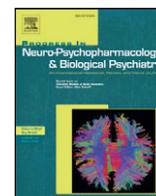




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Characterising resting-state functional connectivity in a large sample of adults with ADHD



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ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood psychiatric disorder that often persists into adulthood. While several studies have identified altered functional connectivity in brain networks during rest in children with ADHD, few studies have been performed on adults with ADHD. Existing studies have generally investigated small samples. We therefore investigated aberrant functional connectivity in a large sample of adult patients with childhood-onset ADHD, using a data-driven, whole-brain approach. Adults with a clinical ADHD diagnosis ($N = 99$) and healthy, adult comparison subjects ($N = 113$) underwent a 9-minute resting-state fMRI session in a 1.5 T MRI scanner. After elaborate preprocessing including a thorough head-motion correction procedure, group independent component analysis (ICA) was applied from which we identified six networks of interest: cerebellum, executive control, left and right frontoparietal and two default-mode networks. Participant-level network maps were obtained using dual-regression and tested for differences between patients with ADHD and controls using permutation testing. Patients showed significantly stronger connectivity in the anterior cingulate gyrus of the executive control network. Trends were also observed for stronger connectivity in the cerebellum network in ADHD patients compared to controls. However, there was considerable overlap in connectivity values between patients and controls, leading to relatively low effect sizes despite the large sample size. These effect sizes were slightly larger when testing for correlations between hyperactivity/impulsivity symptoms and connectivity strength in the executive control and cerebellum networks. This study provides important insights for studies on the neurobiology of adult ADHD; it shows that resting-state functional connectivity differences between adult patients and controls exist, but have smaller effect sizes than existing literature suggested.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD¹) is one of the most frequent childhood psychiatric disorders. According to the Diagnostic

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¹ Non-common abbreviations used throughout this article: ADHD = attention-deficit/hyperactivity disorder. RSN = resting-state network. DMN = default-mode network. ECN = executive control network. CER = cerebellum network. ICA = independent component analysis. DIVA = Diagnostic Interview for Adult ADHD.

and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Organisation, 2000, 2013) ADHD is characterised by symptoms of inattentiveness or hyperactivity/impulsivity, or by a combination of these two symptom domains. In 65% of the cases ADHD symptoms are chronic and persist into adulthood, with at least 15% of the patients still meeting the full criteria for ADHD in adulthood (Faraone et al., 2006). Despite a prevalence of 2.5% in the adult population (Simon et al., 2009) persistent ADHD has received much less attention in research than ADHD in childhood. While ADHD in adults is characterised by abnormalities in the function of several brain areas (Cortese et al., 2012) the neurobiology of adult ADHD is still poorly understood. Similar to the situation in other psychiatric diseases, aetiological modelling of ADHD has now shifted from postulating dysfunctions in isolated brain regions to examining the connectivity of brain networks using both structural and functional measures (Castellanos and Proal, 2012). Structural connectivity depicts anatomical connections, whereas functional connectivity

describes the temporal correlations in neural activity between distributed brain regions (Friston, 1994).

In the past five years there has been an increase in studies aimed at discovering functional connectivity differences between patients and controls. Many of these have focused on the default-mode network (DMN), which is characterised by its higher level of activation during rest and deactivation during tasks (Raichle et al., 2001). DMN dysfunction is hypothesised to cause attentional interference and response variability in patients with ADHD (Sonuga-Barke and Castellanos, 2007). In adult patients with persistent ADHD compared to healthy controls, functional connectivity within the DMN was found to be reduced (Castellanos et al., 2008; Uddin et al., 2008), connectivity between the dorsal anterior cingulate and the DMN was found to be less negative (Castellanos et al., 2008) and abnormal (Sato et al., 2012), and coherence between the dorsolateral prefrontal cortex and the DMN was described as stronger (Hoekzema et al., 2014). These findings of aberrant DMN connectivity are generally in line with findings from a slightly larger body of resting-state connectivity studies in children with ADHD (i.e. Cao et al., 2006; Fair et al., 2010; Tian et al., 2006).

Besides the DMN, aberrant connectivity in several other networks has also been associated with ADHD. McCarthy and colleagues observed decreased functional connectivity within the dorsal and ventral attention networks, and increased functional connectivity within the affective, default-mode and right lateralised cognitive control networks, when comparing adult patients with ADHD and healthy controls (McCarthy et al., 2013). Furthermore, Wang and colleagues showed brain-wide increases and decreases in regional resting-state activity (regional homogeneity) in multiple regions, including the DMN, anterior cingulate cortex, cerebellum, insula, and basal ganglia, that could fairly accurately discriminate adult patients with ADHD from controls (Wang et al., 2013). These findings are in line with task-based fMRI studies that have shown aberrant neuronal activation in multiple networks. Problems with working memory, attention and cognitive control in ADHD have been attributed to reduced activity in brain regions in the right and left frontoparietal networks (Valera et al., 2010), while deficits in reward, timing, response inhibition, and impulsivity have been linked to aberrant functioning of frontal–striatal–cerebellar connections (Cubillo et al., 2012).

Taken together, these findings could be interpreted as widespread neuronal dysfunction in adult ADHD. At the same time, however, it seems that findings are difficult to replicate. As most studies described above rely on relatively small sample sizes (typically with $N = 20$ per group), it is difficult to determine whether these findings hold true at the population level (Button et al., 2013). Additionally, the methods to investigate between-group differences in connectivity vary, being either seed-based (Castellanos et al., 2008; McCarthy et al., 2013; Sato et al., 2012), regional homogeneity (Uddin et al., 2008; Wang et al., 2013) or independent component analyses (Hoekzema et al., 2014). Especially findings from seed-based studies, that rely on a specific region of interest (ROI), are difficult to compare with the results from studies using different ROIs or different analysis techniques (Cole et al., 2010). We therefore adopted a data-driven approach that allows the investigation of functional connectivity in all major resting-state networks (RSNs) and that is not biased by the selection of a particular ROI. With independent component analysis (ICA) resting-state fluctuations in neural activity can be separated into spatially independent components that are consistent over time and across subjects (Beckmann et al., 2005; Damoiseaux et al., 2006) and similar to task-based activation networks (Smith et al., 2009). Through subsequent dual-regression analysis one can analyse how the RSNs are manifested in each participant, after which between-group comparisons can be conducted to test if functional connectivity (i.e. temporal coherence) within these networks differs between patients and controls (Filippini et al., 2009). This method has been shown to be successful as an exploratory and data-driven analysis tool in various clinical and non-clinical populations. For example, to identify novel networks involved in major depression (Veer et al.,

2010), to distinguish young carriers of the *APOE4* allele from non-carriers (Filippini et al., 2009), or to identify networks that can be used as features in a classification model distinguishing autism patients from healthy controls (Uddin et al., 2013).

We applied this method to resting-state data from the largest sample of adult patients with ADHD studied to date, comprising 99 patients and 113 healthy controls from the Dutch part of the IMpACT study (Franke et al., 2010). In addition to between-group differences, we investigated dimensional associations between ADHD symptoms of inattention and hyperactivity/impulsivity and within-network functional connectivity strength. Such an approach may provide a closer association between brain and behaviour and has proven to be effective when investigating childhood ADHD (Chabernaud et al., 2012).

Based on previous findings in adult ADHD, we restricted our analyses to RSNs of interest that we identified through high spatial correspondence to the RSNs described by Smith et al. (2009). These networks are the default-mode, cerebellum, executive control, and the left and right frontoparietal networks. The executive control network has also been called the salience (Seeley et al., 2007), ventral attention (Yeo et al., 2011), or affective network (McCarthy et al., 2013) and includes the anterior insula and anterior cingulate cortex. We expected differences in functional connectivity between patients and controls in these networks. Furthermore, we hypothesised that these effects would be more pronounced when taking a dimensional instead of categorical approach.

2. Material and methods

2.1. Participants

Participants were selected from the Dutch cohort of the International Multicenter persistent ADHD CollaboraTion (IMpACT) (Franke et al., 2010). A total of 212 adult participants were included in the analyses, 113 healthy control participants and 99 patients with ADHD. All participants underwent psychiatric assessments, neuropsychological tests and a MRI session that included functional tasks, functional resting-state, and structural neuroimaging as previously described (Hoogman et al., 2013; Onnink et al., 2014). Patients were included if they had previously been diagnosed with adult ADHD by a psychiatrist according to the DSM (4th edition; DSM-IV-TR; (American Psychiatric Organisation, 2000)) and scored at least five symptoms on either the inattention or hyperactivity/impulsivity domain from the DIVA interview (see below 'ADHD symptoms'). In case the patient did not participate in the DIVA interview, he/she was included based on scores from the ADHD Self Rating scale (see below 'ADHD symptoms'), using the same symptom threshold. Controls were included if they scored less than four symptoms on the DIVA interview, or otherwise on the Self Rating scale.

Patients were excluded if they used medication other than psychostimulants or atomoxetine. Other exclusion criteria for both patients and controls were current diagnosis of major depression, substance use disorder or psychosis (assessed with the Structural Clinical Interviews for DSM-IV, SCID-I and SCID-II (First et al., 1996, 1997), estimated IQ below 80 (assessed with two subtests, block design and vocabulary, of the Wechsler Adult Intelligence Scale-III (Wechsler, 1997)), neurological disorders and sensorimotor disabilities, excessive head motion during the resting-state scan (absolute motion > 1.5 mm and/or the root mean square (rms) of relative motion > 0.2 mm) or other MRI contra-indications. Patients using medication at the time of recruitment were asked to withhold medication for 24 h prior to testing. All participants were asked to refrain from smoking and drinking coffee during testing.

This study was approved by the regional ethics committee (CMO region Arnhem-Nijmegen) and was carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki). After completely describing the study to the subjects, written informed consent was obtained.

2.2. ADHD symptoms

Both patients and controls were assessed using the structured diagnostic interview for adult ADHD (DIVA; <http://www.divacenter.eu>; (Kooij, 2010)). This interview focuses on the 18 DSM-IV symptoms of ADHD and uses concrete and realistic examples to thoroughly investigate whether a symptom is currently present or was present in childhood. Additionally, all participants were asked to fill out the ADHD-DSM-IV Self Rating scale that assesses current inattention and hyperactivity/impulsivity symptoms (Kooij et al., 2005). For both the DIVA interview and the Self Rating scale two scores can be derived, one for each symptom domain, with a maximum score of 9 per domain.

Based on the DIVA interview, patients were classified as having the inattentive-subtype when they presented with six or more symptoms on the inattention domain, as having the hyperactivity/impulsivity-subtype when they had six or more symptoms on the hyperactivity/impulsivity domain and as having the combined-subtype when they had six or more symptoms on both domains.

2.3. MRI data acquisition

Participants completed a nine-minute resting-state scan consisting of 274 interleaved whole-brain functional volumes using echo planar imaging on a Siemens 1.5-Tesla Avanto scanner (repetition time = 1990 ms; echo time = 45 ms; flip angle = 83, 23 slices, matrix size = 224 × 224 × 115 mm; acquisition voxel size = 3.5 × 3.5 × 5 mm). Participants were verbally instructed to lie still with their eyes closed, but not to fall asleep. A high-resolution T1-weighted magnetisation-prepared rapid acquisition gradient echo (MPRAGE) anatomical scan was also obtained (176 sagittal slices, repetition time = 2730 ms, echo time = 2.95 ms, voxel size = 1.0 × 1.0 × 1.0 mm, matrix size = 350 × 263 × 350 mm, inversion time = 1000 ms). The resting-state scan was preceded by the T1 scan and a counting Stroop task (not included in the current analyses) and took place approximately 20 min after the participant had entered the scanner.

2.4. Preprocessing of functional MRI images

Image preprocessing was performed using FSL software, version 5.0.5 (<http://fmrib.ox.ac.uk/fsl>). Preprocessing included deleting the first 5 volumes to allow the magnetisation to reach dynamic equilibrium, and retaining the subsequent 269 volumes, motion correction with MCFLIRT (Wilson et al., 2002), removal of non-brain tissue (i.e., skull stripping), grand-mean scaling to normalise the global 4D data and spatial smoothing using a Gaussian kernel of 6 mm full width at half-maximum. Subsequently, we used ICA-AROMA to identify residual motion-related artefacts (Pruim et al., 2015b). ICA-AROMA is an automated toolbox that uses single-subject ICA to detect components that are associated with head motion by evaluating each component in light of four parameters: the proportion of high frequencies in the power spectrum of the component, the correlation of the component's time course with the realignment parameters derived from the motion correction step, the proportion of signal located at the edge of the brain, and the proportion of the signal located in cerebrospinal fluid (CSF). Components identified as head motion were removed from the signal by means of a linear regression (non-aggressive denoising) using the function *fsl_regfilt*. Details about the identification and removal of motion artefacts, as well as an evaluation of the ICA-AROMA method against alternative motion-correction methods are described elsewhere (Pruim et al., 2015a,b). After removing motion artefacts, signals from the white matter (WM) and CSF were removed using linear regression. WM and CSF signals were derived from conservative anatomical masks that were created using FSL FAST. Lastly, a high-pass temporal filter was used with a cut-off frequency of 0.01 Hz. We did not perform global signal regression, as it

has been shown to induce anti-correlations in resting-state data (Murphy et al., 2009). The preprocessed functional images were linearly registered with FLIRT to the subject-specific high resolution T1 images using boundary-based registration (Greve and Fischl, 2009). The T1 images were registered to Montreal Neurological Institute (MNI152) standard space using 12-parameter affine transformation and non-linear registration with FSL FNIRT (10 mm warp, 4 mm resampling resolution) (Jenkinson and Smith, 2001; Jenkinson et al., 2002).

2.5. Identification of resting-state networks

To obtain functional connectivity networks we conducted group ICA using MELODIC in FSL (Beckmann et al., 2005) (version 3.14). Functional images of all participants were concatenated in the temporal domain to create a single 4D dataset. This concatenated dataset was then decomposed into 50 spatially independent components (ICs). Due to our large sample we chose this higher-order decomposition (i.e. as compared to the more commonly used 35). Components from the group ICA reflected both functional components (characterised by being located mainly in the grey matter and having a signal within the frequency range of 0.1–0.01 Hz) as well as residual noise components.

Functional connectivity patterns of each participant that corresponded to each group-IC were obtained using a dual-regression approach (Beckmann et al., 2009; Filippini et al., 2009) (dual_regression version 0.5). With this approach, the set of 50 spatial maps from the group ICA was used to generate subject-specific versions of the spatial maps, and associated time series, using two sequential multiple regressions. First, for each subject, the 50 group-level spatial maps were used as spatial regressors against the preprocessed individual subjects' fMRI data. This resulted in a set of 50 subject-specific time courses corresponding to each group-level IC. Second, these time courses were variance-normalised and used as temporal regressors against the individual subjects' fMRI data to produce participant-level unique spatial maps for each of the 50 ICs. In this way, the subject-specific spatial maps reflect the relationship (or temporal coherence) between an individual voxel's time course and the IC time course, thus representing the connectivity strength of each voxel in the network (Janes et al., 2012).

Next, we identified the ICs that showed close correspondence to the networks of interest (the default-mode, cerebellum, executive control, and the left and right frontoparietal networks). We identified these networks in our data by spatial correlation between the components from the group ICA and the five relevant network templates from the study by Smith et al. (2009). Six networks from the group ICA showed high spatial correspondence (>0.4) with the five network templates of interest. The cerebellum, executive control, left and right frontoparietal template networks each corresponded to a single component from the group ICA. The DMN template network was represented in two group-level ICs: a full DMN and a posterior part of the DMN. The selected six networks are shown in Fig. 1.

2.6. Categorical comparisons between ADHD patients and controls

Patients with ADHD and healthy controls were compared on age, IQ, education levels, and average head motion during scanning using separate independent samples *t*-tests. Furthermore, they were compared on gender and handedness using Pearson Chi-square tests. The covariate head motion was computed for each participant as the average root mean square (rms) relative (frame-to-frame) head motion. This parameter was computed with MCFLIRT at the motion correction stage during preprocessing (Jenkinson et al., 2002) and was averaged over all volumes to obtain a single measure of head motion per participant.

To identify group differences within the six networks of interest, for each of these networks the corresponding participant-level spatial maps from the dual regression stage were tested voxel-wise for significant differences between the patients with ADHD and the healthy controls via a general linear model. For this, we employed non-parametric

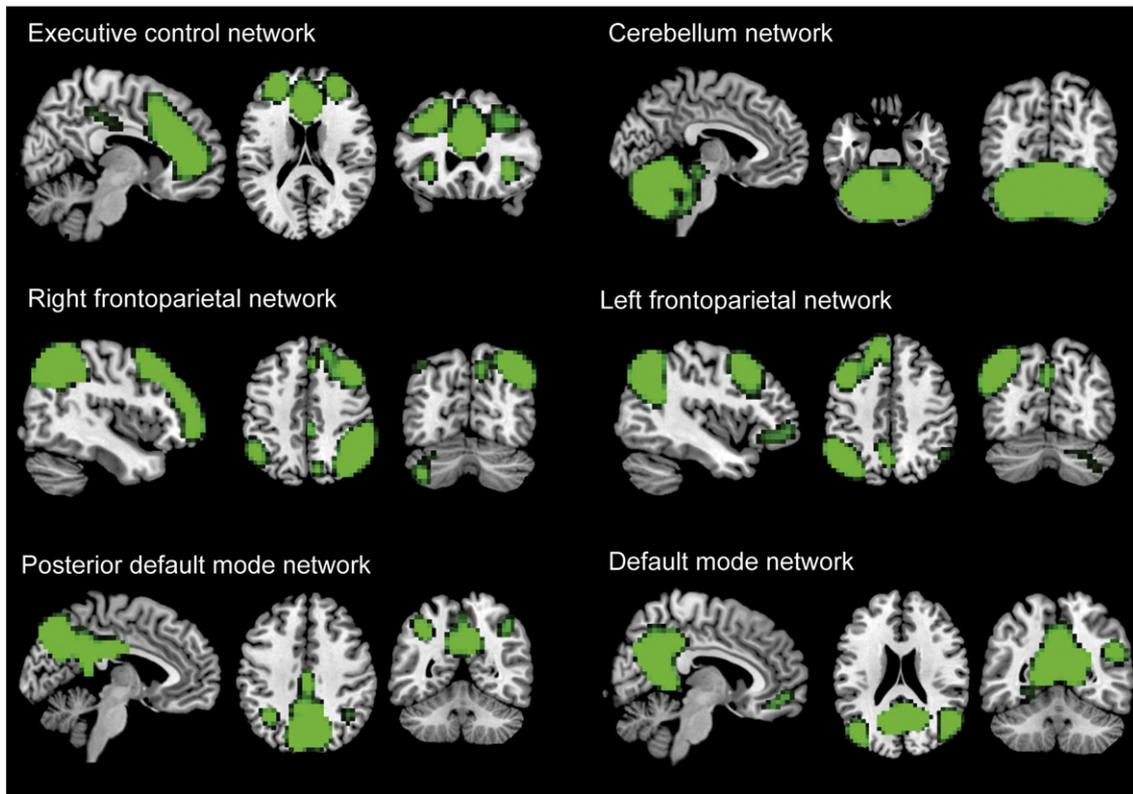


Fig. 1. Six components of interest from group ICA representing networks of interest (green), overlaid on a MNI-template brain (grey). Networks were thresholded at $Z > 5$.

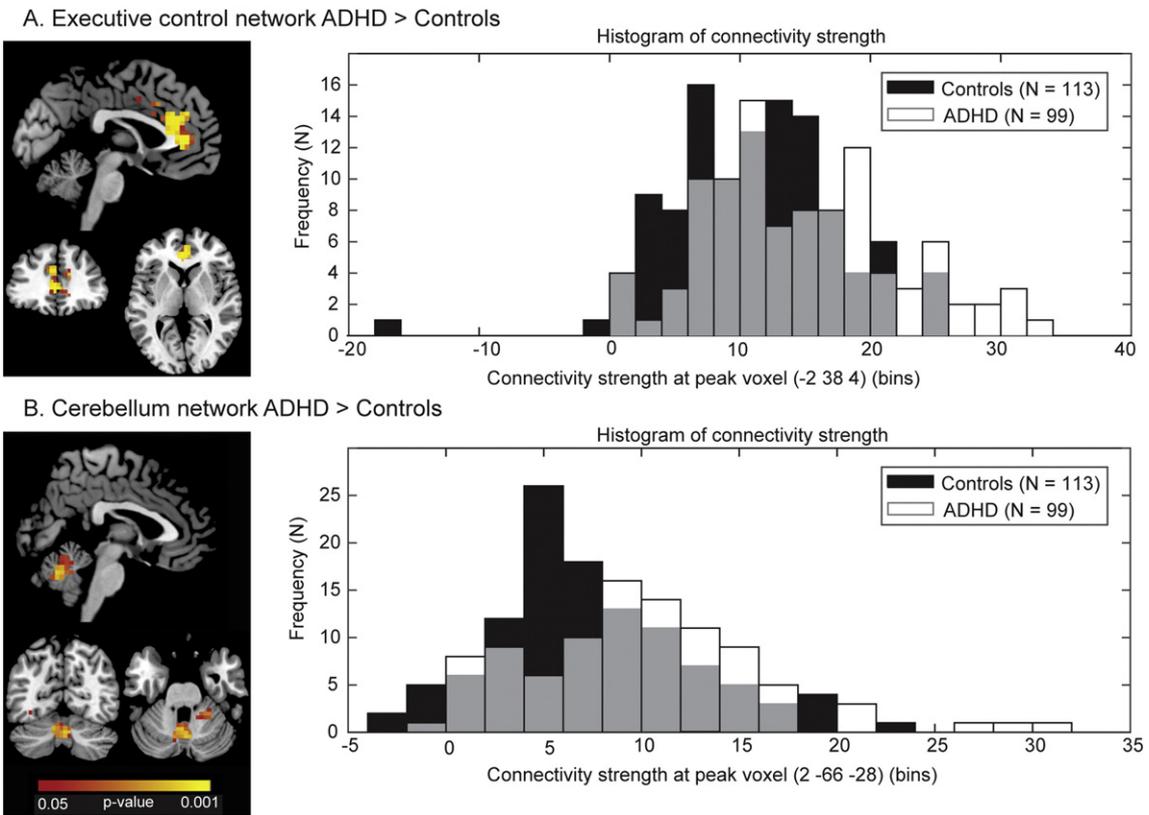


Fig. 2. Stronger connectivity in ADHD patients compared to controls in A) the executive control network and B) the cerebellum network. On the left, significant clusters are depicted in red-yellow at a threshold of $p < 0.05$ (FWE-corrected). On the right, histograms of connectivity strength of the peak voxel from the clusters on the left are shown for control participants (black) and ADHD patients (white). Grey-shaded areas reflect overlap between the two groups.

permutation testing (applying 5000 permutations) with Threshold-Free Cluster Enhancement (TFCE, (Smith and Nichols, 2009) using the Randomise tool of FSL (version 2.9). Voxel-wise tests were masked with a whole-brain mask, consisting of only those voxels that were present in all participants. Gender and age were added to the model as covariates of no interest.

Between-group effects were considered significant if they reached two-tailed p -values of <0.004 (family-wise error (FWE) corrected at the voxel level with TFCE; Bonferroni-corrected for two-sided testing in six networks). However, with respect to the exploratory nature of the analyses we also report effects with a p -value of <0.05 and a minimal cluster size of 5 voxels (FWE-corrected at the voxel level with TFCE). MNI coordinates of peak voxels were linked to anatomical locations using the Harvard–Oxford cortical and subcortical atlases and the cerebellum atlas in MNI152 space that are implemented in FSL. Cohen's d measures of effect size were computed from the t -values of the significant peak voxels of each cluster, using the formula Cohen's $d = 2t / \sqrt{df}$. For visualisation of connectivity strength measures (i.e. Figs. 2 and 3), connectivity strength of the peak voxel was extracted as the voxel's parameter estimate from the second stage of the dual regression (reflecting the coherence of that voxel's time course with the time course of the entire network).

To assess the robustness of the main group effects, we conducted a series of sensitivity analyses. In these analyses, we added handedness, education, IQ or head motion as additional covariates. Furthermore, within the ADHD group we investigated whether duration of medication treatment correlated with the main effects. Lastly, we investigated whether the main group effects would hold when using a lower-dimensional group ICA (35 components) followed by the same procedure of dual-regression, network selection and between-group testing as described above.

2.7. Dimensional analyses with ADHD symptoms

In those networks that showed categorical between-groups differences we investigated the relationship between functional connectivity strength and ADHD symptom severity across the entire sample (controls and patients combined). Inattention and hyperactivity/impulsivity symptom scores were obtained from the DIVA interview and entered in two separate analyses as variable of interest. As data from the DIVA-interview was missing for 20 participants, we included 104 controls and 88 patients in the dimensional analyses. Voxel-wise effects for a correlation with ADHD symptom scores were tested using permutation testing with Randomise as described above.

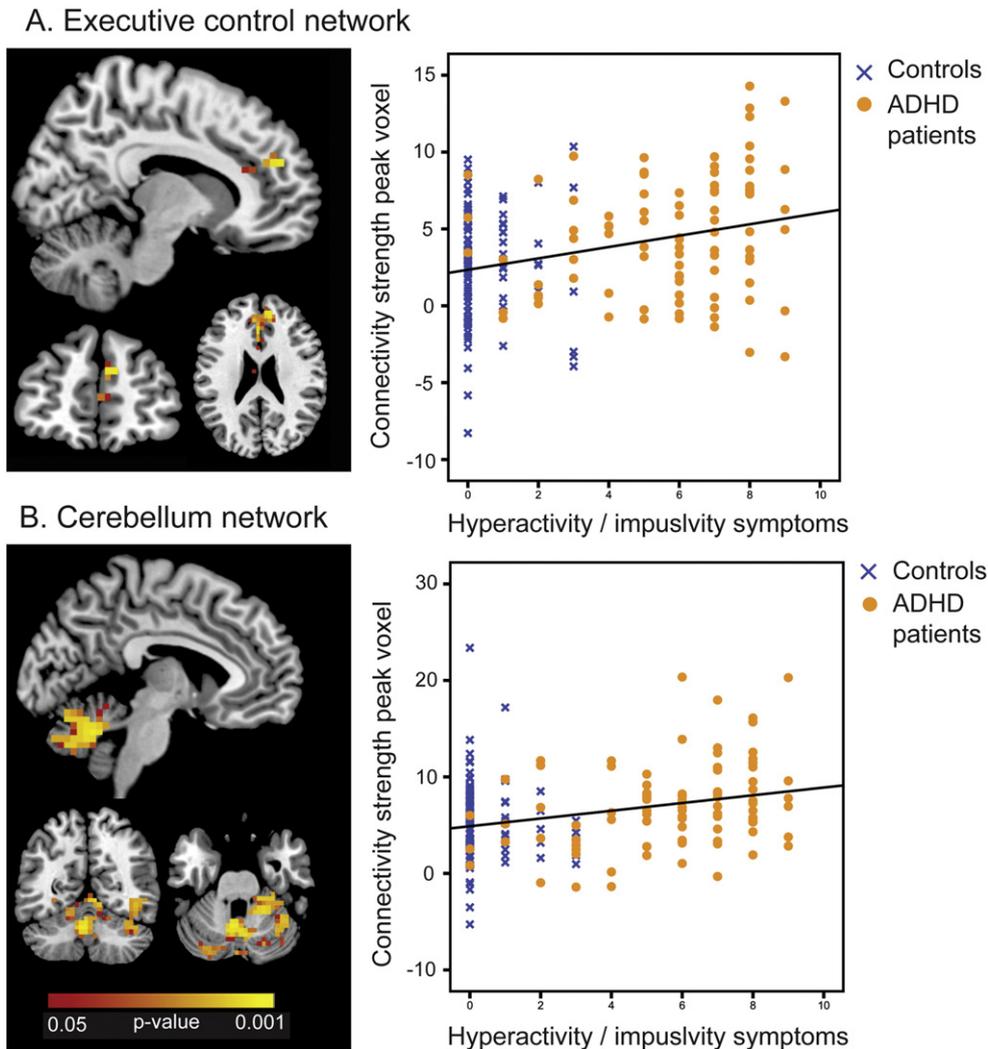


Fig. 3. Significant correlations between hyperactivity/impulsivity symptoms and functional connectivity strength in the executive control network (A) and the cerebellum network (B). Hot colours represent significant regions, thresholded at $p < 0.05$. Scatterplots represent the correlation between connectivity strength (y -axis; parameter estimates from dual regression, corrected for age and gender) and hyperactivity/impulsivity symptoms (x -axis). In A, the peak voxel is located in the right superior frontal gyrus (MNI 10; 50; 24). In B, the peak voxel is located in the left cerebellum vermis VI (MNI -6; -58; -28). See Table 3 for details.

3. Results and statistical analyses

3.1. Demographics of the sample

Characteristics of the sample and differences in demographics between the groups are reported in Table 1. The patient group did not differ from the control group in terms of age, gender, handedness, estimated IQ, or average frame-to-frame head motion during scanning. Controls were on average higher educated than patients ($T = 4.16$, $p < 0.001$). Seventy-five patients with ADHD reported to be taking stimulant medication, with an average treatment duration of 21 months (range 0–168 months, $SD = 28$). Eight patients reported having received medication in the past, and 13 had never been treated with ADHD medication.

3.2. Group differences in networks of interest

The ADHD patient group showed stronger functional connectivity within the executive control network as compared to controls. This cluster of stronger connectivity was located in the anterior cingulate gyrus (MNI coordinates peak-voxel: $-2; 38; 4$, p -value = 0.002). There were no significant effects in the other five networks. However, at a more lenient threshold – not correcting for conducting six two-sided tests, while still correcting for family-wise errors at the voxel level – we also observed stronger connectivity in the cerebellum network, with clusters located in the cerebellar vermis VI and crus II regions, and in the lingual gyrus near the temporo-occipital junction (Table 2; Fig. 2). As shown in Fig. 2, there was a high degree of overlap in the distribution of connectivity values in the executive control and cerebellum networks for the control and patient groups. This was reflected by moderate effect sizes, as shown in Table 2 (Cohen's d 0.47–0.66). Removal of the outlier participant that is apparent in Fig. 2A did not alter the results.

Sensitivity analyses showed that handedness, education, IQ, and further correction for head motion did not influence the direction of the effect, nor was medication duration associated with connectivity strength (see Supplementary Table 1 and Supplementary Figs. 1 and 2). Defining networks with a group ICA set to find 35 networks yielded very similar networks as the 50-component ICA and highly comparable between-groups effects (see Supplementary Table 2 and Supplementary Fig. 3).

3.3. Dimensional analyses in the executive control and cerebellum networks

Based on the findings from the categorical analyses, we tested for positive associations of connectivity strength with inattention and hyperactivity/impulsivity symptoms, respectively, in both the executive control and cerebellum network. We corrected for conducting four tests, considering significant only those results with a p -value of < 0.013 .

In the executive control network, there was a large cluster of voxels in the right superior frontal gyrus that showed a significant positive

correlation between functional connectivity strength and hyperactivity/impulsivity symptoms (Table 3, Fig. 3). Another significant cluster was located near the cluster of the categorical group difference, in the anterior cingulate gyrus, although this cluster did not survive multiple comparison correction. In the cerebellum network, hyperactivity/impulsivity symptoms correlated positively with connectivity strength in clusters in the left cerebellar vermis and lingual gyrus. Effect sizes for the dimensional analyses appeared slightly larger compared to the categorical analyses (Cohen's d 0.57–0.76).

For inattention symptoms, we only found positive correlation with connectivity for a small cluster located in the right frontal pole in the executive control network (MNI-coordinate of the peak voxel: $-26; 46; 24$, p -value = 0.027, cluster size = 5 voxels). In the cerebellum network, there were no significant clusters of correlation with inattention symptoms.

4. Discussion

In this study, we found that functional connectivity within the anterior cingulate gyrus of the executive control network was stronger in adult patients with ADHD compared to healthy adult control participants. This effect survived stringent correction for both voxel-wise testing (FWE-correction) and testing multiple networks. At a less conservative threshold using only FWE-correction (i.e. 'nominal significance'), patients with ADHD also showed signs of stronger connectivity within the cerebellum network. Hyperactivity/impulsivity symptoms showed a positive correlation with functional connectivity strength in the executive control and cerebellum networks, with apparent slightly larger effect sizes than the case-control effect and effects surviving correction for multiple tests in both networks. Positive correlations with symptoms of inattention were located in the cerebellum network, but were only seen at nominal significance.

The executive control network encompasses the cingulate cortex, prefrontal cortex, insular cortex, and the striatum and is involved in cognition, the inhibition of actions, emotions, and in pain perception (Smith et al., 2009). It has also been termed "a transitional network linking cognition and emotion/interoception" (Laird et al., 2011). Abnormalities within the executive control network have been widely associated with ADHD (Bush, 2010; Makris et al., 2009; Posner et al., 2014). Furthermore, functional connectivity of the anterior cingulate cortex (ACC) and cerebellum was previously found to be increased in adults with ADHD (McCarthy et al., 2013; Wang et al., 2013). McCarthy et al. however did not observe significant correlations between functional connectivity in the ACC and hyperactivity/impulsivity, which contrasts our findings. Furthermore, a longitudinal study on children and adolescents with ADHD found stronger resting state connectivity in the ACC within the executive control network to be negatively correlated with a decrease in hyperactivity/impulsivity symptoms (Francx et al., 2015). This suggested that stronger integration between the ACC and PFC is important for the remittance of ADHD, at least during childhood

Table 1
Demographics of the participants included in the analyses.

	Healthy controls (N = 113)	Patients with ADHD (N = 99)	Difference
Mean age (SD)	35.75 (11.79) years	34.71 (10.39) years	$T = 0.68$
Gender	46 (40.7%) male	40 (40.4%) male	$\chi^2 = 0.002$
Mean IQ ^a (SD)	111.12 (14.21)	108.88	$T = 1.15$
Mean education ^b (SD)	5.22 (0.78)	4.76 (0.85)	$T = 4.16^*$
Handedness	102 (90.3%) right	84 (84.8%) right	$\chi^2 = 1.45$
Mean head motion ^c (SD)	0.08 (0.03)	0.08 (0.03)	$T = -0.31$
Mean DIVA inattention symptoms (SD)	0.37 (0.79)	7.55 (1.45)	$T = -41.46^*$
Mean DIVA hyperactivity/impulsivity symptoms (SD)	0.42 (0.83)	5.74 (2.37)	$T = -20.05^*$

^a IQ was estimated based on two subtests, block design and vocabulary, of the Wechsler Adult Intelligence Scale-III (Wechsler, 1997).

^b Education level was coded from 1 (unfinished primary school) to 7 (post-university).

^c Head motion was calculated as the mean root mean square (rms) relative motion during scanning.

* Indicates a p -value < 0.001 .

Table 2
Clusters showing stronger within-network connectivity strength in ADHD patients compared to controls^a.

Network	Coordinates peak voxel ^b	p-Value peak	T-value peak	Cohen's <i>d</i>	Cluster size ^c	Region
Executive control	-2; 38; 4	0.002	4.12	0.57	121	L anterior cingulate gyrus
	6; 18; 40	0.019	3.37	0.47	18	L paracingulate gyrus
Cerebellum	2; -66; -28	0.01	3.79	0.53	91	L cerebellum vermis VI
	-30; -54; -4	0.009	4.79	0.66	23	L lingual gyrus
	22; -74; -36	0.035	3.99	0.55	9	R cerebellum crus II

^a Effects are shown at a threshold of $p < 0.05$ (FWE corrected, with TFCE), before correction for multiple testing, and a minimum cluster size of 5 voxels (voxel size = 4 mm). Effects in bold survived correction for testing multiple networks.

^b Coordinates are in MNI-space.

^c Number of voxels (voxel size = 4 mm).

and adolescence. Both the ACC and PFC are involved in the 'cold' (i.e. response inhibition) aspects (as well as the 'hot' (i.e. delay discounting) aspects) of inhibitory control (Bari and Robbins, 2013). In adults with ADHD performing an inhibitory Stop task and a cognitive switching task, activity in the ACC and cerebellum (as well as in other regions of the executive control network) was found to be negatively correlated with symptoms of inattention and hyperactivity (Cubillo et al., 2010). Hence, aberrant functioning of and connectivity between the ACC and PFC within the executive control network may result in inhibitory control problems, which lead to symptoms of hyperactivity and impulsivity (Bush, 2011). Something similar might be true for the cerebellum network. Such a link remains speculative, however, as our analyses are based on correlations. Furthermore, relatively little is known about how altered functional connectivity measured during rest relates to behaviour.

We observed only a small, positive association between inattention symptoms and connectivity in the executive control network, at nominal significance. This suggests that inattentive symptoms in adult ADHD are associated with different neurobiological mechanisms than hyperactivity/impulsivity symptoms, at least in terms of resting-state functional connectivity. Possibly, the aetiology of inattention symptoms is different from that of hyperactivity/impulsivity symptoms (Larsson et al., 2011).

In contrast to expectation, and despite our large sample size, we did not observe the differences in the default-mode and lateralised frontoparietal networks earlier reported. Furthermore, the effects in the executive control and cerebellum networks were small in both categorical and dimensional analyses. As can be seen in Fig. 2, connectivity strength of the peak-voxels from case-control difference showed strong overlap between the patient and control groups. Although the means of the two distributions differed significantly, the difference between the means was small and the variability large. This was also reflected by the moderate effect sizes (Cohen's *d* between 0.46 and 0.66) of the observed effects. Based on the literature, including several review articles (e.g. Konrad and Eickhoff, 2010; Liston et al., 2011; Posner et al., 2014), we had expected more wide-spread and stronger effects associated with ADHD status. We propose several explanations for the differences.

First, small and underpowered studies are susceptible to the so-called 'winner's curse', which means that the estimate of the effect can be inflated by chance (Button et al., 2013). When early studies report

findings with inflated effects, subsequent studies that do not find any differences are often not published, which results in a biased effect estimate. Functional connectivity differences between adult patients with ADHD and controls may therefore actually be smaller than previously thought. Related to this, effects are likely to be small due to the heterogeneity of (adult) ADHD (e.g. Hervey et al., 2004; Nigg et al., 2005). Patients with ADHD differ in the number of symptoms in the clinical domains of inattention and hyperactivity/impulsivity (i.e. different clinical subtypes), in the cognitive domains in which they show impairment (Coghill et al., 2013), in the comorbidity with various other psychiatric disorders (Biederman et al., 1991; Wählstedt et al., 2009), and in medication use. Although sensitivity analyses showed no direct effects of age, IQ, or medication use, it is likely that different neural mechanisms underlie behavioural symptoms in different patients. This is likely to reduce effect sizes and makes it difficult to compare samples across studies, or to extend research findings to the general patient population (Nigg et al., 2005). To further investigate the aetiology of adult ADHD we conducted additional analyses that were better able to account for heterogeneity. In those dimensional analyses, we investigated the association between functional connectivity and ADHD symptoms subdivided by domain, disregarding the categorical patient-control distinction. Indeed, this enhanced the findings, indicating that the functional connectivity alterations may be better explained by symptom severity than disease status (Chabernaud et al., 2012).

In addition, we were very careful to remove effects from head movements during scanning from the functional data. The issue of spurious effects induced by head motion has received widespread attention in the past few years (e.g. Fair et al., 2013; Van Dijk et al., 2012). To control for this, we adopted a rigorous new approach to remove motion-related signals that were identified with single-subject ICA from each individual's functional data (Pruim et al., 2015b). This method has been shown to outperform alternative methods, such as linear regression with 24 motion parameters or the removal of volumes associated with head motion (scrubbing), in terms of the number of motion-related artefacts removed, reproducibility of resting-state networks across samples, and preservation of temporal degrees of freedom (Pruim et al., 2015a). Furthermore, we confirmed that the addition of another covariate for average frame-to-frame head motion in the group level analyses did not yield different results.

Table 3
Effects for positive correlation between hyperactivity/impulsivity symptoms and connectivity strength^a.

Network	Coordinates peak voxel ^b	p-Value peak	r-Value peak ^c	Cohen's <i>d</i>	Cluster size ^d	Region
Executive control	10; 50; 24	0.005	0.305	0.64	117	R superior frontal gyrus
	-2; 42; 8	0.016	0.273	0.57	18	L anterior cingulate gyrus
Cerebellum	-6; -58; -28	0.004	0.294	0.62	593	L cerebellum vermis VI
	-30; -54; -4	0.005	0.354	0.76	22	Left lingual gyrus

^a Effects are shown at a threshold of $p < 0.05$ (FWE corrected, with TFCE), before correction for multiple testing, and a minimum cluster size of 5 voxels. Effects in bold survived correction for testing multiple networks.

^b Coordinates are in MNI-space.

^c r-Values reflect the correlation coefficient between the peak voxel connectivity value and hyperactivity/impulsivity symptoms.

^d Number of voxels (voxel size = 4 mm).

Another potential difference between the current and previous studies is that our sample included a relatively high proportion of women. Although in childhood ADHD is more prevalent in boys than in girls (Biederman et al., 2004), this gender difference is absent in adulthood. This difference between childhood and adulthood may be due to a referral bias in children, as girls tend to be less disruptive than boys and therefore less easily diagnosed, while adult women are more likely to seek treatment compared to men (Biederman et al., 2004). Nonetheless, previous resting-state functional connectivity studies in adults have included either only male participants (Hoekzema et al., 2014) or a majority of male participants (Castellanos et al., 2008; McCarthy et al., 2013; Uddin et al., 2008). Interestingly, Valera and colleagues showed that neural activity differences between patients with ADHD and healthy controls were only observed when comparing male participants, and not between females (Valera et al., 2010). Although our study set-up is ecologically valid, the high proportion of women may explain why our findings differed from those of previous studies.

The current findings should be viewed in light of several strengths and limitations. Obvious strengths were the large sample size and extensive motion correction. These make our findings more robust against inflated estimates of effect sizes and spurious effects of head motion as compared to previous studies. Of course, we also faced some limitations. First, we did not preselect patients according to subtype of ADHD (inattentive, hyperactive/impulsive and combined subtypes) or for the absence of comorbidity. While this may have led to suboptimal control of heterogeneity, it made the current sample most representative of the adult ADHD population. The resulting wide spread in symptoms also increased the power of our dimensional analyses.

A second limitation of our study was medication use by the patients with ADHD. The use of stimulant medication may affect functional connectivity between brain regions (Rubia et al., 2009; Sripada et al., 2013). Our study included patients that were using medication, that had used medication in the past, and those that were medication-naïve. Those actively using medication withheld it for ≥ 24 h before testing. Although we cannot entirely rule out that medication differences between patients and controls may have influenced our findings, we found no correlations between the duration of medication treatment and connectivity strength in the identified clusters in the main group contrast (Supplementary Fig. 2).

In light of the heterogeneity of (adult) ADHD and the low reproducibility of disease-specific findings across resting-state fMRI studies, we propose that future studies should focus more on dimensional aspects of the disorder rather than the categorical patient–control distinction. Such an approach is in line with the Research Domain Criteria (RDoC) proposed by the U.S. National Institute of Mental Health (NIMH) (Insel et al., 2010) and may enhance our understanding of neurobiological causes for aberrant behaviour and find new targets for treatment. In order to accurately model inter-individual differences in both behaviour and neurobiology, large samples are essential. To achieve this goal, collaborations between institutes and ‘consortium science approaches’ are becoming increasingly important.

5. Conclusion

To conclude, in a large sample of adults with persistent ADHD and healthy adult controls, we found stronger functional connectivity in the executive control network in the ADHD group, and – at a lower significance threshold – also in the cerebellum network. Hyperactivity/impulsivity symptoms correlated positively with connectivity in these networks, showing slightly stronger effects as compared to the case-control findings. Unexpectedly, we did not observe significant differences in the lateralised fronto-parietal and in the default-mode networks. Furthermore, effects were relatively small despite the large sample size. Future studies should include even larger sample sizes and focus more on brain–behaviour relationships rather than categorical

disease status in order to get a better understanding of the aetiology of heterogeneous disorders such as adult ADHD.

Conflict of interest

Authors report no conflicts of interest. Jan. Buitelaar has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Shire, Novartis, Roche and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. Barbara Franke received a speaker fee from Merz.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.pnpbp.2016.01.011>.

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