

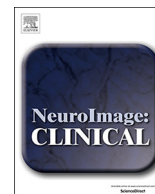
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Neural correlates of cognitive function and symptoms in attention-deficit/hyperactivity disorder in adults



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ABSTRACT

While gray matter (GM) anomalies have been reported for attention-deficit/hyperactivity disorder (ADHD), investigating their associations with cognitive deficits and individual symptom domains can help pinpoint the neural underpinnings critical for the pathology of ADHD, particularly the persist form of ADHD. In this work, we performed both independent component analysis and voxel-based morphometry analysis on whole brain GM of 486 adults including 214 patients, 96 unaffected siblings, and 176 healthy controls, in relation to cognition and symptoms. Independent component analysis revealed that higher GM volume in inferior semilunar lobule, inferior frontal gyri, and superior and middle frontal gyri was associated with better working memory performance, and lower GM volume in cerebellar tonsil and culmen was associated with more severe inattention symptoms. Consistently, voxel-based morphometry analysis showed that higher GM volume in multiple regions of frontal lobe, cerebellum and temporal lobe was related to better working memory performance. Focusing on the networks derived from ICA, our results integrated prefrontal regions and cerebellar regions through associations with working memory and inattention symptoms, lending support for the theory of 'cool'-cognition dysfunction being mediated by inferior fronto-striato-cerebellar networks in ADHD. Siblings showed intermediate cognitive impairments between patients and controls but presented GM anomalies in unique focal regions, suggesting they are a separate group potentially affected by the shared genetic and environmental risks with ADHD patients.

1. Introduction

ADHD is a childhood-onset neuropsychiatric disorder characterized by attentional problems, and/or hyperactivity and impulsivity, and can seriously affect patients' interpersonal and academic performance (American Psychiatric Association, 2013). A meta-analysis of follow-up studies has shown that in about 15% children with ADHD the disorder persists into adulthood, and the persistence percentage increases to 65% if partially remitted patients are taken into account (Faraone et al., 2006). In the general adult population, the average prevalence rate of ADHD is about 2.5%–4.9% (Simon et al., 2009). This specific patient group deserves increased attention from a clinical treatment viewpoint as well as from the basic research community to understand the neuropathology.

Adult ADHD abnormalities in cortical brain regions remain poorly understood. While in structural magnetic resonance imaging (sMRI) studies of childhood ADHD, significant and relatively consistent brain structure alterations have been reported in patients, including smaller global brain volume than healthy controls (Castellanos et al., 1996; Castellanos et al., 2002; Greven et al., 2015), gray matter (GM) reductions in caudate nucleus (Frodl and Skokauskas, 2012; Nakao et al., 2011), right globus pallidus and putamen (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012), fronto-striatal-parietal pathway (Dickstein et al., 2006; Filipek et al., 1997), and cerebellum (Valera et al., 2007). In contrast, GM changes identified in adult ADHD were inconsistent. A meta-analysis study conducted by Frodl and Skokauskas highlighted GM reduction in anterior cingulate cortex (Frodl and Skokauskas, 2012), while another meta-analysis study by Nakao et al.

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(2011) showed no group difference in regional networks. These ambiguities may be due to the limited sample size and methodological differences of studies. Recently, Hoogman et al. (2017) investigated the subcortical brain volumes with the largest sample size to date and reported that nucleus accumbens, amygdala, caudate nucleus, hippocampus, and putamen showed reduced volume in ADHD with effect sizes decreasing from youth (< 15 years) to adults (> 21 years); in fact, no significant brain volume reductions were found for adult patients.

In addition to significant functional deficits in the two symptom domains (i.e. inattention and hyperactivity/impulsiveness), ADHD patients also often present with impaired cognitive ability (American Psychiatric Association, 2013). Children with ADHD have been documented with many aspects of neurocognitive dysfunction, including executive function, working memory, inhibition, delay aversion, and timing response (Martinussen et al., 2005; Sjowall et al., 2013). In adults, cognitive impairments have also been observed (Mostert et al., 2015), most consistently in executive function (Boonstra et al., 2005), followed by long term memory (Skodzik et al., 2017), set-shifting (Rohlf et al., 2012), inhibition (Fuermaier et al., 2015), and delayed discounting (Marx et al., 2010), each affecting a subset of patients (Mostert et al., 2018). Neurocognitive dysfunctions in specific cognitive domains along with the two distinct symptom domains suggest a high phenotypic and etiologic heterogeneity in ADHD (Nigg et al., 2005). Identifying and understanding the neuronal circuits underlying each symptom domain and specific aspects of cognition would help us parse the heterogeneity in ADHD.

Through integrating the deficits in cognition, symptom and brain structure, a systematic analysis on the interrelationship can provide us with more information about how the persistence of ADHD manifests in the brain resulting in impaired behavior and cognition. While a few studies with smaller sample sizes have been conducted focusing on a specific type of cognition or symptom domain in adult ADHD (Makris et al., 2007; Makris et al., 2015), in this study, we leveraged data of relatively large samples combined from the NeuroIMAGE project (von Rhein et al., 2015) and the IMPACT Dutch consortium (Onnink et al., 2014), including patients, unaffected siblings and controls. We employed both independent component analysis (ICA) (Xu et al., 2009) and voxel-based morphometry analysis (VBM) (Good et al., 2001). ICA groups covarying voxels, not limited to physically connected voxels, into one component, and thus forms a network-based analysis. Brain imaging data of participants included in this study have been previously analyzed with focuses on GM differences in adult ADHD (Onnink et al., 2014) or broad ADHD (including children and adults) (Bralten et al., 2016; Hoogman et al., 2017). While Bralten et al. also investigated GM regions related to symptom counts, where inattention and hyperactivity symptoms were added together, cognition and individual symptom domains (i.e. inattention or hyperactivity) have not been studied explicitly, and not with combined larger adult only samples. To shed light on these unknowns, we aim to identify GM regions underlying working memory and inhibition deficits, as well as the two symptom domains of ADHD. Given previous reports that unaffected siblings of ADHD patients also show brain abnormalities and cognitive impairments to an extent (Bralten et al., 2016; Castellanos et al., 2003; Durston et al., 2004; Faraone et al., 1993; Slaats-Willemse et al., 2003), we also investigated how unaffected siblings behave in cognitive function, symptom domains, and associated neural correlates comparing with patients and healthy controls.

2. Materials and methods

2.1. Participants

This study employed a large cohort of 486 European Caucasian adults aggregated from two projects: 301 samples from the NeuroIMAGE project (age range: [18, 30], female/male:127/174) (von Rhein et al., 2015) and 185 samples from the Dutch chapter of the

IMPACT consortium (age range: [18, 63], female/male:136/49) (Mostert et al., 2015; Onnink et al., 2014). Written informed consent was obtained from all participants. The inclusion and exclusion criteria were described in detail in the original papers (Mostert et al., 2015; Onnink et al., 2014; von Rhein et al., 2015). In brief, adult ADHD patients were included if they met the DSM-IV (NeuroIMAGE project) (American Psychiatric Association, 1994) or DSM-IV-TR (IMPACT consortium) (American Psychiatric Association, 2000) criteria for adult ADHD. In addition, IMPACT included ADHD diagnosis in childhood; NeuroIMAGE, which is a longitudinal study, also required a formal and research diagnosis in childhood. Unaffected siblings were enrolled from NeuroIMAGE ADHD families, and healthy controls were recruited from the families free of ADHD. For adult samples from the NeuroIMAGE cohort, a total of 206 families were involved, including 124 independent participants, 71 two-member families, 11 three-or-four-member families. The participants from the Dutch IMPACT cohort were all independent. All participants had IQ ≥ 70 , no diagnosis of autism, epilepsy, brain disorders and any genetic or medical disorders related to externalizing behaviors which might be confused with ADHD (Onnink et al., 2014; von Rhein et al., 2015). In NeuroIMAGE project, medicated patients have received psychostimulant treatment (von Rhein et al., 2015). In IMPACT project, medicated patients have received ADHD medication (Hoogman et al., 2011). Medicated participants were required free of medication at least 48 h in NeuroIMAGE project (van Lieshout et al., 2016) or 24 h in IMPACT project (Hoogman et al., 2011) prior to assessments. One healthy control also reported to take psychostimulant medication. The rationale of including both medicated and medication-naive cases in this analysis can be summarized as follows: (1) About 50% of ADHD patients were medicated in our samples. Including both patient groups increased the power to detect GM associations with symptoms and cognition; and (2) Including both patient groups helped us better parse the neural correlates of symptoms and cognition in adult ADHD. As a result, we found that both medicated and medication-naive cases showed significantly higher symptoms and worse cognition than healthy controls. Two symptom domains, inattention (IA) and hyperactivity/impulsivity (HI), were evaluated for all participants consistently between two cohorts based on 18 DSM-IV symptom questions. The final symptom scores for both domains range from 0 to 9 and the larger the score, the more severe the disorder. Siblings had < 5 in either the inattention or hyperactivity/impulsiveness symptom score. Healthy controls were filtered to have scores < 2 in either domain. Detailed demographics, symptom, comorbidity, and MRI scanning sites of this study can be seen in Table 1.

2.2. Neurocognitive assessments

Two cognitive functions, working memory and inhibition, were assessed in both projects. For working memory, the WAIS Digit Span task (Wechsler et al., 2000) was employed for almost all participants (N = 480) in both projects. Here we used maximum digit span forward and backward as measures of working memory. For inhibition, the NeuroIMAGE project employed a stop task for 202 participants with stop-signal reaction time and the total number of commission and omission error as outcome measures (Logan et al., 1984), while the Dutch IMPACT project utilized a go/no-go task for 150 participants with standard deviation of response time in go digits and standard deviation of response time of commission errors as outcome measures (Mostert et al., 2015). These variables were selected for each assessment because they showed case-control differences ($p < 0.05$). Since each assessment task measures different aspects of inhibition, and the variables cannot be simply combined. Thus, we treated them separately in the association analysis.

2.3. Neuroimaging

T1-weighted MRI images were acquired with three 1.5 T scanners

Table 1
Demographics of the study population.

Variables	Diagnosis group (#)			
	Healthy control (176)	Unaffected sibling (96)	ADHD (214)	
			Medicated ADHD (105)	Unmedicated ADHD (109)
Age	28.93 ± 11.79	21.41 ± 2.34	28.04 ± 9.56	22.76 ± 6.55
Sex (F/M)	125/51	47/49	56/49	35/74
Estimated IQ	108.19 ± 14.88	104.80 ± 15.75	105.50 ± 16.33	101.59 ± 17.05
Inattention (IA)	0.56 ± 1.24	1.60 ± 1.97	7.49 ± 1.52	7.01 ± 1.75
Hyperactivity/impulsiveness (HI)	0.70 ± 1.12	1.48 ± 1.65	5.92 ± 2.26	5.69 ± 2.48
Major depression	13	0	30	7
Anxiety disorder	4	1	17	3
Scan site 1	47	40	15	43
NeuroIMAGE 1				
Scan site 2	32	56	20	48
NeuroIMAGE 2				
Scan site 3	97	0	70	18
IMPACT (Dutch)				

Note: Major depression and anxiety disorder were diagnosed consistently between two cohorts based on DSM-IV criteria (Onnink et al., 2014; von Rhein et al., 2015). The full-scale IQ was estimated consistently between two cohorts based on Wechsler Adult Intelligence Scale III (Bralten et al., 2016; Mostert et al., 2015).

(NeuroIMAGE project using Siemens SONATA and Siemens AVANTO, and IMPACT project in Dutch site using Siemens SONATA) with closely matched settings, such as, a voxel size of $1 \times 1 \times 1 \text{ mm}^3$, TI 1000 ms, TR 2730 ms, TE 2.95 ms, field of view 256 mm and 176 sagittal slices. For NeuroIMAGE project, two sMRI scans were obtained for every participant and their qualities were evaluated by two independent raters on a 4-point scale (1 = good; 2 = useable; 3 = poor; 4 = very poor) (von Rhein et al., 2015). Only those rated as good by NeuroIMAGE team were used for this analysis. For the Dutch IMPACT project, sMRI scans were visually checked by the IMPACT team (Onnink et al., 2016; Onnink et al., 2014; Wolfers et al., 2017), and selected scans were used for this analysis. Then, all included sMRI scans were segmented into six types of tissues using Statistical Parametric Mapping 12 (SPM12, <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). GM data were normalized to the Montreal Neurological Institute (MNI) template, and modulated (to keep local GM volume information as we are more interested in GM volume co-variation networks) and smoothed with a $6 \times 6 \times 6 \text{ mm}^3$ Gaussian kernel. In addition to sMRI scan quality check by NeuroIMAGE and IMPACT teams, all included GM images had to pass our quality check with a correlation higher than 0.8 with the mean gray matter image. A GM mask was applied to include voxels with mean gray matter volume larger than 0.2 resulting in 456,921 voxels. For each included voxel, the confounding effects of age, sex and site were corrected using a linear regression model, where the regression coefficients were estimated from data on controls only to eliminate potential influences of diagnosis interactions with age or sex. We further confirmed that after correcting age, sex and site effects, the total GM volume did not differ between the two cohorts ($p = 0.71$), and adding the cohort as an additional variable into the analyses did not change the significance of the reported results (see Appendix A for details). Therefore, we combined the imaging data from two cohorts to

increase the detection power in subsequent imaging analysis.

2.4. GM component decomposition and association analyses

The preprocessed GM data (dimension: subject \times voxel) was decomposed into 22 distinct components using ICA (Xu et al., 2009), where the component number was estimated using the minimum description length algorithm (Rissanen, 1978) and ICA was implemented with the infomax algorithm (Bell and Sejnowski, 1995) within the GIFT toolbox (<http://mialab.mrn.org/software/gift>). Infomax decomposes the preprocessed GM data into linear combinations of independent components; i.e., preprocessed GM data (X) = loadings (A) \times components (S), where the independence among components is achieved by maximizing the entropy of components. For extracted GM components S (dimension: component \times voxel), each row is an independent component and represents a GM covariation network where highly weighted voxels express very similar GM patterns. For the loading matrix A (dimension: subject \times component), each column is the loading vector of the corresponding component presenting the weights of this component across all subjects. To make sure the decomposition is stable, ICASSO (Himberg et al., 2004) with 10 ICA runs was used to generate stability indices for each component, where the stability index equals 1 in the ideal case. The most stable run was selected as the final ICA decomposition.

Next, in order to identify GM components underlying cognition and symptoms, associations between GM components and two symptom domains, as well as working memory and inhibition performance were tested using a linear mixed effect model (model 1 in Table 2), where family ID was used as a random effect to control for relatedness (the same for models 2–5), and other predictors (i.e. age, sex and GM loading of a component) were treated as fixed effects. Significance was

Table 2
Linear mixed effect models used in the analysis.

Model	Function	Response	Predictors	
			Fixed effect	Random effect
Model 1	Test association	Cognitive/symptom variable	Age, sex, GM loading of a component	Family ID
Model 2	Test group difference (4 groups) for GM loadings of a component	GM loadings of a component	Diagnosis (4 groups)	Family ID
Model 3	Test group difference (4 groups) for cognition/symptom	Cognition/symptom variable	Age, sex, diagnosis (4 groups)	Family ID
Model 4	Test group difference (3 groups) for GM loadings of a component	GM loadings of a component	Diagnosis (3 groups)	Family ID
Model 5	Test medication effect for GM loadings of a component	GM loadings of cases of a component	Medication status	Family ID

Note: 4 groups included unmedicated cases, medicated cases, unaffected siblings and controls. 3 groups included cases, unaffected siblings and controls.

corrected for multiple comparisons for all networks at a false discovery rate (FDR) of 0.05. Then, the potential confounding effects from medication, comorbidity with major depression and anxiety, IQ as well as cohort were examined by adding them as covariates into the model 1 (Table 2) separately to evaluate their impact on the significance of associations, in which medication and comorbidity were treated as binary variables. Moreover, pairwise group difference among medicated cases, medication-naïve cases, healthy controls and unaffected siblings were tested for the GM loadings of identified components, and associated cognitive function and symptom severity using models 2 and 3 in Table 2, respectively.

Finally, we also tested GM components for ADHD differences regardless of their association with cognition or symptom severity using GM loadings of patients and controls only, which was tested by model 4 in Table 2, and multiple comparisons were corrected at FDR $p < 0.05$. Subsequently, medication effects were tested on GM loadings of patients only using model 5 in Table 2, where medication status was treated as a fixed effect. Potential confounding effects of comorbidity and IQ as well as cohort were also tested for these components by adding them as covariates into the model 4 (Table 2) separately. In addition, the differences of GM loading of siblings compared with those of ADHD patients and healthy controls were also examined using model 4 in Table 2.

2.5. VBM analysis

In order to validate ICA results to an extent, we also employed the VBM analysis on the same preprocessed GM data. To identify GM regions underlying cognition or symptom, we performed similar linear mixed effect model as listed in Table 2 model 1 with substituting GM loadings of a component with GM volumes of voxels. Multiple comparison correction FDR $p < 0.05$ was applied. Similarly, ADHD differences were tested on voxels of healthy controls and ADHD patients by model 4 in Table 2 with the response variable as GM volumes of voxels, and FDR $p < 0.05$ was utilized. The extent threshold was set at 10 voxels to include almost all identified regions except for isolated voxels.

3. Results

3.1. ICA results

By decomposing the GM data of 486 adults including 214 ADHD patients, 96 unaffected siblings and 176 healthy controls (detailed demographics information see Table 1), 22 distinct GM components were generated and their ICASSO stability indices were all larger than 0.97. Out of 22 GM components extracted by the most stable ICA run, four GM components were significantly related to either working memory or inattention symptom severity measures. The stability index, related phenotype (i.e. working memory or symptom domain or ADHD status), brain regions of each component (regions were thresholded by Z-score of 2.5 and cluster volume larger than 1 cm^3), and peak voxel coordinates are listed in Table 3 (ICs 1–4) and also plotted in Fig. 1.

GM loadings of both component 1 (inferior semilunar lobule: $p_{\text{association}} = 1.38 \times 10^{-4}$, $t(476) = 3.84$, variance explained (VE) = 3.08%) and component 2 (inferior frontal gyrus: $p_{\text{association}} = 2.68 \times 10^{-3}$, $t(476) = 3.02$, VE = 1.90%) presented significant positive associations with forward digit span performance. GM loadings of both component 2 (inferior frontal gyrus: $p_{\text{association}} = 3.95 \times 10^{-3}$, $t(476) = 2.90$, VE = 1.73%) and component 3 (superior and middle frontal gyri: $p_{\text{association}} = 1.66 \times 10^{-3}$, $t(476) = 3.16$, VE = 2.05%) showed significant positive relations with backward digit span performance. GM loadings of component 4 were significantly and negatively associated with IA score (cerebellar tonsil and culmen: $p_{\text{association}} = 2.26 \times 10^{-3}$, $t(462) = -3.07$, VE = 1.88%). No significant confounding effects of medication,

comorbidity, IQ or cohort were found for these associations. We did not observe any significant associations of GM components with inhibition and hyperactivity/impulsiveness.

Fig. 2 shows pairwise comparisons for digit span performances (forward and backward) and IA symptom as well as associated four GM components (ICs) among medicated cases, medication-naïve cases, siblings and controls ($p < 0.05$ was used for statistical significance). As plotted in Fig. 2(a), patients, both medicated and unmedicated, showed significantly worse working memory performance compared to controls, while siblings presented in-between performances with no significant difference from either of the other groups in forward digit span task but with significant worse performance compared to controls in backward digit span task. For IA, four groups were significantly different from each other with medicated cases showing the most severe symptoms, followed by medication-naïve cases, siblings and then healthy controls. In Fig. 2(b), all GM loadings are normalized scores with standard deviations around 1 and thus are much larger than the mean values. GM reduction in patients compared to controls was found in components 1 (medicated cases vs. controls: $p = 1.06 \times 10^{-2}$, $t(279) = -2.57$), 2 (unmedicated cases vs. controls: $p = 1.01 \times 10^{-2}$, $t(283) = -2.59$) and 4 (medicated cases vs. controls: $p = 1.06 \times 10^{-2}$, $t(279) = -2.57$, unmedicated cases vs. controls: $p = 4.56 \times 10^{-2}$, $t(283) = -2.01$). Even though there were some differences between test results of medicated cases and unmedicated cases in comparison to controls for components 1, 2 and 4, no significant group differences were observed between medicated and unmedicated cases for any of the four GM components. Siblings did not show any significant difference from controls, but differed from patients in components 1 (medicated) and 2 (unmedicated). In component 4, siblings presented GM volume values in-between cases and controls, but did not significantly differ from either group. No GM differences were observed in component 3 for any groups.

In the case-control comparison, component 5, located in the middle frontal gyri as listed in Table 3 (IC 5) and shown in Fig. 3, was identified showing significant GM anomalies. A significant medication effect was observed for component 5, and after regressing out the medication effect, the GM loadings still showed significant reduction in patients as shown in Fig. 4 (Cohen's d [95% CI] = -0.78 [-0.98 , -0.57]; $p = 5.56 \times 10^{-6}$, $t(387) = 4.61$). Siblings also presented significantly different GM loadings compared to controls in component 5 ($p = 1.93 \times 10^{-6}$, $t(269) = 4.87$). Potential GM abnormalities were also observed in two additional interesting components encompassing cingulate, occipital gyri, though they did not pass FDR correction (denoted as components 6 and 7 in Appendix E). No comorbidity, IQ or cohort effects were found for these GM alterations.

Most of the identified GM components associated with working memory and ADHD status were replicated when running ICA on two cohorts separately (see Appendix C for details). And the identified associations held to a large extent with less significance in female and male participants, separately. (see Appendix G for details). We also ran ICA on independent subjects only (i.e. excluding the 95 relatives), and confirmed that both the ICA decomposition and association pairs were largely kept (see Appendix D for details).

3.2. VBM results

Fig. 5 plotted regions (FDR corrected at $p < 0.05$; cluster size threshold $k = 10$) showing significant associations with working memory task performance or ADHD diagnosis (all regions were listed in Appendix F). No voxels were significantly associated with inhibition or symptom domains. Multiple regions in frontal lobe, temporal lobe, and cerebellum in subplot A were significantly and positively correlated with forward digit span performance, and regions in frontal lobe in subplot B were significantly and positively associated with backward digit span performance. Subplot C presents regions in cingulate gyrus showing a significant GM reduction in ADHD patients.

Table 3Stability indices, related phenotype, Talairach labels, peak voxel coordinates and volume of GM components 1–5 ($|Z| > 2.5$, volume $> 1 \text{ cm}^3$).

IC: stability index	Related phenotype	Brain region	L/R volume (cm^3)	L/R: max Z (x, y, z)
IC1: 0.98	FW (+)	Inferior semilunar lobule (+) Tuber (+)	1.2/1.3 1.0/1.0	7.8 (-22, -84, -36)/7.8 (21, -85, -35) 8.5 (-19, -89, -29)/8.2 (18, -88, -30)
IC2: 0.99	FW (+) BW (+)	Inferior frontal gyrus (+) Inferior frontal gyrus (-)	1.3/1.4 1.2/0.9	4.8 (-30, 15, -22)/5.7 (22, 12, -22) 6.6 (-21, 22, -15)/4.9 (24, 24, -13)
IC3: 0.99	BW (+)	Superior frontal gyrus (+) Middle frontal gyrus (+)	3.2/3.0 2.2/2.0	7.2 (-22, 60, -16)/6.4 (21, 59, -18) 6.4 (-36, 57, -12)/5.5 (37, 57, -13)
IC4: 0.99	IA (-)	Cerebellar tonsil (+) Culmen (+) Tuber (+)	2.2/1.9 1.3/0.8 1.0/0.7	9.4 (-48, -49, -37)/8.1 (45, -44, -36) 8.9 (-48, -45, -29)/6.5 (48, -45, -29) 8.9 (-52, -54, -30)/6.4 (52, -50, -30)
IC5: 0.98	ADHD status (-)	Middle frontal gyrus (+) Middle frontal gyrus (-)	1.8/1.9 1.1/1.3	9.9 (-33, 27, 26)/11.0 (34, 22, 32) 8.6 (-24, 18, 39)/9.7 (25, 19, 38)

Note: IC denotes the component. The ‘+’ or ‘-’ sign in the Related phenotype column indicates that GM volume of the component is positively or negatively related to the cognition performance, symptom or diagnosis. The ‘+’ or ‘-’ sign in the Brain region column indicates positive or negative contribution to this component from the regions, which are mapped to red colored or blue colored regions in the component spatial map, respectively. FW, BW and IA denote forward digit span performance, backward digit span performance and inattention symptom severity. For ADHD status, ADHD was coded as 1 and control was coded as 0.

4. Discussion

In this study, we investigated the neural correlates of cognitive deficits, symptom domains and ADHD status in adult ADHD patients, their unaffected siblings and controls. From ICA analysis, we identified three GM components associated with working memory involving superior, middle and inferior frontal gyri, and inferior semilunar lobule, one GM component associated with IA symptoms involving cerebellar tonsil and culmen and one GM component associated with case-control status, including the middle frontal gyri. From the VBM analysis, multiple regions correlated to working memory performance involving frontal lobe, cerebellum, superior and middle temporal gyri, which are largely overlapped with ICA components associated with working memory. A small area in middle cingulate presented GM reduction in ADHD patients. No significant GM components or VBM regions underlying response inhibition and hyperactivity/impulsivity were observed for both methods.

Both VBM identified brain regions and ICA components highlighted

frontal lobe and cerebellum being associated with working memory performance, even though VBM reported many sparse and small regions across the brain, while ICA extracted several coherent networks (small and separate regions were ignored). Moreover, ADHD patients showed GM reduction in cingulate in both methods (marginal significance for ICA analysis, see Appendix E, Fig. E1, IC 6). ICA also extracted one component associated with inattention symptom (Fig. 1, IC4), and one component associated with ADHD status (Fig. 3, IC5), while in VBM analysis the corresponding regions did not pass FDR correction. The discrepancy likely highlights the benefit of network-based analyses. VBM identified a relatively larger region in the temporal lobe underlying working memory (Appendix F, A subplot) than ICA (volume $< 1 \text{ cm}^3$ not reported), which may indicate that only a small part of temporal gyrus shared a covariation pattern with frontal lobe and cerebellum so that ICA grouped them into one component. Overall, we observed high correspondence between ICA and VBM analyses, and ICA provided more organized network-based results, therefore the following discussion is based on ICA results.

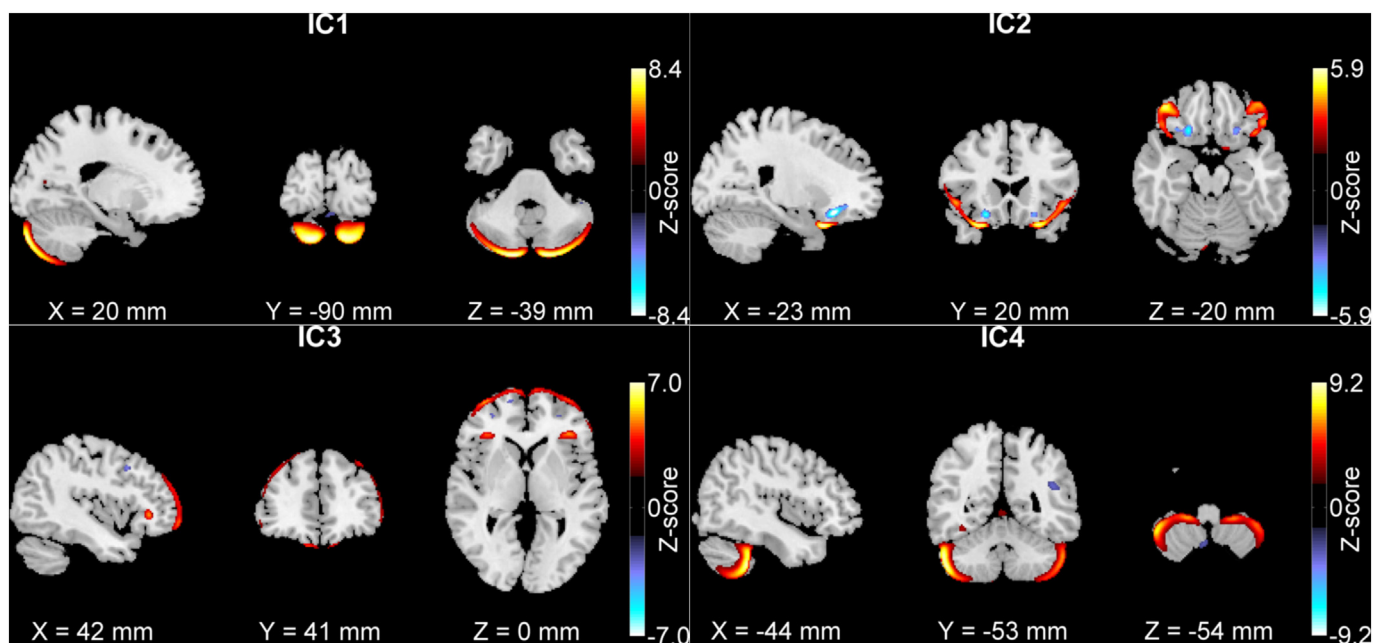


Fig. 1. Four significant GM components (ICs) associated with either working memory or inattention symptoms ($|Z| > 2.5$). GM loadings of IC1 in inferior semilunar lobule were positively related to forward digit span performance. GM loadings of IC2 in inferior frontal gyrus were positively associated with both forward and backward digit span performance. GM loadings of IC3 in superior and middle frontal gyri were positively related to backward digit span performance. GM loadings of IC4 encompassing cerebellar tonsil, culmen and tuber were negatively associated with inattention symptom severity. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

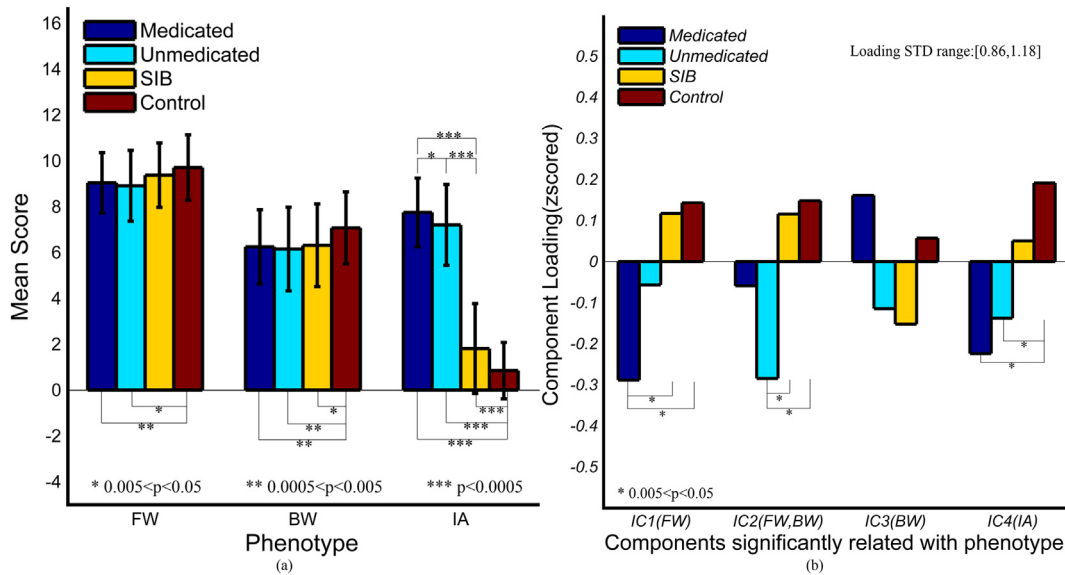


Fig. 2. Group comparisons in working memory, inattention symptom, and associated GM components (ICs). One star, two stars and three stars indicate significant group differences at $0.005 < p < 0.05$, $0.0005 < p < 0.005$ and $p < 0.0005$, respectively. FW, BW and IA in (a) and (b) stand for forward and backward digit span performance and inattention symptom severity, respectively. The total whisker length in (a) represents two standard deviations (STD). The STD in (b) range from 0.86 to 1.18, therefore they were not plotted here. Colors indicate medicated cases (Medicated), unmedicated cases (Unmedicated), siblings (SIB) and healthy controls (Control). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

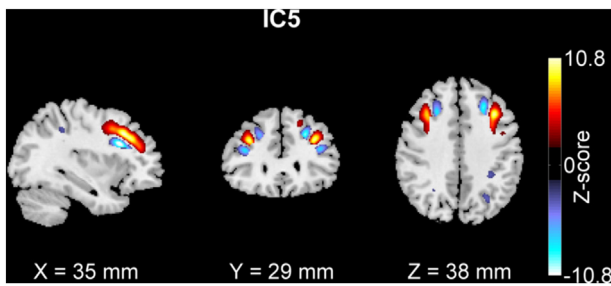


Fig. 3. One additional GM component (IC5 in middle frontal region) showing significant case-control differences ($|Z| > 2.5$). GM decrease was observed in the middle frontal gyrus colored in red and GM increase was observed in a smaller adjacent region colored in blue for ADHD patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

NeuroIMAGE and IMPACT used different assessment tasks for inhibition which (together with the resultant drop in sample size) may be partially responsible for no significant results. The absence of association for hyperactivity/impulsivity may be due to its decline with age (Spencer et al., 2007) as explained later on. GM components 1, 3, and 4, included outward cortical regions, which are known to be susceptible to scanning effects or motion. We double checked their correlation with scanning sites in the control group and confirmed no significant scanning effects. Furthermore, we compared them with typical scanning parameters-related GM components reported in Chen's paper (Chen et al., 2014), of which the scanning related 'edge' components cover outward region of multiple lobes forming a ring shape. The GM components we observed here were more focal regions, and the thin layer of cortical regions likely reflects the more precise and thin cortex segmentation from SPM12. Regarding the likelihood of motion artifacts, we did several examinations on the original data and subgroup data to guard against false discoveries (see Appendix B), even though no direct motion measures were available.

The three GM components (ICs 1–3, Fig. 1) were related significantly to either forward or backward digit span performance, and two of them (ICs 2 and 3, Fig. 1) were in fact related to both if a

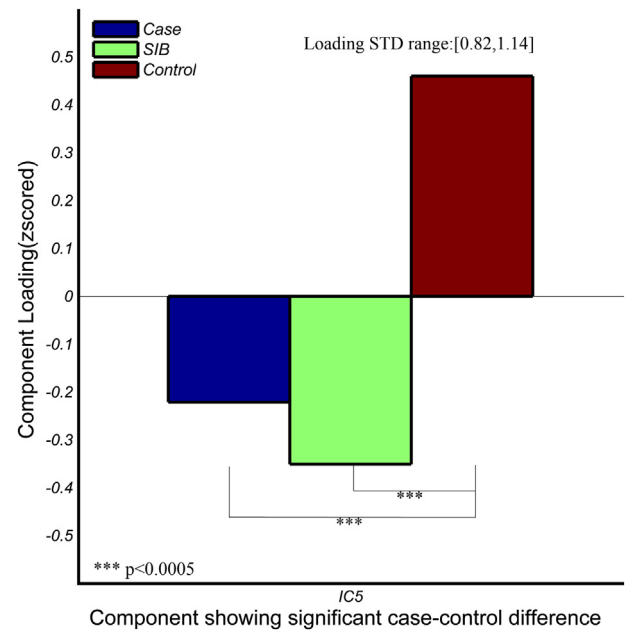


Fig. 4. Group differences of the GM component 5 (IC5). Three stars represent significant group difference at $p < 0.0005$. The loading standard deviation (STD) of component 5 ranges from 0.82 to 1.14. Colors indicated patients (Case), siblings (SIB) and healthy controls (Control). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

nominal p value ($p < 0.05$, data not shown) was applied, enhancing their overall relevance to working memory. The regions highlighted in our results, superior, middle, and inferior frontal cortex, have been repeatedly associated with working memory by brain functional MRI studies (Brodziak et al., 2013; Narayanan et al., 2005; Pessoa et al., 2002), and recent subdural electrocorticographic neural signals (Cogan et al., 2017). In contrast, evidence of brain structural variation underlying the variability of working memory capacity is very limited, but also points to prefrontal regions. For instance, the cortical surface in

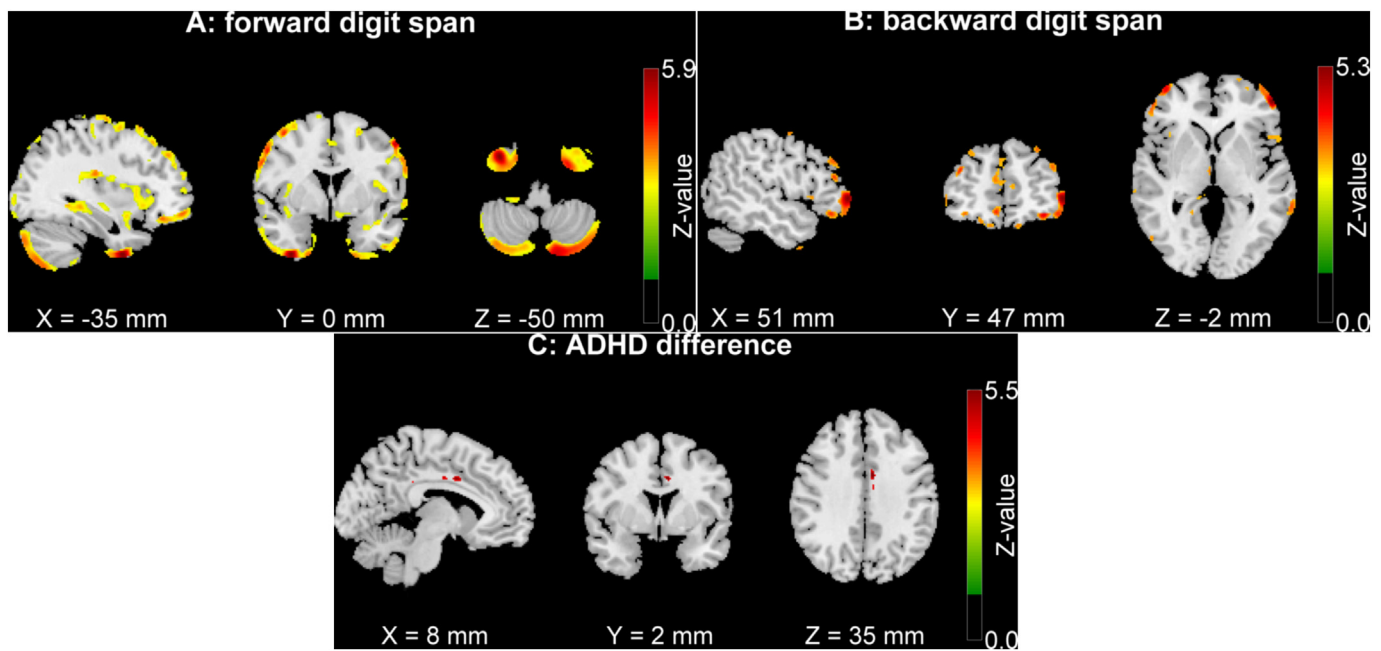


Fig. 5. Results of VBM analysis (FDR corrected at $p < 0.05$; $k > 10$). Colors are coded for association coefficients. GM volume in regions in subplot A showed a significantly positive correlation with forward digit span performance, GM volume in regions in subplot B was significantly and positively associated with backward digit span performance. GM volume in subplot C in middle cingulate showed a significant GM reduction in ADHD patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

right inferior and superior frontal gyri has demonstrated a significant positive association with working memory performance in healthy older subjects (Nissim et al., 2016). Specific to adult ADHD, GM reduction has been found in inferior frontal gyrus compared to healthy controls (Depue et al., 2010; Pironti et al., 2014) and related to cognitive deficits of patients, including response inhibition (Depue et al., 2010) and sustained attention (Pironti et al., 2014). Extending to previous studies, we observed that worse working memory performance was associated with lower GM volume in the superior, middle, and inferior frontal areas (red regions in Fig. 1, ICs 2 and 3), where patients had decreased GM volume compared to controls, though not the most significant GM reduction across whole brain.

Another GM component positively associated with working memory was present in the inferior semilunar lobule (IC1, Fig. 1). Baier and colleagues studied patients with cerebellar ischemic stroke and found that lesions in inferior semilunar lobule, tonsil, and vermal pyramid specifically impaired working memory performance when the to-be-remembered targets were presented together with task-irrelevant items (Baier et al., 2014). More similar to our findings are the published observations that GM volume in inferior semilunar lobule was significantly positively associated with working memory performance during development (Moore et al., 2017) and in adulthood (Ding et al., 2012). Furthermore, GM reduction in right inferior semilunar lobule (right Crus II) has been documented in ADHD patients both in childhood (Ivanov et al., 2014) and adulthood (del Campo et al., 2013), in line with our observation of lower GM volume in patients. Together, the associated GM components in prefrontal and inferior semilunar regions provide additional support for the idea that the fronto-striato-cerebellar circuitry serves working memory function (Giedd et al., 2001), and their GM abnormality might underline the ‘cool’-cognition dysfunction in ADHD patients (Rubia, 2011).

Interestingly, another cerebellar component (IC4, Fig. 1) in tonsil and culmen was related to IA, reinforcing the role of cerebellum in cognition. Specific to culmen and cerebellar tonsil, induced activation by sustained attention has been reported in healthy adults and ADHD patients (Lawrence et al., 2003; Norman et al., 2017), and symptom severity in ADHD patients was negatively correlated to cerebellar

activation including posterior lobe and cerebellar tonsil (Cubillo et al., 2011; Norman et al., 2017). Our results further delineate that it is IA, not hyperactivity/impulsivity, which is significantly affected by alterations in this cerebellar network in adult ADHD patients. GM reduction in this region in adult ADHD patients has been frequently reported (del Campo et al., 2013; Seidman et al., 2011), which is consistent with our findings. The fact that we did not find any associations with hyperactivity/impulsivity agrees with previous observations showing that in individuals with ADHD hyperactivity/impulsivity declines with age, while attentional impairments remain (Spencer et al., 2007).

In addition to the 4 components related to either working memory performance or inattention symptoms, component 5, associated with case-control status, including the middle frontal gyri, demonstrated significant GM abnormalities in patients with the largest effect size (i.e. the largest Cohen's d value), confirming a previous report showing GM reduction in middle frontal gyrus in adult ADHD patients (Seidman et al., 2011). Additional two components (cingulate and occipital components in Appendix E, Fig. E1), though not passing multiple comparison correction, showed strikingly consistent ADHD anomalies with previous reports, where GM reductions in anterior cingulate in adult ADHD patients have been documented (Frodl and Skokauskas, 2012; Seidman et al., 2006), along with decreased cortical thickness in left posterior cingulate gyrus (Makris et al., 2007), and GM increase in occipital gyrus and cuneus (Pirontia et al., 2014; Seidman et al., 2011). Regarding the functional impact of such GM abnormalities, future investigations with measures from more aspects of cognition in ADHD are needed.

A further break-down of participants into four groups, as shown in Fig. 2, provided additional insights into the interrelationship among cases, siblings, and controls. Consistent with previous studies (Alderson et al., 2013; Mostert et al., 2015), our patients presented significant cognitive impairment in working memory. This result (in general) propagated into associated GM components, where GM reduction was observed for patients and independent of medication effects. Interestingly, ADHD-unaffected siblings, who have demonstrated some level of lower performance, particularly in backward digit span task, did not

show GM reduction in the associated components, and instead presented GM similar to that of controls, suggesting other brain regions involved in cognition may be responsible for such lower performance in the siblings. This speculation is strengthened by the middle frontal gyri component (IC5, Fig. 5), where GM loadings in siblings were significantly different from those of controls, but not patients. For IA symptoms, all four groups significantly differed from each other. Medicated patients showed the most severe symptoms, indicating this group carried the most prominent attention deficits. Siblings clearly presented themselves as an intermediate group (i.e. based on the data they could not be categorized into either controls or cases). In line with IA symptoms, the cerebellar tonsil and culmen component (component 4) reflected four distinct groups (even though some differences were not significant ($p > 0.05$)). Overall, siblings presented intermediate cognition/behavioral impairments between patients and controls, and also GM anomalies in selected focal regions, suggesting they are a separate group potentially affected by the shared genetic and environmental risk factors with cases (Bralten et al., 2016).

It is noteworthy that GM volume in a relatively smaller area in the inferior frontal cortex (blue regions in Fig. 1, IC2) was negatively associated with working memory performance, where patients showed higher GM volume than controls. This result, along with the GM volume increase in a smaller part of middle frontal gyrus (blue regions in Fig. 3, IC5), occipital gyrus and cuneus (Appendix E, Fig. E1, IC7) in patients, is hard to explain. Previous studies have documented increased gray matter volume in ADHD patients in the occipital region (Nakao et al., 2011; Pironti et al., 2014). A possible explanation may be inefficient pruning/thinning processes during the development (Duerden et al., 2012; Pironti et al., 2014). Additionally, we noticed that GM volume increases were located at the boundaries between gray and white matter, near the white matter tracks, compared to GM reduction regions in patients. We speculate that the increased GM volume might rather reflect decreased white matter volume of the same area. Further verification is warranted.

Interestingly, subcortical regions such as caudate and putamen consistently implicated in children ADHD did not show any associations with cognitive deficits or disease related differences in adult ADHD. This result supports the uprising view of delayed maturation in subcortical regions in ADHD patients (Hoogman et al., 2017), thus leading to no significant effects in adult patients, while the frontal-cerebellum regions remain altered in adulthood for patients, linking to the persistent cognitive deficits and symptoms.

The findings presented here should be considered in the context of several strengths and limitations. This study made use of sMRI data of adults from the Dutch NeuroIMAGE and IMpACT cohorts, which benefited us with enhanced detection power, while the unbalanced distributions of age, sex, as well as case-sibling-control ratio between two cohorts might bias our results. We have done several exercises to mitigate the potential cohort effect, including the preprocessing analysis of correcting age, sex and scanning site effects and post-hoc analysis by considering cohort as a covariate. Given no straightforward motion measurements available, we did several examinations on the original data quality and association retests on the subgroup of controls only to eliminate the likelihood of identified components being motion artifacts. Due to the inconsistency of inhibition measurements between two cohorts and smaller sample size for each measure, we have limited power to identify GM components significantly related to inhibition measures.

In summary, our results demonstrate that with a relatively large sample size, GM abnormalities underlying working memory and inattention symptoms can be observed in adult ADHD patients in localized prefrontal and cerebellar regions. Our results fit nicely into the theory of 'cool'-cognition dysfunction mediated by inferior fronto-striato-cerebellar network in ADHD (Rubia, 2011). We did not observe any subcortical regions associated with adult ADHD. This is consistent with the results of a recent mega-analysis showing that subcortical

abnormalities present in children are no longer seen in adults with ADHD (Hoogman et al., 2017). Siblings of ADHD patients showed significant differences in symptoms and working memory and had unique GM regions associations to those compared to either patients or healthy controls, suggesting they present a separate group potentially influenced by the shared genetic and environmental risks with ADHD (Bralten et al., 2016).

Author contributions

J.L. contributed to idea generation, experiment design and writing assistant; K.D. conducted analyses and wrote the manuscript. J.C and D.L. assisted in the analyses. The remaining authors contributed to the participant recruitment and data collection. All authors critically reviewed the content and approved the final version for publication.

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Conflict of interest

Jan K 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, Lundbeck, Shire, Roche, Medice, Novartis, and Servier. He has received research support from Roche and Vifor. 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, royalties. B. Franke has received educational speaking fees from Merz and Shire. The other authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2018.04.035>.

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