2.0, corrected $p < 0.05$). Brain renderings on the middle left and bottom are from the cerebellum

(sideview). Intraparietal sulcus, IPS; motor cortex, MC; superior parietal lobule, SPL; visual cortex, VC; cerebellum, Cb.
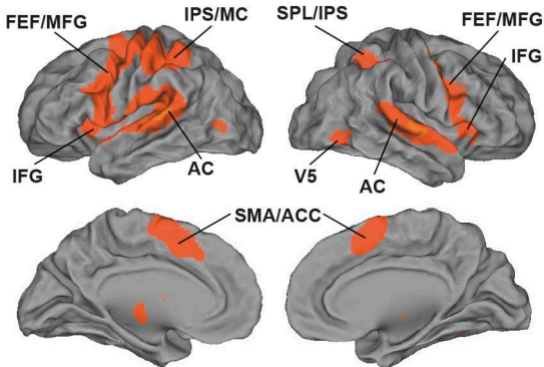
Supplementary Figure 1. Activity in the visual bimodal > unimodal focused attention, visual and auditory focused attention, divided attention, and the simple button press task in all participants (Z > 3.0, corrected $p < 0.05$). Contrast between the auditory focused attention task with audiovisual stimulation and the auditory focused attention task with auditory stimulation only was conducted in the neurotypical (NT) group, as no significant activity was observed in this comparison across all participants. All comparisons in this figure were made in the rest condition.

Supplementary Figure 2. a) The post-hoc analysis for the differences between auditory and visual focused attention and divided attention conditions showed higher activity in the divided attention condition than in the auditory focused attention conditions among the ADHD participants. b) The post-hoc analysis of the distractor effects, specifically in the divided attention conditions, suggested higher activity among the individuals with ADHD in widespread areas covering the default mode network, dorsolateral and ventrolateral prefrontal, temporal areas in the right hemisphere in particular, and also in subcortical structures such as the striatum and thalamus (Z > 2.0, corrected $p < 0.05$).

a) Visual stimuli Auditory stimuli Time

b) Pitch up Rotation left Rotation right Pitch down

c) ...

Divided attention
-20 auditory ND's
20 visual ND's
-5 IMD's + 5 CMD's

Rest period

Auditory unimodal
focused attention
-20 auditory ND's
-5 IMD's + 5 CMD's

Rest period

Visual bimodal
focused attention
-20 auditory ND's
20 visual ND's
-5 IMD's + 5 CMD's

Time

ms

Button-press task | **Unimodal focused** | **Bimodal focused** | **Bimodal divided**

ms

Button-press task | **Unimodal focused** | **Bimodal focused** | **Bimodal divided**

■ Auditory, no distractor
■ Visual, no distractor

■ Auditory, auditory distractor
■ Visual, auditory distractor

■ Auditory, visual distractor
■ Visual, visual distractor

□ NT   ⬚ ADHD

All attention tasks vs. control tasks (all participants)
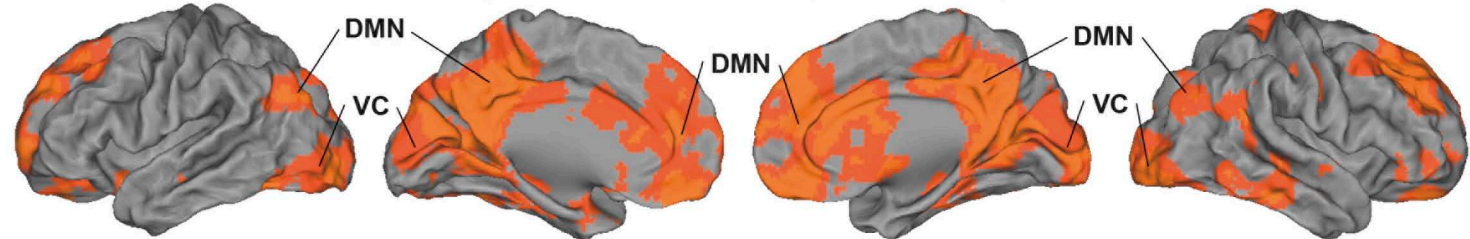
a) Bimodal vs. unimodal visual focused attention (ADHD > NT)

SMA/ACC

MC
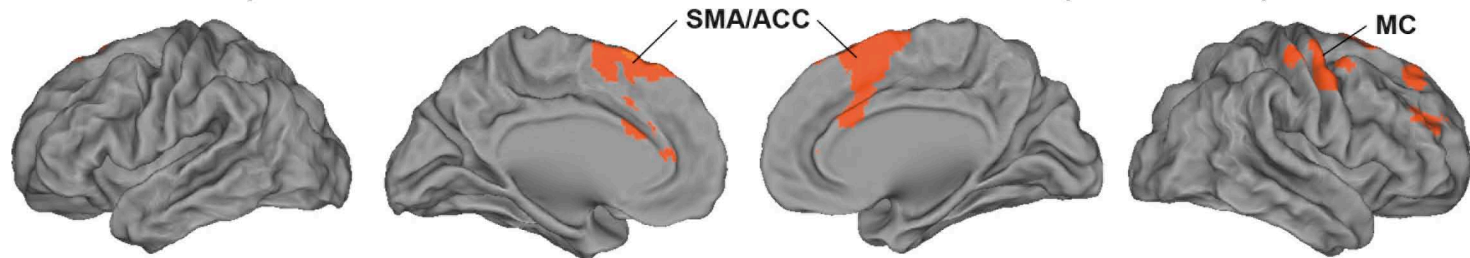
b) Visual focused attention (ADHD > NT)
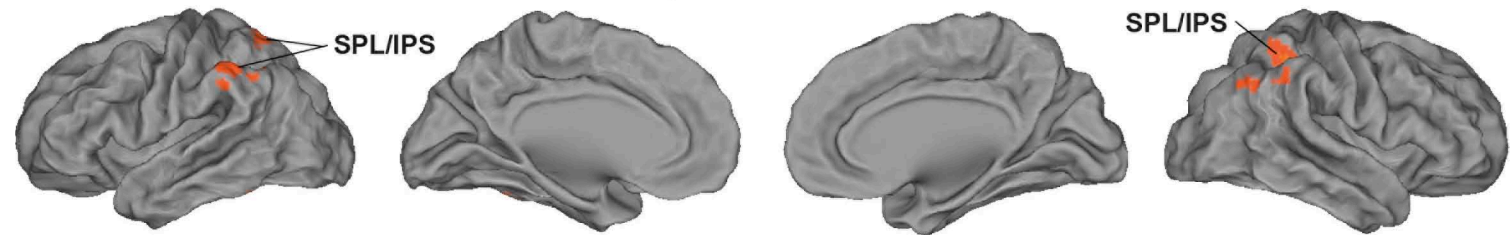
DMN
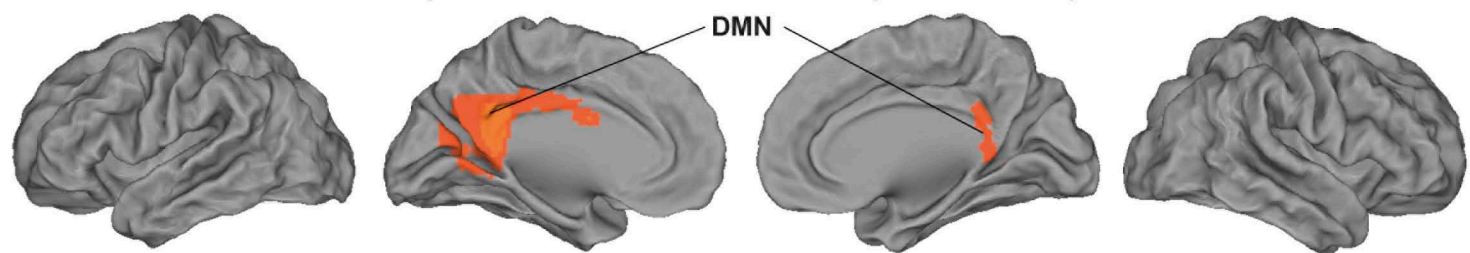
c) Auditory focused attention (ADHD > NT)

VC

VC
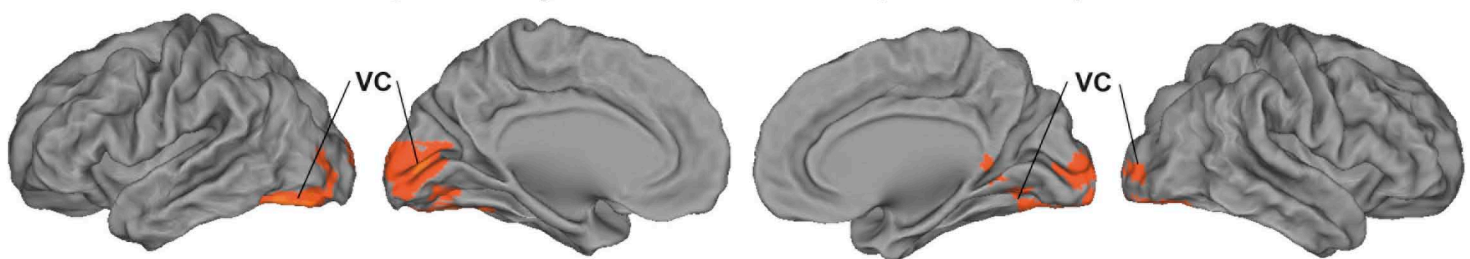
d) Divided attention (ADHD > NT)

DMN

VC

DMN

DMN

VC

e) Button press task (NT > ADHD)

DMN

DMN

DMN

a) All distractors

SPL/IPS

SPL/IPS

b) Auditory distractors

MC/SPL/IPS

MC/SPL/IPS

VC

VC

Cb.
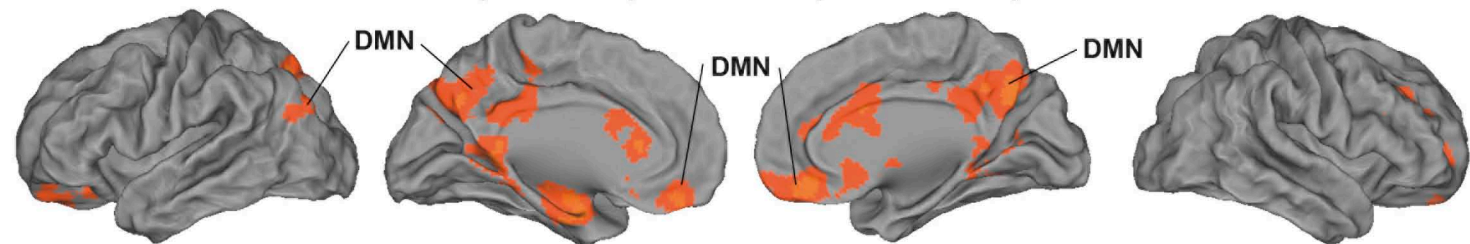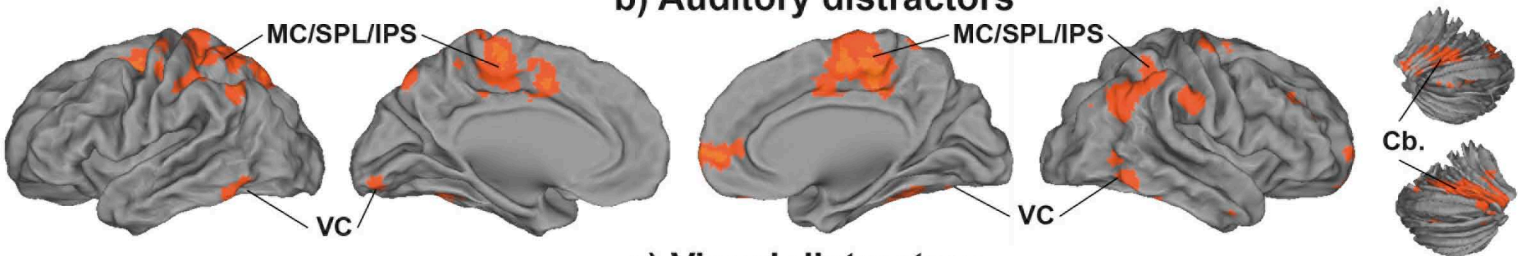
c) Visual distractors

Cb.
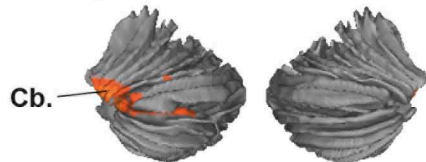
Highlights

We reveal brain functions reflecting altered attention control processes in ADHD

ADHD participants showed enhanced compensatory activity in networks not related to task

Attention effects were observed in the irrelevant sensory modality in ADHD participants

Allocation of task-positive and task-negative networks did not occur on demand

Top-down network was activated when irrelevant information was present