Research Paper

Brain Structural Correlates of Intelligence in Attention Deficit Hyperactivity Disorder (ADHD) Individuals

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ABSTRACT

Introduction: Neuroimaging evidence has shown the relationship of intelligence with several structural brain properties in normal individuals. However, this relationship with attention deficit hyperactivity disorder (ADHD) needs to be investigated.

Methods: We estimated grey matter (GM) density of the brain using magnetic resonance imaging (MRI) scan on 56 ADHD individuals, including 30 combined individuals (Mean±SD age: 10.44±2.41, intelligence quotient: [IQ]=112.13±13.15, male, 24 right hands) and 26 inattentive individuals (mean age =11.39±2.1, IQ=107.44±13.98, male, 28 right hands) as well as 30 IQ matched healthy control group (mean age=11.08±2.15, IQ=115±13.56, male, 23 right hands).

Results: In this study, two statistical approaches were used. In the first approach, region-based as well as the whole association patterns between full-scale IQ and GM were computed and compared between groups. The second approach was to examine the differential pattern of GM density without considering IQ in three groups.

Conclusion: Results showed significant differences between the ADHD group and the control. This finding could indicate that intelligence is not purely based on the density of GM in certain brain regions; it is a dynamic phenomenon and drastically changes neurodevelopmental disorders.

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Highlights

- In ADHDs as compared to healthy controls the relation between GM and IQ was decreased at right hemisphere;
- In ADHDs as compared to healthy controls the relation between GM and IQ was increased at left hemisphere;
- Differenceses of the observed relation between control group and IQ matched ADHDs suggest a compensatory mechanism in ADHDs to maintaine an adequate cognitive performance;
- GM is not the only determiner of intelligence. IQ score may be affected by neural dynamic of the brain; therefore, the structural covariate could be a better alternative for GM density.

Plain Language Summary

In this study, we estimated the relation between GM density and IQ score in 2 subtypes of ADHD (combined and inattentive) and IQ matched healthy control group. We compared the association between groups and found that the pattern of association in ADHDs were different from controls. In the other words, the decreased association at right hemisphere, were compensated by increased association at left hemisphere in ADHDs to maintaine adequate performance. We conclude that, the brain structure is not the single determiner of intelligence, rather intelligence may underpine by neural dynamics of the brain. Therefore, the structural covariate may be a better alternative for GM density.

1. Introduction

Intelligence is a capacity involving planning, reasoning, comprehension, abstraction, and learning (Gottfredson, 1997) that can predict critical life outcomes (Deary, Johnson, & Houlihan, 2009). Therefore, understanding the biological systems taking apart intelligence can be necessary for psychological science (Deary et al., 2009). The neural basis of intelligence has been investigated by a range of neuroimaging studies, including magnetic resonance imaging (MRI) (McDaniel, 2005), electroencephalogram (EEG) (Thatcher, North & Biver, 2005), positron emission tomography (PET) (Tang et al., 2014), task-based functional magnetic resonance imaging (fMRI) (Jung & Haier, 2007) and resting-state fMRI (Li & Tian, 2014). Most structural studies associate intelligence quotient (IQ) with frontal and parietal lobes (Anderson et al., 2004; Basten, Hilger & Fiebach, 2015; Vakhtin, Ryman, Flores, & Jung, 2014; Jung & Haier, 2007). For instance, a relationship between grey matter (GM) volume in the posterior cingulate cortex (PCC) and intelligence has been reported (Deary, Penke, & Johnson, 2010). Moreover, the involvement of subcortical regions, such as the right striatum (Burgaleta et al., 2014), basal ganglia (McNab & Klingberg, 2008), hippocampus (Burgess, Maguire, & O'Keefe, 2002), and caudate (G: has been observed. In addition, the relationship between (GM) volume and cognitive deficits have been investigated in lesion studies (Karussis, Leker, & Abramsky, 2000), (Pinter, Eliez, Schmitt, Capone, & Reiss, 2001). Despite these findings, studies addressing the relationship between brain structures with intelligence in the attention deficit hyperactivity disorder (ADHD) population are rare (Vilgis, Sun, Chen, Silk, & Vance, 2016; McAlonan et al., 2007).

In this study, we hypothesized that the structural basis of intelligence should not be different in normal and ADHD individuals. Therefore, 56 ADHD individuals, including 30 individuals from the combined and 26 individuals from the inattentive subcategory, and 30 healthy individuals in the control group were scanned by MRI. Then, GM densities of anatomically separated brain regions were estimated from the brain images. Subsequently, Pearson's correlation analysis was employed to detect the association between the GM densities of the brain regions and IQ. The whole pattern of association is also estimated. Then, analysis was performed at the group level and the correlation of IQ and GM densities in ADHD groups were compared with each other as well as the healthy control group. Furthermore, the differential pattern of GM density was observed in three groups. The main aim of the study was to find out whether the relationship between GM density and IQ in ADHD is similar to healthy individuals or is aligned with the disorder.

2. Materials and Methods

Study participants

A total of 56 ADHD subjects, including 30 combined subjects and 26 inattentive subjects, as well as 30 healthy subjects in the control group, with similar age and IQ range, underwent a session of MRI scanning. Table 1 presents the demographic information of each group. According to age, IQ, and handedness, no significant differences were observed among the groups (P<0.05).

Children in the ADHD group had to meet diagnostic criteria defined by the diagnostic and statistical manual, fourth edition, text revision (DSM-IV-TR) for ADHD as well as determine parent and child's answers to the kiddie schedule for affective disorders and schizophrenia present and lifetime version (KSADS-PL) confirmed by a psychiatrist to be involved in this study. The exclusion criteria included comorbid mood or anxiety disorder, autistic or Asperger's disorder, medical illness that was unstable or could cause psychiatric symptoms, or substance abuse within 2 months of participation.

Assessment of cognitive performance: intelligence quotient (IQ) scores

All participants completed the Wechsler abbreviated scale of intelligence (WASI) presented in Table 1 . The Wechsler abbreviated scale of intelligence (WASI) is general intelligence, or IQ test designed to measure overall cognitive abilities or a specific cognitive capability in individuals in the age range of 6-89 years. (American Psychological Association (APA PsycNet))

The experimental validation of our proposed method was performed on a dataset gathered from 4 data centers including Kennedy Krieger Institute (KKI), Oregon Health and Science University (OHSU), Peking University (PEK), and New York University (NYU). These data are related to ADHD-200 global completion and are publically.

Magnetic Resonance Imaging (MRI) data acquisition

All participants underwent a T1-weighted high-resolution MRI scanning using a siemens3T scanner system. The imaging data were collected using the following protocols, Kennedy Krieger Institute (KKI) (relaxation time [T1]: Contrast enhancement, echo time [TE]: Shortest, repetition time [TR]: Shortest, flip angle: 8°, field of view [FOV]: 256 mm, slice thickness: 1 mm); Oregon Health and Science University (OHSU) (T1: 900 ms, TE: 3.58 ms, TR: 2300 ms, flip angle: 10°, FOV: 256 mm, slice thickness: 1.1 mm); Peking University (PEK) (T1: 1100 ms, TE: 3.45 ms, TR:2530 ms, flip angle: 7°, FOV: 256mm, slice thickness: 1mm); New York University (NYU) (T1: 1100 ms, TE: 3.25 ms, TR: 2530 ms, flip angle: 7°, FOV: 256 mm, slice thickness: 1.33 mm).

MRI data processing

A standard processing pipeline was performed on the MRI data using the functional MRI of the brain (FMRIB) Software Library (FSL) and Analysis Of Functional Neuroimaging (AFNI). First, the brain MRI images were deobliqued, then re-oriented and the skull strip was removed. Then, images were registered to the MNI space. After that, MRI images were segmented into different tissue types and were parcellated into 392 regions of interest (ROI) using MNI normalized Craddock atlas (Craddock, James, Holtzheimer, Hu, & Mayberg, 2012) or 116 regions using Automated Anatomical Labeling (AAL) (Tzourio-Mazoyer et al., 2002). Results of the Craddock method are presented in the main text body and results of the AAL parcellation are provided in the supplementary materials.

Statistical analysis

Pearsons' correlation was calculated between IQ and GM densities of separate brain regions and a significant relationship was recognized by setting a threshold of P<0.05. Then statistical analysis was performed using the statistical analysis toolbox of MATLAB 2015. Later, the group comparison of correlation values was performed using the cocor package (Diedenhofen & Musch, 2015). Then, the brain net viewer (Xia, Wang, & He, 2013) was used to visualize the significant results. The whole association pattern is also acquired using SPSS software. We also observed a differential pattern of GM density in groups as a second approach (Figure 1)

It should be mentioned that suggested regions of interest (ROIs) in the Craddock atlas were too fragmented (392 regions), so for the ease of presentation, the significant results were re-indexed to the frontal, occipital, temporal, parietal, cerebellum, and subcortical structures.

3. Results

Significant structural correlates of intelligence quotient (IQ)

The relationship between IQ scores and GM densities was found in several brain regions. Tables 2-4 and Figures 2-4 show the detailed information of significant results (P<0.05). Significant positive relationships between GM density and intelligence are shown in red and negative relationships are shown in blue.

In ADHD combined group, a positive correlation was observed between IQ scores and GM density in the frontal region (inferior operculum and orbitofrontal on the right side), temporal region (superior part in the left hemisphere, inferior part in the right hemisphere, and middle part bilaterally), occipital region (inferior part bilaterally), cerebellum (CRB 4-5 in the left hemisphere and CRB-Crus1, in the right side and CRB-Crus2 bilaterally), angular gyrus in the right side, fusiform in the right side, and the precentral region on the right side. In addition, negative correlations were observed in the left inferior temporal region and the left fusiform region (Figure 2, Table 2).

In ADHD inattentive group, no significant negative correlation was observed between IQ and GM density of the brain regions. While a positive correlation was identified in bilateral fusiform areas, caudate and cerebellum crus1, and the inferior parietal region in the right hemisphere (Figure 3, Table 3)

Table 1. Demographic characteristics of subjects

Variables	Mean±SD			F	Sig.
	Combined (n=30)	Inattentive (n=26)	Control (n=30)		
Age	10.44±2.41 (8-13)	11.39±2.1 (9-13)	11.08±2.15 (8-13)	1.58	0.211
IQ	112.13±13.15 (99-125)	107.44±13.98 (93-121)	115±13.56 (101-129)	2.46	0.092
Handedness	6 left-handed	1 left-handed	7 left-handed	0.915	0.405

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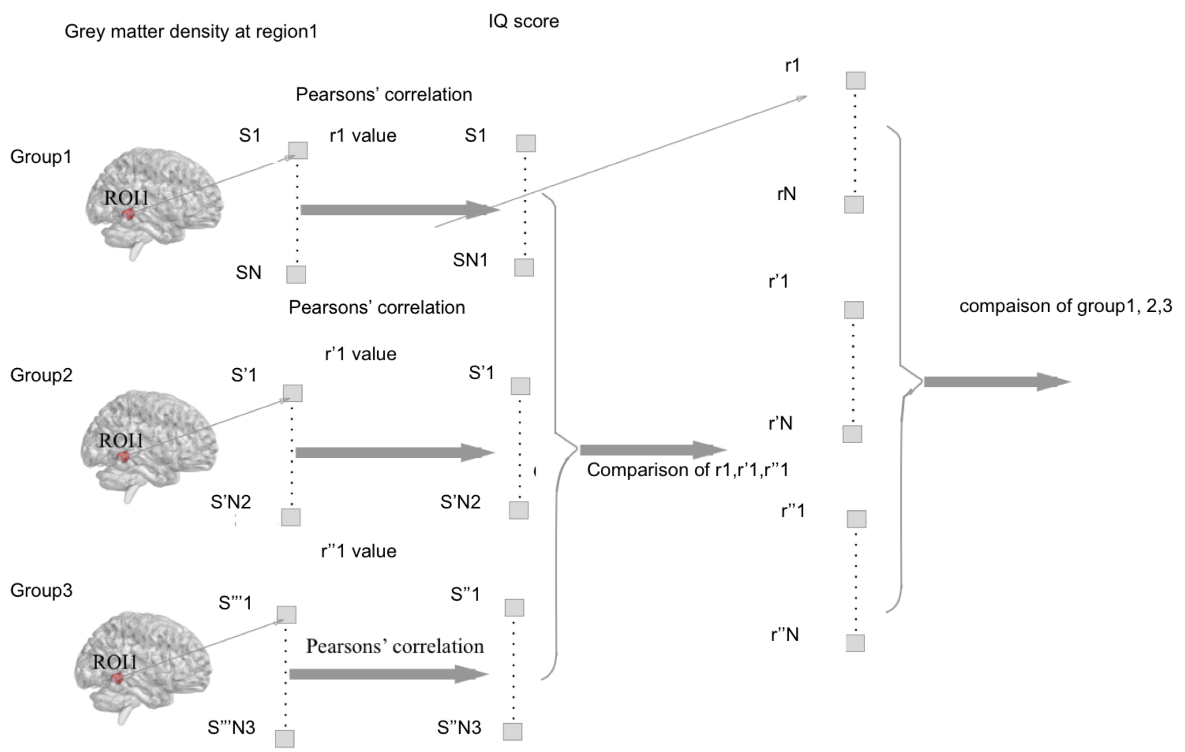

Figure 1. Schematic of experimental desighn

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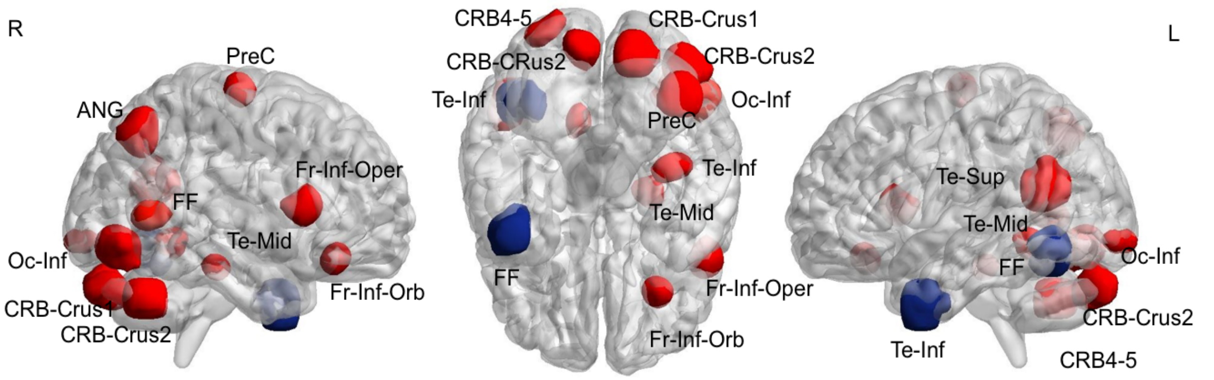

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Figure 2. Significant association between grey matter density and intelligence in ADHD combined group

PreC: Precentral; ANG: Angular; Te-Mid: Middle Temporal; Te-Inf: Inferior Temporal; Te-Sup: Superior Temporal; Oc-Inf: Inferior Occipital; CRB: Cerebellum; CEB-Crus1: Cerebellum Crus1; CRB-Crus2: Cerebellum- Crus2; Fr-Inf-Oper: Inferior Operculum; Fr-Inf-Orb: Inferior Orbito frontal; FF: Fusiform.

Table 2. Significant association between grey matter density and intelligence in ADHD combined group

Section	Side	Region	Coordination (x, y, z)	Cluster Size	r, p
Frontal	Right	Fr-Inf-Oper	53.8, 16.5, 10.3	124	0.439, 0.015
		Fr-Inf-Orb	28, 19.4, -17.7	69	0.381, 0.037
		PreC	25.3, -30.1, 66.2	105	0.362, 0.049
Temporal	Right	Te-Mid	50.3, -48.9, 18.9	132	0.363, 0.048
		FF	37.8, -55.9, -17.6	130	0.451, 0.012
	Left	Te-Mid	-46.3, -70, 5.9	161	0.409, 0.024
		Te-Sup	-47.2, -20.9, 8.2	120	0.388, 0.003
		FF	-31.1, -6.9, -33.9	70	-0.376, 0.040
		Te-Inf	49.9, -62.4, -8.3	141	-0.541, 0.001
Parietal	Right	ANG	38.1, -65.1, 45.3	138	0.374, 0.041
Occipital	Right	Oc-Inf	43.5, -76, -10	132	0.396, 0.030
	Left	Oc-Inf	-30.8, -85.6, -15.4	99	0.46, 0.010
Cerebellum	Right	CRB-Crus1	-40.5, -74.5, -26.5	112	0.523, 0.002
		CRB-Crus1	48.7, -58.7, -25.7	110	0.478, 0.007
		CRB-Crus2	18.6, -81.6, -31.3	111	0.433, 0.016
	Left	CRB-Crus2	-8.6, -84.6, -28.1	112	0.385, 0.035
		CRB4-5	-10.5, -49.4, -7.3	111	0.407,0.025

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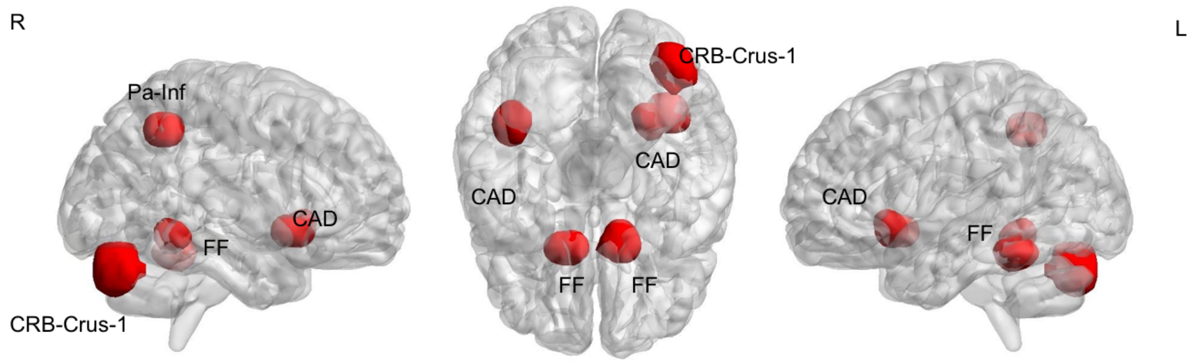

Figure 3. Significant association between grey matter density and intelligence in ADHD inattentive group NEUROSCIENCE

Pa-Inf: Inferior Parietal; FF: Fusiform; CAD: Caudate; CRB-Crus1: Cerebellum Crus1

In the healthy control group, a positive and significant correlation was observed bilaterally in the precuneus, and fusiform. In the left hemisphere, a positive correlation was seen in temporal regions (inferior and superior temporal pole), calcarine, superior occipital, and middle frontal regions. In the right hemisphere, a positive correlation was observed at cerebellum 6, frontal inferior operculum, and cingulate cortex. Moreover, a negative correlation was identified in the left superior medial frontal cortex (Figure 4, Table 4).

Comparing the cluster size of each section showed that the most significant relationship for the ADHD combined group is located in the temporal, cerebellum, and frontal regions. In the ADHD inattentive group, the most significant relationship was observed in the temporal, subcortical region, and cerebellum. And in the healthy control group, the most significant relationship was observed in the temporal, frontal, and parietal regions (Table 5).

The results of the relationship between GM density and intelligence via AAL parcellations are presented in the supplementary materials (Figures S1-S3, Table S1).

Group comparison

Figure 5-7 and Table 6 present significant results of comparing correlations observed in each group (significant P-values have been bolded in Table 6). Significantly increased relationships between GM density and intelligence are shown in red and decreased relationships are shown in blue.

Comparing ADHD combined versus ADHD inattentive showed significantly increased associated GM density with intelligence at superior temporal and cerebellum-6 in the left hemisphere and angular region in the right hemisphere. Decreased associated grey matter density with intelligence was observed at the middle cingulate on the right side (Figure 5).

ADHD combined compared to the healthy control had an increased relationship between GM density and intelligence at middle temporal and orbitofrontal in the right

Table 3. Significant association between grey matter density and intelligence in ADHD inattentive group (N=26)

Section	Side	Region	Coordination (x, y, z)	Cluster Size	r, p
Temporal	right	FF	27.6, -47.1, -10	130	0.422, 0.0314
	left	FF	-40.4, -45.8, -18.7	116	0.529, 0.0054
Parietal	right	Pa-Inf	37.8, -50.9, 43.5	97	0.410, 0.0371
Subcortical	right	CAD	13.1, 13.7, -7.8	108	0.433, 0.0271
	left	CAD	-12.6, 17, -6	100	0.453, 0.0198
Cerebellum	right	CAR-Crus1	40.5, -75.5, -26.5	112	0.443, 0.0232

Pa-Inf: Inferior Parietal; FF: Fusiform; CAD: Caudate; CRB-Crus-1: Cerebellum Crus1. NEUROSCIENCE

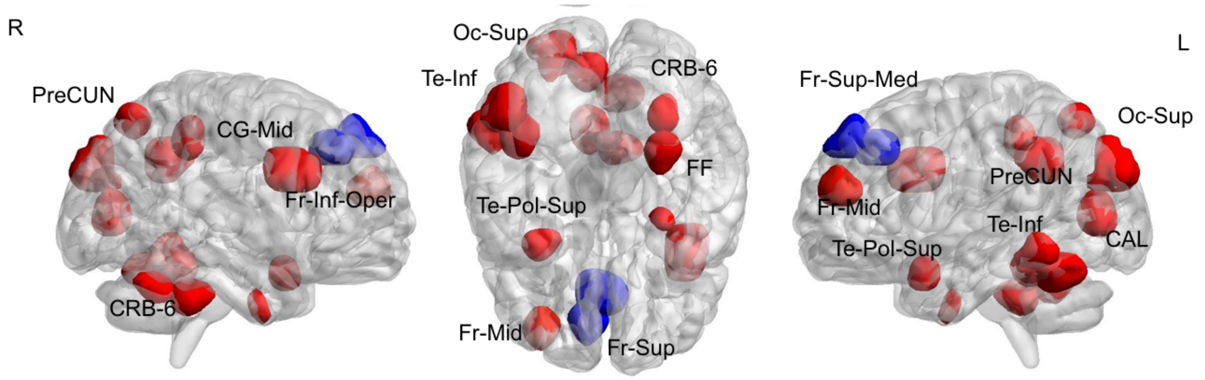

Figure 4. Significant association between grey matter density and intelligence in healthy control group NEUROSCIENCE

PreCUN: Precuneus; CG-Mid: Middle Cingululate; Fr-Inf-Oper: Frontal inferior operculum; CRB6: Cerebellum6; Oc-Superior: Superior Occipital; CAL: Calcarine; FF: Fusiform; Te-Inf: Inferior Temporal; Te-Pol-Sup: Superior Temporal Pole; Fr-Mid: Middle Frontal; Fr-Sup-Med: Medial Superior Frontal

hemisphere as well as rectus and superior parietal on the left side. Decreased relationship in GM density was seen at the inferior occipital, medial orbitofrontal, and superior frontal in the right hemisphere (Figure 6).

ADHD inattentive compared to the healthy control group showed increased associated GM density with intelligence in the middle and anterior cingulate and superior motor area in the right hemisphere as well as the precuneus, superior parietal, and rectus on the left side. Decreased relationship of GM density with intelligence was observed in the inferior occipital, putamen, caudate, medial orbitofrontal, and precentral region in the right hemisphere as well as middle occipital and cerebellum6 on the left side (Figure 7).

Compared to healthy control, ADHD groups (combined and inattentive) had increased associated GM density with intelligence at superior parietal and rectus in the left hemisphere, while decreased associated GM density with intelligence was seen at inferior occipital and medial frontal in the right side. The results of comparing the

Table 4. Significant association between grey matter density and intelligence in healthy control group

Section	Side	Region	Coordination (x, y, z)	Cluster Size	r, p
Frontal	right	Fr-inf-oper	41.2, 11.3, 29.9	125	0.391, 0.032
		Fr-sup- Med	-0.8, 31.3, 40.6	135	-0.368, 0.045
		Fr-Mid	-30, 49.3, 21.2	120	0.383, 0.036
Temporal	right	FF	29.5, -4.7, -37.3	75	0.363, 0.048
	left	Te-Inf	-48, -58.8, -20.4	124	0.384, 0.035
		Te-pol-sup	-30.3, 7.5, -21.4	98	0.401, 0.027
		FF	-40.4, -45.8, -18.7	116	0.390, 0.032
Parietal	right	pre CUN	8.8, -66.5, 54	144	0.412, 0.023
	left	Pre CUN	-6.6, -49.8, 35.5	143	0.523, 0.002
Occipital	left	CAL	-7.2, -77.3, 7.7	162	0.420, 0.020
		Oc-sup	-22.5, -85.5, 31	103	0.392, 0.031
Subcortical	right	CG-Mid	8.5, -39.3, 45	141	0.362, 0.049
Cerebellum	right	CRB-6	29.8, -56.2, -27.8	117	0.362, 0.049

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Table 5. Total significant associated cluster size with intelligence in brain lobes as well as cerebellum and subcortical region

Type	No.	Cluster Size					
		Frontal	Temporal	Parietal	Occipital	Sub cortical	Cerebellum
ADHD Combined	30	298	754	138	231	-	446
ADHD inattentive	26	-	246	97	-	208	112
Healthy control	30	380	413	287	265	258	-

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Table 6. Comparing association between grey matter density and intelligence in ADHD combined, ADHD inattentive and health control groups

Region	Side	Combined vs inattentive	p	Combined vs control	p	Inattentive vs control	p
Te-sup	Left	0.594	0.022	0.463	0.068	-0.131	0.63
Te-Mid	Right	0.158	0.547	0.599	0.023	0.441	0.099
ANG	Right	0.541	0.04	0.086	0.722	-0.455	0.09
CG-Ant	Right	0.223	0.403	0.336	0.205	0.559	0.036
CG-Mid	Right	0.282	0.282	0.285	0.273	0.003	0.001
CG-Mid	Right	-0.544	0.039	-0.045	0.86	0.499	0.058
Oc-Inf	Right	-0.264	0.283	-0.643	0.003	-0.379	0.012
Oc-Mid	Left	0.447	0.097	-0.114	0.651	-0.561	0.035
PUT	Right	0.339	0.212	-0.208	0.393	-0.547	0.036
SMA	Right	-0.322	0.215	0.308	0.248	0.631	0.017
CAD	Right	0.126	0.64	-0.055	0.836	-0.649	0.005
Pre-CUN	Left	-0.187	0.47	0.363	0.176	0.55	0.039
Pa-sup	Left	0.081	0.759	0.606	0.02	0.525	0.047
Fr-Med-Orb	Right	0.009	0.973	-0.801	0	-0.801	0
Fr-Mid-Orb	Right	0.234	0.352	0.61	0.019	0.376	0.165
Fr-sup	Right	-0.245	0.369	-0.53	0.042	-0.285	0.266
CRB6	Left	0.707	0.007	0.093	0.71	-0.614	0.02
REC	Left	-0.07	0.764	0.71	0.006	0.78	0.002
PreC	Right	-0.284	0.291	-0.226	0.33	-0.51	0.043

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Te-Sup: superior temporal; Te-Mid: Middle temporal; ANG: Angular; CG-Ant: Anterior cingulate; CG-Mid: Middle Cingulate; Oc-Inf: Inferior Occipital; Oc-Mid: Middle Occipital; PUT: Putamen; SMA: Superior Motor Area; CAD: Caudate; Pre-CUN: pre-cuneus; Pa-sup: superior parietal; Fr-Med-Orb: Medial orbitofrontal; Fr- sup: superior frontal; CRB6: Cerebellum6; REC: Rectus; PreC: precentral area

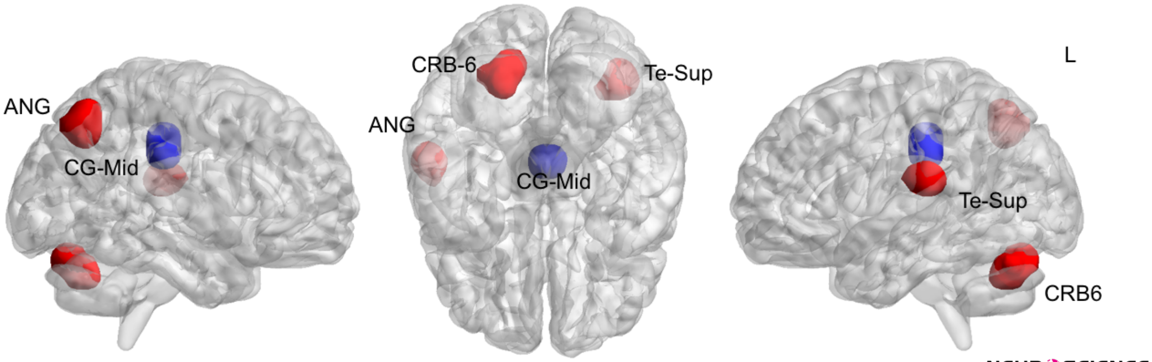

Figure 5. Comparing significant association between grey matter density and intelligence in ADHD combined versus ADHD inattentive group

Te-Sup: Superior Temporal; ANG: Angular; CG-Mid: Middle Cingulate; CRB-6: Cerebelum6.

relationship between GM density and intelligence via AAL software are presented in supplementary materials (Figures S4-S6, Table S2).

Multiple comparisons of whole brain association patterns also showed differences between groups. Although ADHD combined was significantly different from the other groups, this was not the case for ADHD inattentive group (Table 7), (Figure S14). We also compare raw data of grey matter density to show structural differences in terms of grey matter density whithin groups. Results from CC400 are shown in Table S3, Figures S8-S10 and those of AAL116 are presented in Table S4, Figures S11-S13).

4. Discussion

ADHD is a heritable phenotype that can be influenced by genetic factors. Therefore, genetics can influence brain morphometric properties in ADHD as reported in previous studies (Bellgrove et al., 2005; Swanson et al., 2007). Intelligence is also a heritable phenotype and overlapping effects of genetics on the intelligence score and ADHD also can be investigated. If IQ score is only related to brain morphometry properties, there should not be any significant differences between IQ-matched ADHD and control individuals. Otherwise, the relationship between IQ score and brain anatomy follows another mechanism that we investigate in this study. In this study, the regional GM density and full-scale IQ were compared between two groups of ADHD subtypes, including a combined and inattentive and a healthy control group. Two different parcellation strategies, including functionally separated regions (CC400) and anatomically separated regions (AAL116), were applied to detach the brain to 392 and 116 regions, respectively. After statistical analysis, it was observed that the relationship of IQ with regional GM density is mainly positive and located in the right hemisphere. The right hemisphere plays a vital role in cognition (Robertson, 2014), language (Gainotti, 2013), arithmetic (Knops & Willmes, 2014), and visuospatial attention (Longo, Trippier, Vagnoni, & Lourenco, 2015). These findings are not impressed by the parcellation technique and the results of CC400 were almost the same as AAL116.

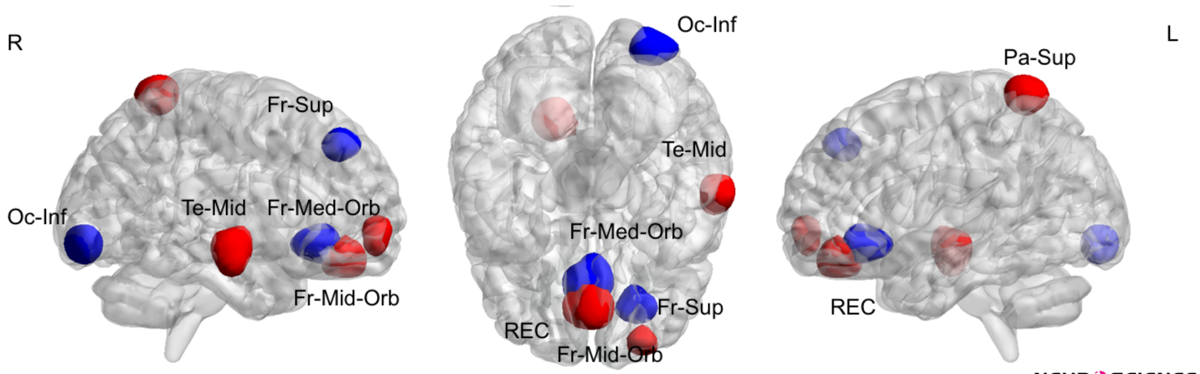

Figure 6. Comparing significant association between grey matter density and intelligence in ADHD combined versus health control group

Te-Mid: Middle Temporal; Oc-Inf: Inferior Occipital; Pa-Sup: Superior Parietal; Fr-Mid-Orb: Middle orbito frontal; Fr-Sup: Superior frontal; REC: Rectus

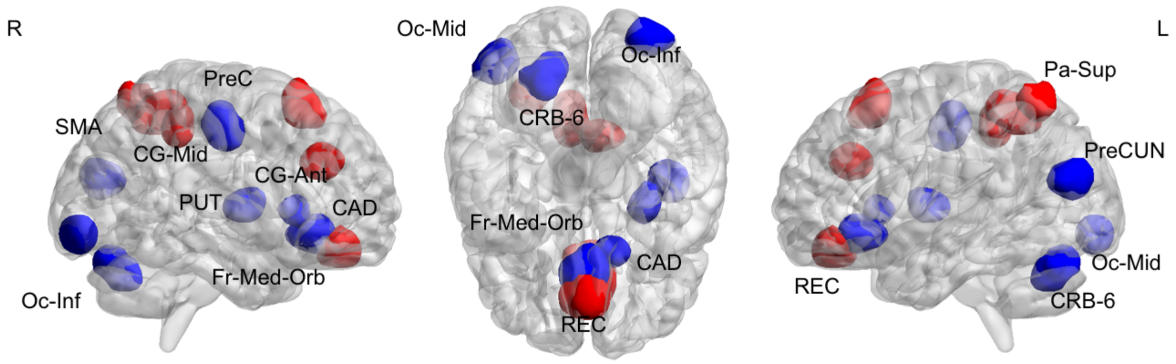

Figure 7. Comparing significant association between grey matter density and intelligence in ADHD inattentive versus health control group

CG-Ant: Anterior Cingulate; CG-Mid: Middle Cingulate; Oc-Inf: Inferior Occipital; Oc-Mid: Middle Occipital; PUT: Putamen; SMA: Superior Motor Area; CAD: Caudate; PreCUN: Precuneus; Pa-Sup: Superior parietal; Fr-Med-Orb: Medial orbito frontal; CRB6: Cerebelum6; REC: Rectus; PreC: Precentral.

The changes in GM density may alter behavior and cognitive functions discussed in the following. Our findings of the healthy control group showed a significant positive relationship between GM density and IQ score in the inferior and middle frontal, precuneus, fusiform, inferior temporal, calcarine, superior occipital, and middle cingulum, and cerebelum6. The inferior frontal is involved in selecting responses in uncertain situations (Frangou, Chitins, & Williams, 2004) and reasoning ability (Goel, Gold, Kapur, & Houle, 1997), and the relationship of frontal and parietal with intelligence has been shown in previous studies (Jung & Haier, 2007). Another finding was the inferior part of the temporal lobe which is involved in the analysis of visual form, motion, and representation of individuals and is directly related to the intelligence score (Frangou et al., 2004). Our results about fusiform may also reflect its role in language proficiency (Tan et al., 2011), recognition, and elaboration on the visual inputs (Colom et al., 2009). Furthermore, the significant relationship between cingulum GM density and IQ, observed in this study, in the healthy control group may reflect its role in spatial learning and memory (Aggleton, Neave, Nagle, & Sahgal, 1995). Last but not least, the relationship of cerebellum GM density with intelligence has also been reported in previous studies (Stoodley & Schmahmann, 2009). These findings confirm the results compared to previous studies.

On the other hand, ADHD showed a significantly different mechanism and pattern of association between GM density and intelligence, compared to the healthy control group. Comparing the whole association pattern, also suggest a discrepancy between the groups. The difference between ADHD combined and control group was more significant than the difference between ADHD inattentive and control, which seems rational because of more severe deficit symptoms in ADHD combined.

The IQ score represents a score for verbal and visual abilities, fluid reasoning, working memory, and processing speed (Wechsler, 1949). In previous studies, the strengths and weaknesses of ADHD individuals in these cognitive functions have been reported (Frazier, Demaree, & Youngstrom, 2004). Mayes's group has tried to suggest a neurobiological basis for ADHD by emphasizing ADHD strengths in verbal, and visual reasoning and their weakness in attention, processing speed, and graph motor skill (Mayes & Calhoun, 2006). Given that the ADHD and healthy control groups in our study are matched for IQ, observed differences in associated

Table 7. Multiple comparison of whole pattern of association

Groups	Mean Difference	Standard Deviation	Sig.	Confidence Interval (0.95)	
				Lower band	Upper band
ADHD combined versus ADHD inattentive	0.0572	0.0108	0.000	0.0306	0.0839
ADHD combined versus control	0.0370	0.0108	0.003	0.0104	0.0637
ADHD inattentive versus control	-0.0202	0.0108	0.179	-0.0469	0.006

GM density with IQ between ADHD and healthy control groups may suggest a compensatory mechanism in ADHD to maintain adequate performance. This mechanism can be discussed in our research findings. In ADHD groups, combined and inattentive, a decreased association between GM density and intelligence score was observed in the right inferior occipital and right medial frontal regions. The inferior occipital region is involved in visual imaging (Goldenberg et al., 1989) and the medial frontal is engaged in the switching tasks (Rushworth, Hadland, Paus, & Sipila, 2002). In contrast, an increased association was observed between the left superior parietal and the left rectus. The superior parietal region is involved in the manipulation of information in working memory (Koenigs, Barbey, Postle, & Grafman, 2009) and the rectus is engaged in the paradigm of reward learning (Kringelbach, 2005). Therefore, the lessened association between GM density and intelligence in the right hemisphere (inferior occipital and medial frontal) could be compensated by the increased association in the left hemisphere (superior parietal and rectus). This mechanism helps the ADHD subject to maintain an adequate level of cognitive performance.

Comparing row data of GM density in groups also reinforced the idea of a compensatory mechanism. In this regard, GM differences between ADHD inattentive and control group in our study was greater than between ADHD combined and control. This alteration in GM density may help ADHD inattentive individuals compensate for their brain deficiency and perform compared to ADHD combined.

Previous studies have shown that the cortical compensatory mechanisms can cope with the deficit in several cognitive processes in ADHD (Ma et al., 2012). Hence, a different association between regional GM density with the IQ score in the ADHD and control group may indicate that brain structure is not the only determiner of intelligence; rather, intelligence may also be underpinned by neural dynamics of the brain.

Limitation

The results of this study had several limitations; for example, the correlation was done for full-scale IQ and wechsler intelligence scale for children (WISC) subtests were not analyzed. Moreover, this study only focused on male participants in the age range of 8 to 13 years, which can be extended in future works. Therefore, a developmental study on both genders could provide additional insights into the mechanism of structural changes in the brain involved with intelligence.

5. Conclusion

To the best of our knowledge, this is the first study to investigate brain structural correlates of IQ in ADHD individuals. The study provides evidence that IQ may be closely related to GM density in specific brain regions but the pattern can be influenced by a disorder. The significant changes observed in the association scores of the ADHD individuals compared to the healthy individuals in the control group suggest a compensatory mechanism for having a suitable cognitive performance (IQ). Our findings indicate that IQ score may be affected by neural dynamics; therefore, the structural covariates can be a better alternative for the GM density. We hope that these findings can provide additional information for a better understanding of the relationship between brain morphometry and intelligence.

Ethical Considerations

Compliance with ethical guidelines

All ethical principals are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished and if desired, the research results would be available to them. A written cosent has been obtain from the subjects. Priciples of the Helski convention was also observed.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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Supplementary Material

Table S1. Significant association between grey matter density and intelligence in ADHD combined, ADHD inattentive and healthy control (AAL)

Type	Region		Cluster Coordination	Cluster Size (x, y, z)	r, p
ADHD combined	Right	FF	33.97, -39.1, -20.18	2767	0.405, 0.026
		CRB-Crus-1	37.46, -67.14, -29.55	2554	0.492, 0.0056
		CRB-Crus-2	32.06, -69.02, -39.95	2223	0.443, 0.01
ADHD inattentive	Right	CRB-8	25.06, -56.34, -49.47	2291	0.411, 0.0365
	Left	Fr-Inf	-48.43, 12.73, 19.02	2330	0.396, 0.04
		PoCr	-42.46, -22.63, 48.92	3839	0.394, 0.0458
Healthy control	Right	CAL	15.99, -73.15, 9.4	1986	0.380, 0.038
		PCL	7.48, -31.59, 68.09	1249	0.422, 0.018

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FF: Fusiform; CRB-Crus-1: Cerebellum-Crus-1; CRB-Crus-2: Cerebellum-Crus-2; CRB-8: Cerebellum-8; Fr-Inf: Inferior frontal; PoCr: Post central; CAL: Calcarine; PCL: Paracentral loube.

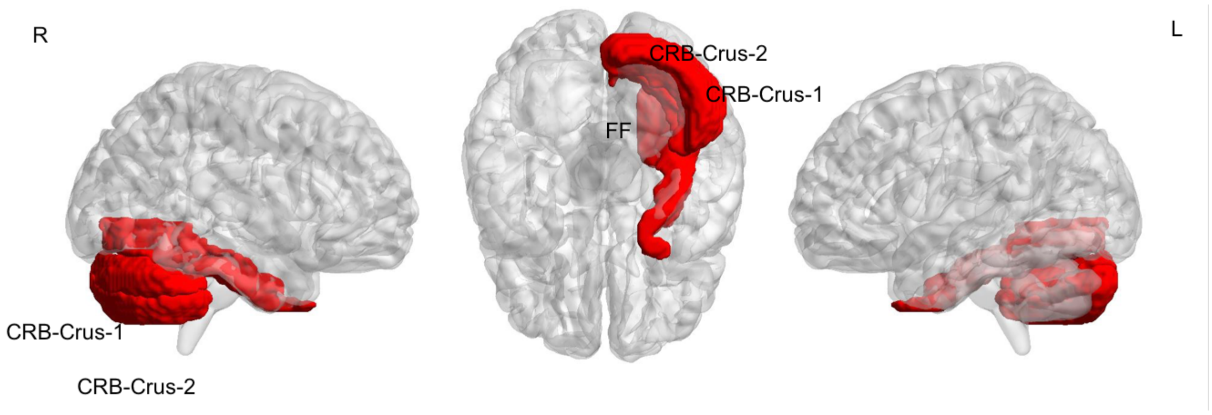

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Figure S1. Significant association between grey matter density and intelligence in ADHD combined group (AAL)

CRB-Crus-1: Cerebelum crus1; CRB-Crus-2: Cerebelum crus2; FF: Fusiform.

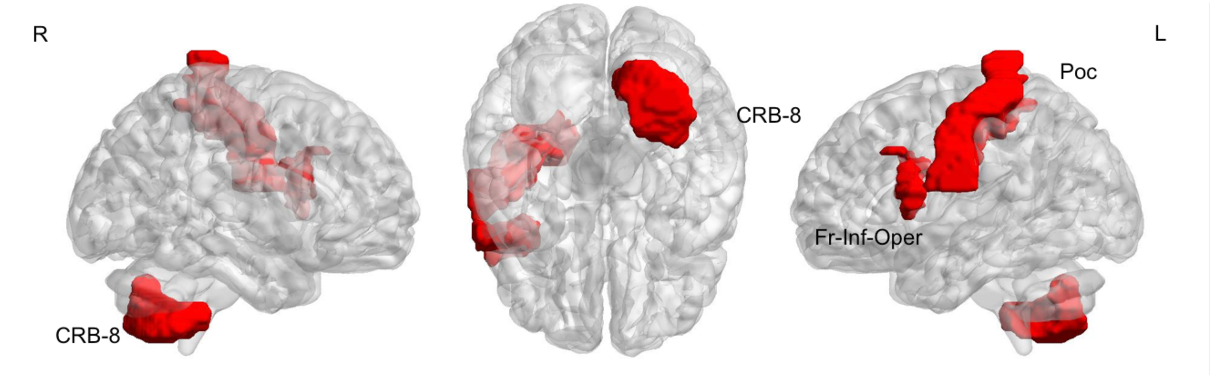

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Figure S2. Significant association between grey matter density and intelligence in ADHD inattentive group (AAL)

CRB-8: Cerebelum8; Fr-Inf-Oper: Inferior Opperculum frontal; Poc: Post central region

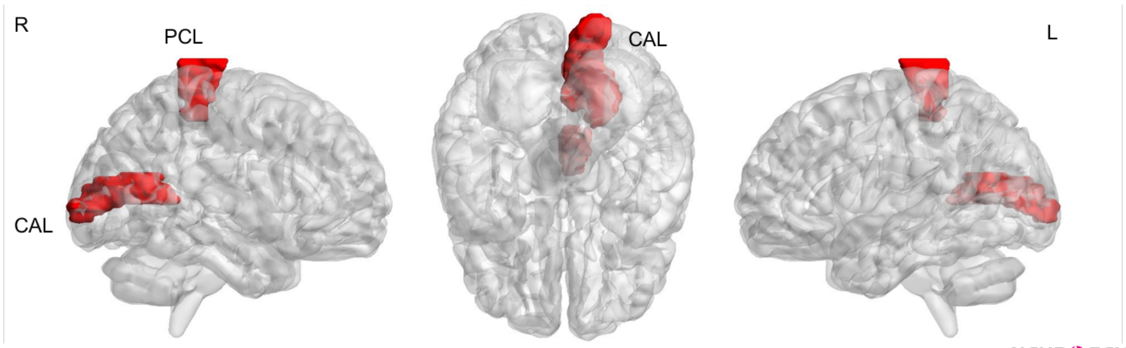

Figure S3. Significant association between grey matter density and intelligence in health control group (AAL)
PCL: Para central loube; CAL: Calcarine

Table S2. Comparing association between grey matter density and intelligence in ADHD combined, ADHD inattentive and health control group (AAL)

Region	Side	Combined vs Inattentive	P	Combined vs Control	P	Inattentive vs Control	P
OLF	Right	-0.285	0.552	-0.538	0.042	-0.382	0.157
REC	Left	-0.354	0.185	-0.633	0.01	-0.27	0.288
CAL	Left	0.374	0.157	-0.149	0.579	-0.523	0.049
	Right	0.428	0.11	-0.247	0.327	-0.675	0.01
Oc-Mid	Left	0.547	0.04	0.14	0.58	-0.407	0.133

Abbreviation: OLF: Olfactory; REC: Retus; CAL: Calgarine; Oc-Mid: Middle occipital

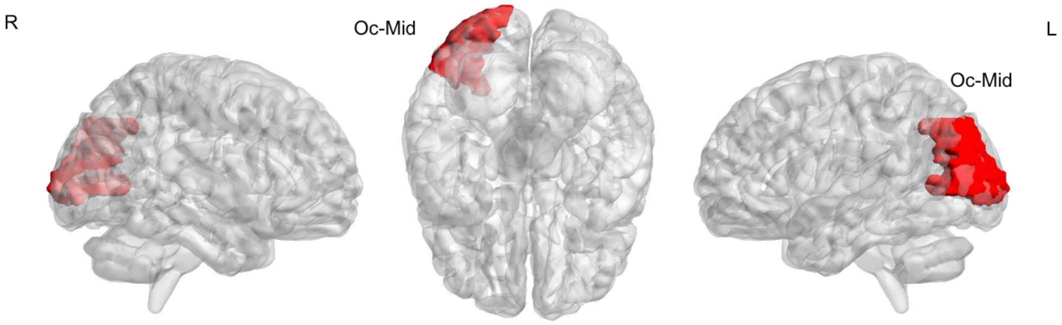

Figure S4. Comparing of association between grey matter density and intelligence in ADHD combined versus ADHD inattentive (AAL)
Oc-Mid: Middle Occipital.

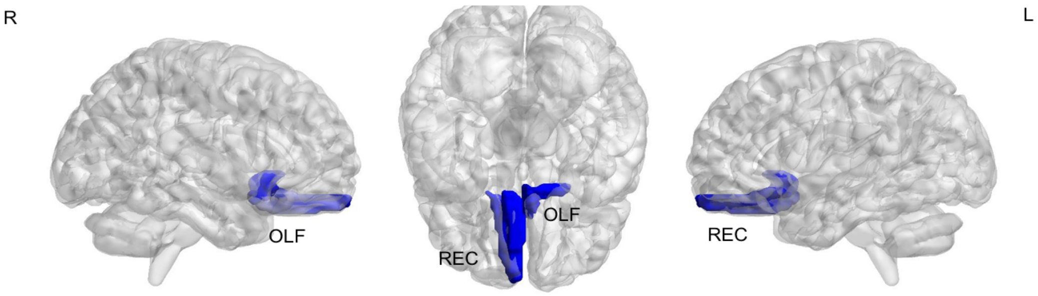

Figure S5. Comparing of association between grey matter density and intelligence in ADHD combined versus health control (AAL)
OLF: Olfactory; REC: Rectus

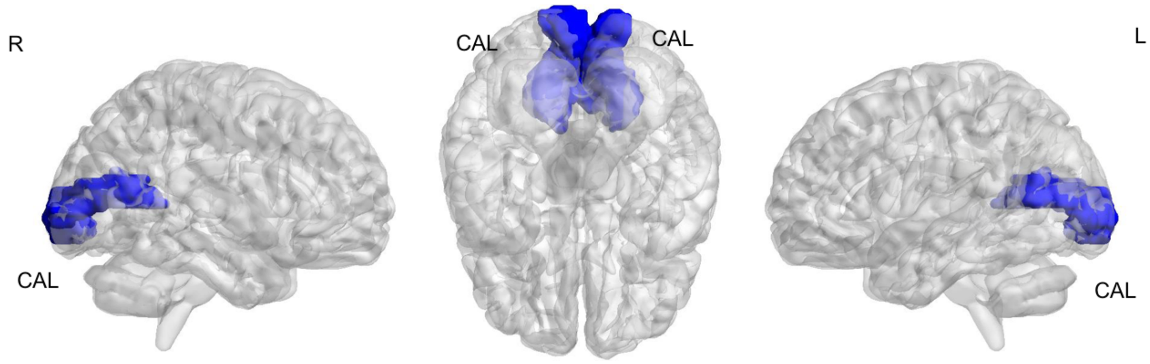

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Figure S6. Comparing of association between grey matter density in ADHD inattentive versus health control (AAL)
CAL: Calcarine

Second approach (comparing grey matter density)

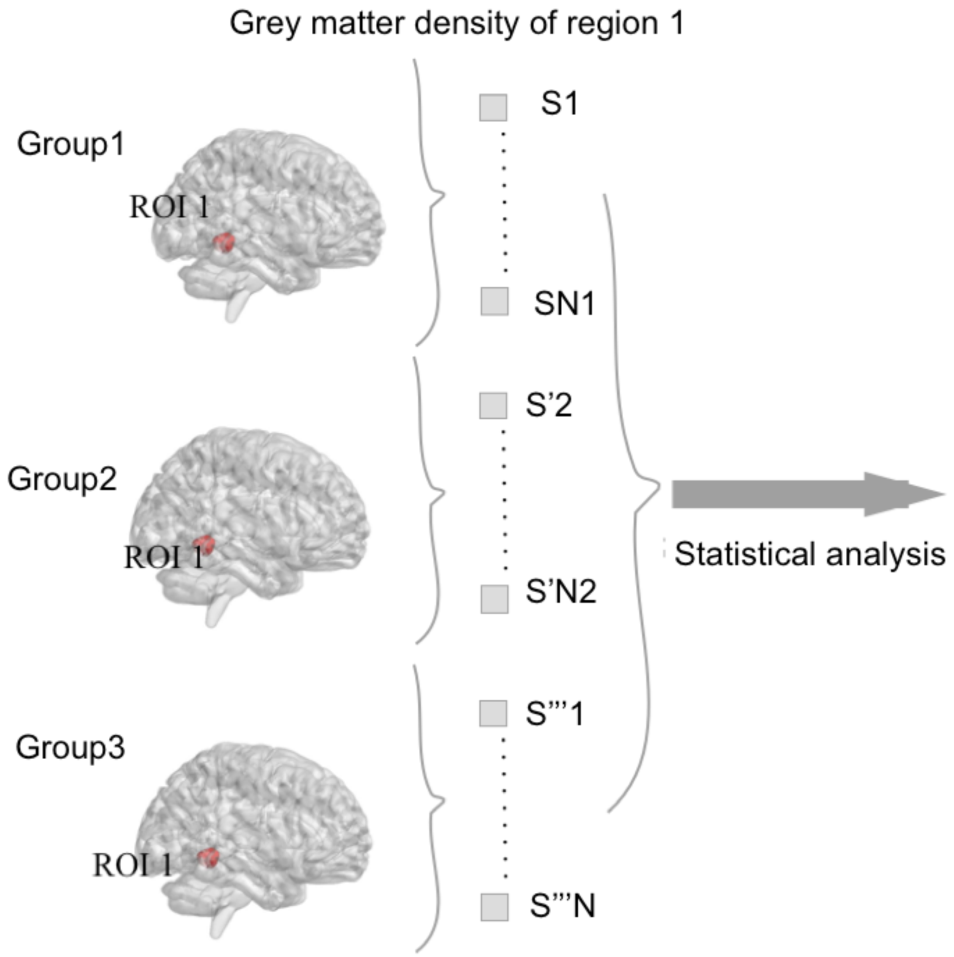

Figure S7. Schematic of experimental design2

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Table S3. Comparing grey matter density in ADHD combined, ADHD inattentive and health control group (CC400)

Region	Side	Combined Versus Inattentive	P	Combined Versus Control	P	Inattentive Versus Control	P
CG-Mid	Left	14.37	0.012			-12.6	0.031
VRM4-5						-16.39	0.017
VRM7		-17.55	0.021			19.98	0.007
Oc-Mid	Left					9.5	0.046
Oc-Inf	Left	-10.09	0.028			9.74	0.035
Te-Inf	Right					8.68	0.045
Te-Inf	Left	-8.76	0.029			13.34	0
Te-Pol-Sup	Left					7.82	0.012
Te-Pol-Mid	Left	-7.28	0.01			7.34	0.01
Te-Mid	Right					8.96	0
Fr-Sup-Med	Left			6.94	0.04	-15.48	0.03
Fr-Mid	Right	7.96	0.01			-7.38	0.018
	Left	10.44	0.01			-10.7	0.008
LING	Right	8.82	0.023			-10.26	0.007
LING	Left					15.8	0.047
CRB-4-5	Left			23.92	0.033		
	Right	11.54	0.031			-15.12	0.003
CRB8	Left	22.36	0.011			-27.09	0.002
CRB6	Right	20.27	0.031			-26.6	0.003
CRB9	Left	15.61	0.02			-24.12	0
CRB-Crus1	Right	-18.53	0.018			26.95	0
	Left	-35.19	0.001			41.09	0
CRB-Crus2	Left	-22.26	0.032			24.44	0.016
CUN	Right					11.27	0.003
PreC	Left	9.8	0.013	7.9	0.011	-11.76	0.002
PoC	Left	13.4	0.005			-15.51	0.001
	Right	-8.11	0.027			8.9	0.012
CAD	Right	-7.37	0.039			-8.8	0.043
PHG	Left	-9.12	0.017				
	Right	3.48	0.049				
FF	Left					16.83	0.048
	Right	-9.27	0.044			14.49	0.001
PUT	Right			-8.43	0.022		
OLF	Right	-9.36	0			8.11	0.002
TAL	Right	4.85	0.027				

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CG-Mid: Middle cingulate; VRM: Vermis; Oc-Mid: Middle occipital; Oc-Inf: Inferior occipital; Te-Inf: Inferior temporal; Te-Pol-Sup: Superior temporal pole; Te-Pol-Mid: Middle temporal pole; Te-Mid: Middle temporal; Fr-Sup-Med: Superior medial frontal; Fr-Mid: Middle frontal; LING: Lingual; CRB: Cerebellum; CUN: Cuneus; PreC: Precentral; PoC: Post central; CAD: Caudate; PHG: Parahipocampal gyrus; FF: Fusiform; PUT: Putamen; OLF: Olfactory; TAL: Talamus

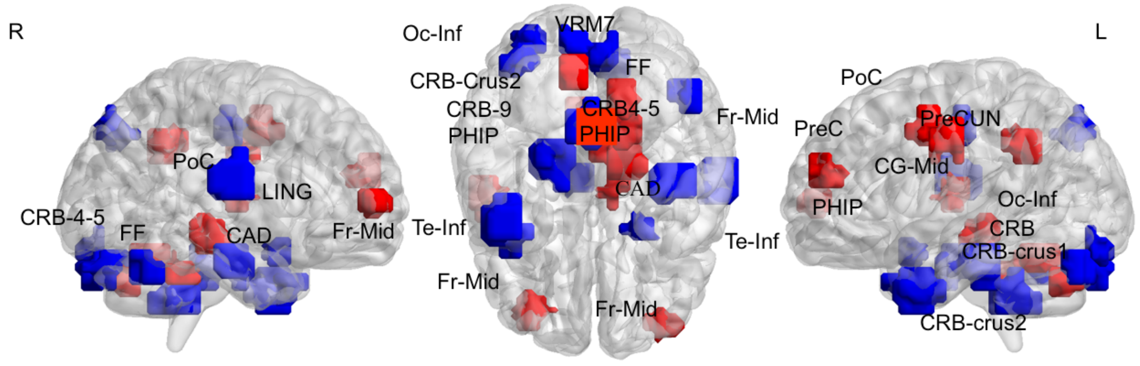

Figure S8. Comparing grey matter density in ADHD combined versus ADHD inattentive (CC400)

NEUROSCIENCE

Fr-Mid: Middle frontal; LING: Lingual; CAD: Caudate; PoC: Post central; PreC: Precentral; FF: Fusiform; PHP: Parahippocamp; PreCUN: Precuneus; CG-Mid: Middle cingulate; Te-Inf: Inferior temporal; Oc-Inf: Inferior occipital; CRB: Cerebellum; CRB-Crus1: Cerebellum Crus1; CRB-Crus2: Cerebellum Crus2; VRM: Vermis

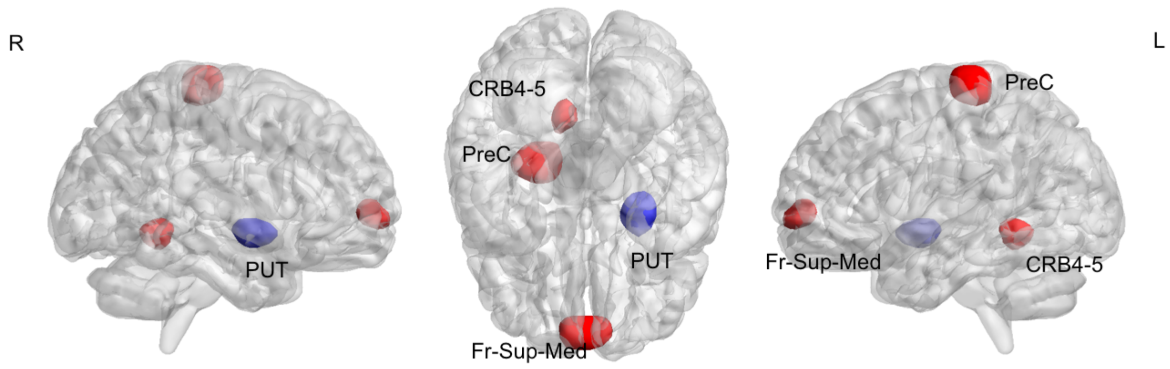

Figure S9. Comparing grey matter density in ADHD combined versus health control (CC400)

NEUROSCIENCE

Fr-Sup-Med: Medial superior frontal; PUT: Putamen; PreC: Precentral; CRB4-5: Cerebellum4-5

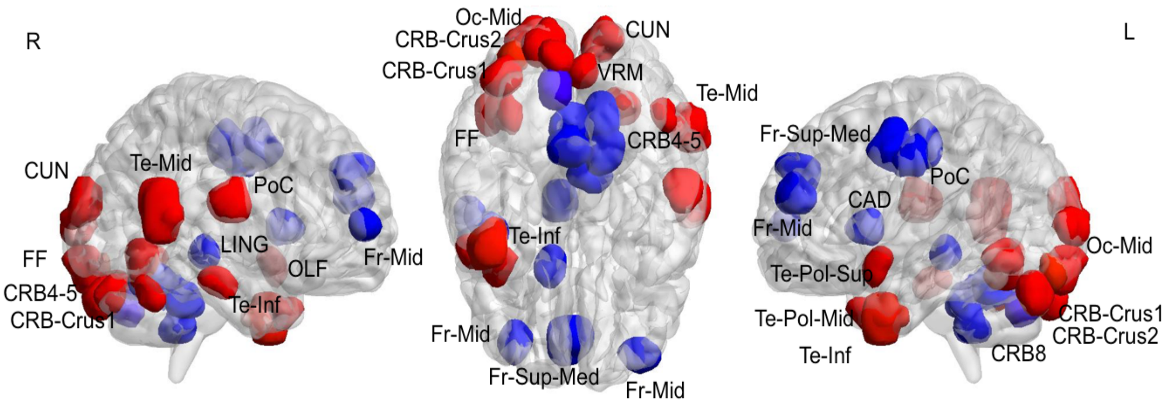

Figure S10. Comparing grey matter density in ADHD inattentive versus health control (CC400)

NEUROSCIENCE

Fr-Mid: Middle frontal; Fr-Sup-Med: Medial superior frontal; OLF: Olfactory; LING: Lingual; PoC: Poct central; FF: Fusiform; CUN: Cuneus; Te-Mid: Middle temporal; CRB: Cerebellum; CRB-Crus1: Cerebellum Crus1; CRB-Crus2: Cerebellum Crus2; CRB4-5: Cerebellum4-5; Oc-Mid: Middle occipital; VRM: Vermis

Table S4. Comparing grey matter density in ADHD combined, ADHD inattentive and health control group (AAL)

Region	Side	Combined vs Inattentive	P	Combined vs Control	P	Inattentive vs Control	P
Fr-inf	Left					-1020.7	0.031
Fr-Mid	Right	1428.39	0.016			-1351.56	0.024
Fr-Mid-Orb	Right	446.07	0.034			496.77	0.016
Fr-Inf-Tri	Right	882.43	0.002			-845.86	0.002
Rol-Oper	Left	-484.46	0.038			639.4	0.004
Rol-Oper	Right	-706.76	0.045			1213.4	0
OLF	Right					259.05	0.03
Fr-Sup-Med	Left	2.358	0.022			-2461.4	0.004
Fr-Sup-Med	Right	1750	0.019			-2324.7	0.001
INS	Right					1629.6	0.007
PHG	Left					1247.1	0.015
PHG	Right					1152.09	0.043
AMG	Left	-757	0.001				
AMG	Right	-825.7	0				
FF	Left	-7558.2	0.032			10894.1	0.001
FF	Right	-5480.68	0.042			9262.43	0
SMG	Left	1719.8	0.038				
ANG	Left	2287.6	0.025				
PAL	Left					-862.35	0.021
Te-Pol-Sup	Left	-5141.5	0.031			7950.01	0
Te-Pol-Sup	Right	-6763.4	0.002			6880.3	0.002
Te-Mid	Right			9972.3	0.004	10490.6	0.004
Te-Pol-Mid	Left	-5559.85	0.004			7267.9	0
Te-Pol-Mid	Right	-6665.4	0.005			7956.8	0.001
Te-Inf	Left	-14718.8	0.026			19970.2	0.002
Te-Inf	Right	-18046.4	0	9522.1	0.049	27568.6	0
CRB-Crus1	Left	-18379.4	0.038			23142.2	0.006
CRB-Crus1	Right					20778.4	0.003
CRB-Crus2	Left	-27693.2	0.001			33346.6	0
CRB-Crus2	Right	-20743.3	0.007			25926.6	0.001
CRB-7b	Left	-7698.3	0			10075.5	0
CRB-7b	Right	-6449.2	0.002			8283.59	0
CRB8	Left	-10993.9	0.014			12851.7	0.003
VRM 1-2		362.27	0.008			-296.96	0.035
VRM 4-5						-2229.9	0.034
VRM-10		693.56	0.005			-521.52	0.047

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Fr-Inf: Inferior Frontal; Fr-Mid: Middle Frontal; Fr-Mid-Orb: Middle orbito frontal; Fr-Inf-Tri: Triangle inferior frontal; Rol-Oper: Rolandic operculum; OLF: Olfactory; Fr-Sup-Med: Medial superior frontal; INS: Insula; PHG: Parahipocampal gyrus; AMG: Amygdala; FF: Fusiform; SMG: Superior motor gyrus; ANG: Angular; PAL: Palidum; Te-Pol-Sup: Superior temporal pole; Te-Mid: Middle temporal; Te-pol-Mid: Middle temporal pole; Te-Pol-Mid: Middle temporal pole; Te-Inf: Inferior temporal; CRB-Crus: Cerebelum crus; VRM: Vermis

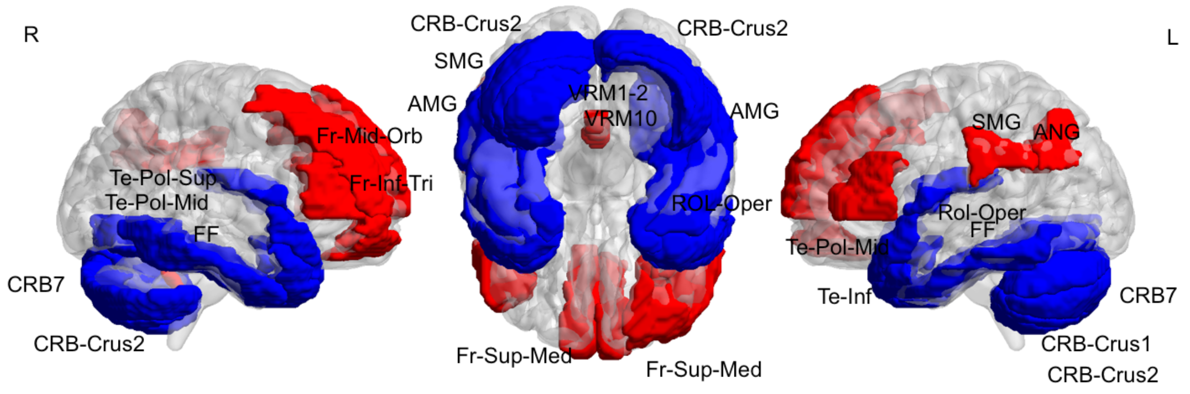

Figure S11. Comparing grey matter density in ADHD combined versus ADHD inattentive (AAL) NEUROSCIENCE

Fr-Mid-Orb: Middle orbito frontal; Fr-Inf-Tri: Inferior triangle frontal; FF: Fusiform; AMG: Amygdal; SMG: Superior Motor gyrus; ROL-Oper: Rolandic operculum; Te-Pol-Sup: Superior temporal pole; Te-pol-Mid: Middle temporal pole; Te-Inf: Inferior temporal; CRB7: Cerebellum7; CRB-Crus1: Cerebellum Crus1; CRB-Crus2: Cerebellum Crus2; VRM: Vermis

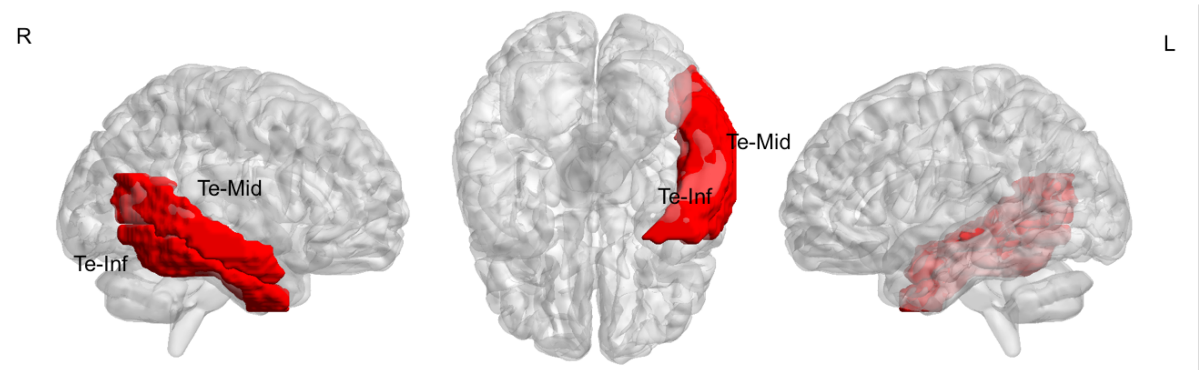

Figure S12. Comparing grey matter density in ADHD combined versus health control group (AAL) NEUROSCIENCE

Te-Mid: Middle temporal; Te-Inf: Inferior temporal

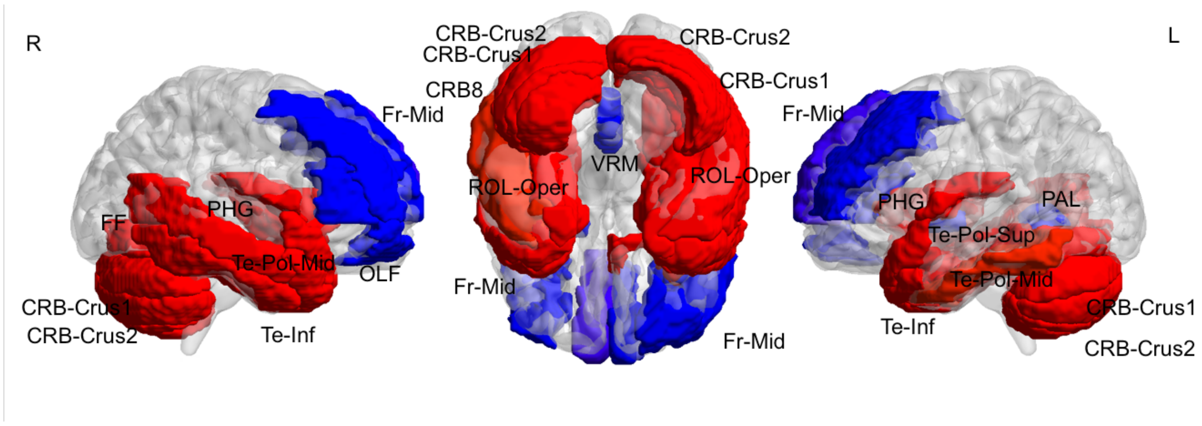

Figure S13. Comparing grey matter density in ADHD inattentive versus health control group (AAL) NEUROSCIENCE

Fr-Mid: Middle frontal; OLF: Olfactory; PHG: Parahipocamp gyrus; FF: Fusiform; ROl-Oper: Rolandic operculum; PAL: Palidum; Te-Pol-Sup: Superior temporal pole; Te-pol-Mid: Middle temporal pole; CRB-Crus1: Cerebellum Crus1; CRB-Crus2: Cerebellum Crus2; VRM: Vermis

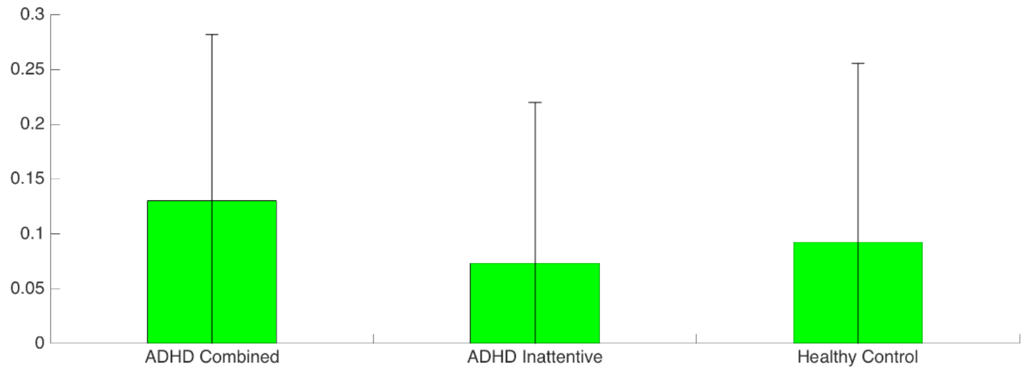

Figure S14. Comparing whole pattern of association between grey matter density and intelligence

NEUROSCIENCE

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