Abstract: 250
Main text: 3472
Table: 3
Figure: 2
Reference: 81

Neural correlates of the dual pathway model for attention-deficit/hyperactivity disorder in adolescents

Chun Shen[+], M.Sc.; Qiang Luo[*,+], Ph.D.; Tianye Jia, Ph.D.; Qi Zhao, M.Sc.; Sylvane Desrivières, Ph.D.; Erin Burke Quinlan, Ph.D.; Tobias Banaschewski, M.D., Ph.D.; Sabina Millenet D.Psych.; Arun L.W. Bokde, Ph.D.; Christian Büchel, M.D.; Herta Flor, Ph.D.; Vincent Frouin, Ph.D.; Hugh Garavan, Ph.D.; Penny Gowland, Ph.D.; Andreas Heinz, M.D., Ph.D.; Bernd Ittermann, Ph.D.; Jean-Luc Martinot, M.D., Ph.D.; Eric Artiges, M.D., Ph.D.; Marie-Laure Paillère-Martinot, M.D., Ph.D.; Frauke Nees, Ph.D.; Dimitri Papadopoulos Orfanos, Ph.D.; Tomáš Paus, M.D., Ph.D.; Luise Poustka, M.D.; Juliane H. Fröhner, M.Sc.; Michael N. Smolka, M.D.; Henrik Walter, M.D., Ph.D.; Robert Whelan, Ph.D.; Fei Li*, M.D., Ph.D.; Jianfeng Feng*, Ph.D.; Gunter Schumann, M.D.; Barbara J. Sahakian, Ph.D., D.Sc.; for the IMAGEN consortium.

[+]Contributed equally to this work
*Shared corresponding authors

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The IMAGEN consortium authors and affiliations are listed at the end of this article.

Corresponding Author: Associate Principal Investigator Qiang Luo, Ph.D., Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai 200433, PR China

Tel: +86-20-65648454; Email: qluo@fudan.edu.cn

Or

Professor Fei Li, M.D., Ph.D.

Developmental and Behavioral Pediatric Department & Child Primary Care Department, MOE-Shanghai Key Laboratory for Children's Environmental Health, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, PR China

Email: feili@shsmu.edu.cn

Or

Professor Jianfeng Feng, Ph.D.

Ministry of Education-Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence, Fudan University, Shanghai 200433, PR China

Email: jianfeng64@gmail.com

Location of work and address for reprints: Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai 200433, China

Conflict of Interest Disclosures: Dr. Sahakian consults for Cambridge Cognition and Peak, UK. Dr. Banaschewski has served as an advisor or consultant to Actelion, Hexal Pharma, Lilly, Lundbeck, Medice, Neurim Pharmaceuticals, Novartis, Shire. He received conference support or speaker's fee by Lilly, Medice, Novartis and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma; the present work is unrelated to these relationships. Dr. Walter received a speaker honorarium from Servier (2014). All other authors declare no conflict of interest.

Acknowledgement

IMAGEN data are available by application to consortium coordinator Dr Schumann (http://imagen-europe.com) after evaluation according to an established procedure. We would like to thanks to the ADHD-200 Consortium (http://fcon_1000.projects.nitrc.org/indi/adhd200/) for their generosity in contributing data publicly available.

Funding/Support: Dr. Luo was supported by the National Key Research and Development Program of China (grant 2018YFC0910503), National Natural Science Foundation of China (grants 81873909), the Natural Science Foundation of Shanghai (grant 17ZR1444400), Shanghai Municipal Science and Technology Major Project (grant 2018SHZDZX01), and Zhangjiang Lab. During the preparation of this manuscript, Dr. Luo was a Visiting Fellow at Clare Hall, Cambridge, UK. Dr. Feng was partially supported by the key project of Shanghai Science and Technology Innovation Plan (grant 16JC1420402), the Shanghai AI Platform for Diagnosis and Treatment of Brain Diseases, the Project of Zhangjiang Hi-Tech District Management Committee, Shanghai (grant 2016-17) and the 111 project (grant B18015). Dr. Li was partially supported by the Shanghai Municipal Commission of Health and Family Planning (grants 2017ZZ02026, 2018BR33, 2017EKHWYX-02 and GDEK201709), Shanghai Shenkang Hospital Development Center (grant 16CR2025B), Shanghai Municipal Education Commission (grant 20152234), National Natural Science Foundation of China (grants 81930095, 81571031, 81761128035, and 81703249), Shanghai Committee of Science and Technology (grants 17XD1403200 and 18DZ2313505), Xinhua Hospital of Shanghai Jiao Tong University School of Medicine (grants 2018YJRC03, talent introduction-014, and Top talent-201603). This work received support from the following sources: the European Union-funded FP6 Integrated Project IMAGEN (Reinforcement-related behavior in normal brain function and psychopathology) (LSHM-CT- 2007-037286), the Horizon 2020 funded ERC

Advanced Grant “STRATIFY” (Brain network based stratification of reinforcement-related disorders) (695313), ERANID (Understanding the Interplay between Cultural, Biological and Subjective Factors in Drug Use Pathways) (PR-ST-0416-10004), BRIDGET (JPND: BRain Imaging, cognition Dementia and next generation GEnomics) (MR/N027558/1), the FP7 projects IMAGEMEND (602450; IMAging GEnetics for MENtal Disorders) and MATRICS (603016), the Innovative Medicine Initiative Project EU-AIMS (115300-2), the Medical Research Council Grant “c-VEDA” (Consortium on Vulnerability to Externalizing Disorders and Addictions) (MR/N000390/1), the Swedish Research Council FORMAS, the Medical Research Council, the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King’s College London, the Bundesministeriumfür Bildung und Forschung (BMBF grants 01GS08152; 01EV0711; eMED SysAlc01ZX1311A; Forschungsnetz AERIAL 01EE1406A), the Deutsche Forschungsgemeinschaft (DFG grants SM 80/7-1, SM 80/7-2, SFB 940/1). Further support was provided by grants from: ANR (project AF12-NEUR0008-01-WM2NA, and ANR-12-SAMA-0004), the Fondation de France, the Fondation pour la Recherche Médicale, the Mission Interministérielle de Lutte-contre-les-Drogues-et-les-Conduites-Addictives (MILDECA), the Assistance-Publique-Hôpitaux-de-Paris and INSERM (interface grant), Paris Sud University IDEX 2012; the National Institutes of Health, Science Foundation Ireland (16/ERCD/3797), U.S.A. (Axon, Testosterone and Mental Health during Adolescence; RO1 MH085772-01A1), and by NIH Consortium grant U54 EB020403, supported by a cross-NIH alliance that funds Big Data to Knowledge Centres of Excellence, and the NIHR Cambridge Biomedical Research Centre (Mental Health Theme).

Abstract

Objective: The dual pathway model has been proposed to explain the heterogeneity in symptoms of attention-deficit/hyperactivity disorder (ADHD) by two independent psychological pathways based on distinct brain circuits. The authors aimed to test whether the hypothesized cognitive and motivational pathways had separable neural correlates.

Method: Using a longitudinally community-based cohort of 1,963 adolescents, the neuroanatomical correlates of ADHD were identified by a voxel-wise association analysis, and then validated using an independent clinical sample (99 never-medicated patients with ADHD, 56 medicated patients with ADHD and 267 heathy controls). The cognitive and motivational pathways were assessed by neuropsychological tests of working memory (WM), intra-subject variability (ISV), stop signal reaction time and delay discounting (DD). The associations were tested between the identified neuroanatomical correlates and both the ADHD symptoms 2 years later and the polygenic risk score for ADHD.

Results: Gray matter volumes (GMV) of both a prefrontal cluster and a posterior-occipital cluster were negatively associated with inattention. Compared with healthy controls, never-medicated, but not medicated patients had significantly lower GMVs in these two clusters. WM and ISV were associated with the posterior-occipital cluster while DD was independently associated with both clusters. The baseline GMV of the posterior-occipital cluster predicted the inattention symptoms in a 2-year follow-up and was associated with the genetic risk for ADHD.

Conclusions: The dual pathway model has both shared and separable neuroanatomical correlates, and the shared correlate in the occipital cortex has a potential to serve as an imaging trait marker of ADHD, especially the inattention symptom domain.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders, affecting 5.9-7.1% children and adolescents worldwide (1), 50-66% of which persist into adulthood (2, 3). This disorder has been characterized by its significant heterogeneity as patients receiving the same diagnosis often present neuropsychological impairments in distinct domains (4). Therefore, identification of the neural abnormalities underlying these heterogeneous impairments may improve both diagnostic accuracy and treatment efficiency of this disorder.

To account for such heterogeneity, a dual pathway model has suggested two separable psychopathophysiological pathways leading to the symptoms of ADHD (5-7), including cognitive dysfunctions, such as deficits in working memory (WM) (8), attention regulation (intra-subject variability; ISV) (9), and response inhibition (stop signal reaction time; SSRT) (10), and motivational dysfunction, such as preferring small immediate rewards over larger delayed rewards (delay discounting; DD) (11). As the frontostriatal dysfunction has been frequently associated with ADHD by neuroimaging studies (12), one hypothesis has been proposed that these two pathways can be dissociated into the fronto-dorsal striatal circuit responsible for cognitive dysfunction and the fronto-ventral striatal circuit for motivational dysfunction (5). Previous behavioral studies have reported that children with ADHD have cognitive and motivational deficits (13, 14), both of which independently contribute to ADHD symptoms (15-17). However, it is still under debate whether the cognitive and motivational deficits are independent from (18, 19) or associated with each other (20, 21). Recent studies seem to suggest a functional overlap between these two pathways, for example, WM training could also improve DD (22, 23). In neuroimaging studies, a large-scale brain system beyond the frontostriatal model has also been

discussed (24), for example, a 2016 meta-analysis reported ADHD patients with structural abnormalities in both the right basal ganglia/insula and prefrontal cortex, and also in the left occipital lobe (25). Therefore, the main goal of the current study is to test whether these two pathways are linked to ADHD symptoms by shared and/or separable neuroanatomical correlates.

Given ADHD has been considered as an extreme of a quantitative trait (26), we first analyzed a large-scale population-based sample to identify its neuroanatomical correlates, and then validated the findings using an independent clinical sample. With both never-medicated and medicated patients with ADHD in this clinical sample, we were also able to assess the effects of medication on these neuroanatomical correlates. For the first time, to our knowledge, we assessed the independent associations of the identified neuroanatomical correlates with both cognitive (i.e. WM, ISV, SSRT) and motivational deficits (i.e. DD) in one comprehensive study. To demonstrate the potential of our findings to be an intermediate phenotype of ADHD (27), we further tested whether the identified neuroanatomical correlates contributed to explaining ADHD symptoms 2 years later and whether these correlates were associated with genetic risks for this disorder.

Method

Participants

Population-based cohort

IMAGEN is a community-based longitudinal study of adolescent brain development (28). Detailed recruitment procedure has been published elsewhere, and written informed consents were obtained from all participants and their legal guardians. 1,963 participants (952 males [49%]) who had completed

psychometric assessments and quality controls of neuroimaging data at the baseline (i.e. at the age of 14 years old) were included in the present study (Table 1).

Clinical Cohort

ADHD-200 is a multi-center clinical study (29) approved by the local research ethics review boards at each center. 233 ADHD patients (188 males; mean age $= 11.75 \pm 3.01$; 129 with combined subtype, 8 with hyperactive/impulsive subtype and 96 with inattentive subtype; 56 medicated, 99 never-medicated and 78 missing medication information) and 267 typically-developed controls (TD; 141 males; mean age $= 11.98 \pm 3.04$) who had quality controlled MRI data were included in the present study (eMethod 1; Table S1). A full-scale IQ score above 80 was required as an inclusion criterion (Table S2).

Measurements

ADHD

The Strengths and Difficulties Questionnaire (SDQ), assessed at both baseline and follow-up in IMAGEN, is a validated assessment tool for mental health problems in youth (30), and has been demonstrated to be a promising assessment for ADHD symptoms in IMAGEN (31-34). The hyperactivity-inattention subscale is composed of 5 items covering 3 key symptom domains for ADHD with the internal consistency (Cronbach's α=0.75) at an acceptable level (α>0.6) (35). As used in nationwide epidemiological studies (36), a 3-band classification was established for the SDQ using a cut-off score of 6 (normal: < 6, 80%; borderline: $= 6$, 10%; abnormal: > 6, 10%). We used the parent-reported SDQ, because the parent version is more reliable than the self-reported version by the children, and the parent-SDQ also has a stronger association with clinical assessment (odds ratio: 32.3 vs. 5 for

ADHD) (30, 36). If a participant had abnormal (or normal) scores at both ages 14 and 16 years, then this participant was classified into the persistent (or typically-developed control) group.

Delay discounting

The Monetary Choice Questionnaire (37), which is an efficient and reliable measurement of DD and has been validated in adolescents (38), was assessed at baseline. It contains 27 dichotomous choice items pitting a smaller-immediate reward against a larger delayed reward for three levels of reward magnitude (i.e. small, medium, large). Higher value of k-coefficient in a hyperbolic discounting equation for each reward level represents greater preference for small immediate rewards and higher impulsivity (eMethod 2). The geometric mean was calculated and logarithmically transformed to use in our analyses.

Working memory

The spatial working memory in the Cambridge Neuropsychological Testing Automated Battery (39) was measured at baseline. This is a self-ordered searching task to measure participants' ability to preserve spatial information (40), and it is widely used in studies of ADHD in children and adolescents (41). The number of errors was used as an index of WM.

Intra-subject variability and stop signal reaction time

ISV and SSRT were obtained by behavioral data for the stop signal fMRI task (42) (n=1,846). ISV was estimated by the standard deviation of reaction time in successful GO trials. SSRT was estimated by subtracting the mean stop signal latency from the mean correct go response time. Participants who had fewer than 50% correct hits and who had negative SSRT were excluded.

Structural MRI

The Magnetic Resonance Imaging (MRI) acquisition protocols and quality controls in IMAGEN have been described in detail (28). The high resolution T1-weighted magnetization prepared gradient echo sequence was collected using 3T scanners and preprocessed using the VBM8 toolbox as reported previously (43) (eMethod 3).

Genetic data

Genotyping was carried out from blood drawn from IMAGEN participants (28). Genotype information was collected at 582,982 markers using the Illumina Human Genotyping Bead Chip. After quality control, 1,790 cases were included in our sample totaling 506,932 SNPs available for establishing the polygenic risk score (PRS) for ADHD (eMethod 4).

Statistical analysis

Voxel-wise brain-wide association analysis

A whole-brain analysis was conducted at the voxel level using the general linear model in SPM12 to identify clusters with GMV associated with ADHD total score at the baseline in IMAGEN. Age, sex, handedness, total intracranial volume (TIV) and site were considered as covariates. IQ is not recommended to be controlled in cognitive studies of neurodevelopmental disorders, since it is often affected by the disorder (44). An uncorrected $p<0.001$ at voxel-level, with a cluster-level family-wise error (FWE; $p<0.05$) was applied to identify significant clusters (45).

Neuropsychological association analysis

Separate partial correlation analyses were conducted between neuropsychological measures (i.e. WM, ISV, SSRT or DD) and both ADHD symptoms and GMV of the significant clusters, controlling for age, sex, handedness, TIV and site. Confidence interval was given by 5,000 bootstraps. Next, we included other variables as covariates for the association analysis of one variable. If a significant association becomes insignificant after controlling other variables, this association is not independent to other variables but is contributed by some common factor shared between cognitive and motivational deficits.

Prospective association analysis

We extended our analysis to ADHD symptoms at the age of 16 years in IMAGEN. Hierarchical multiple regression was applied to identify significant association between the baseline features and ADHD symptoms 2 years later. In these regression models with covariates and corresponding baseline symptoms, the behavioral variables and GMVs of the significant clusters were entered one-by-one. A variable was retained in the model when it significantly elevated the model performance (i.e. a significant ΔR^2 with $p<0.05$).

Analysis of covariance was performed between the persistent group and the TD control group in IMAGEN while controlling for the sex, handedness, TIV and site. Significance of the results were given by 10,000 random permutations (reported as p-perm), and validated by the comparisons between well-matched samples (healthy controls were selected by an R package *MatchIt* to match the sample size with the persistent group) (46).

Polygenic analysis

The latest genome-wide association meta-analysis of 20,183 patients with ADHD and 35,191 controls was used as the discovery dataset (47), the summary statistics were downloaded from the Psychiatric Genomics Consortium (http://www.med.unc.edu/pgc/results-and-downloads). The primary analyses are based on the threshold of $p<0.50$ since it maximally captures phenotypic variance (48), using the PRS software (PRSice; http://prsice.info/) (49). Associations of PRS with the neuropsychological variables were tested by partial correlation analyses while controlling for age, sex and site, while its associations with GMV of the significant clusters were assessed by additionally controlling for handedness and TIV.

Validation

We applied the identical preprocessing pipeline of structural neuroimaging data as used in IMAGEN to the ADHD-200 clinical sample. Using a mask of the significant clusters identified in IMAGEN, GMV of each cluster was extracted for analyses. We tested 1) whether patients with ADHD had lower GMVs of the significant clusters by comparing patients with controls; 2) which ADHD patient subtype had the lowest GMVs of the significant clusters by comparing between two ADHD subtypes (hyperactive/impulsive subtype was excluded because of a small sample size of 8) and controls; 3) whether medication had any remedial effect on the reduced GMVs of the significant clusters by group comparison among never-medicated patients, medicated patients, and controls. All analyses were controlled for age, sex, handedness, TIV and site.

Results

Descriptive statistics

In the IMAGEN cohort at the baseline (Table 1), WM, ISV and DD were positively associated with

ADHD symptoms, and the correlations were not confounded by each other (Table 2). There was no significant correlation between ADHD symptoms and SSRT (p>0.05), and therefore it was not included in further analyses. Greater DD rate was associated with more WM errors (r_{1952}=0.13, p<0.001, 95% CI=0.08, 0.17) and increased ISV (r_{1835}=0.09, p<0.001, 95% CI=0.04,0.13).

Neuroanatomical correlates of inattention in a population-based cohort

In IMAGEN at the baseline, we found that higher ADHD total score was associated with lower GMVs of two brain clusters in both the prefrontal cortex ($x = -19.5$, $y = 49.5$, $z = 3$, 3,357 voxels; peak $t_{1950} = -4.29$; cluster-level $pFWE < 0.001$) and the posterior-occipital cortex ($x = -1.5$, $y = 91.5$, $z = 15$, 1,295 voxels; peak $t_{1950} = -4.32$; cluster-level $pFWE = 0.025$), respectively. The prefrontal cluster covered the left ventromedial prefrontal cortex, dorsal anterior cingulate cortex and anterior insula, while the posterior-occipital cluster was mainly in the left cuneus and extended to the left calcarine (Figure 1). These associations were not confounded by either data collection sites (Figure S1) or IQ (eResult 2). These associations became insignificant after controlling for the inattention score but remained significant after controlling for the hyperactivity/impulsivity score (the prefrontal cluster: r_{1949}=-0.08, p<0.001, 95% CI = -0.03 to -0.13 ; the posterior-occipital cluster: r_{1949}=-0.07, p=0.002, 95% CI = -0.03 to -0.11).

Neuroanatomical correlates of inattention selectively associated with WM, ISV or DD

In IMAGEN at the baseline, we found that more WM errors was associated with lower GMV of the posterior-occipital cluster even after controlling for ISV and DD (r_{1831}=-0.07, p=0.005; Table 2). Similar to WM, increased ISV was associated with lower GMV of the posterior-occipital cluster even after

controlling for WM and DD (r_{1831}=-0.05, p=0.027; Table 2). Greater DD rate was associated with lower GMV's of both clusters even after controlling for WM and ISV (the prefrontal cluster: r_{1831}=-0.05, p=0.042; the posterior-occipital cluster: r_{1831}=-0.05, p=0.049; Table 2).

Prospective associations with inattention 2 years later

After controlling for the corresponding ADHD symptom at age 14 years, WM and DD at age 14 years were selectively associated with inattention (t_{1505}=2.35, p=0.019) and hyperactivity/impulsivity (t_{1505}=2.24, p=0.025) at age 16 years, respectively. In the multivariate regression model, we found that both WM (t_{1404}=2.04, ΔR^2=0.002, p=0.042) and GMV of the posterior-occipital cluster (t_{1404}=-3.55, ΔR^2=0.005, p<0.001) at age 14 years were associated with inattention 2 years later (Table 3).

Adolescents with persistent ADHD symptoms (n=29) had reduced GMVs of both the prefrontal cluster as compared with the typically-developed controls (n=1,278; $5.63 \pm 1.03 ml^3$ vs. $6.23 \pm 1.19 ml^3$; $F_{1,1295}$=6.37; p-perm=0.012; partial eta-squared $\eta_p^2 = 0.005$), and the posterior-occipital cluster ($2.06 \pm 0.35 ml^3$ vs. $2.19 \pm 0.28 ml^3$; $F_{1,1295}$=5.12, p-perm=0.022; $\eta_p^2 = 0.004$; Figure S2). Significant results with even larger effect sizes were found using matched-group comparisons (29 vs. 58; eResult 3).

Associations of neuropsychological and neuroanatomical intermediate phenotypes with polygenetic risk for ADHD

In IMAGEN, we found higher PRS for ADHD was associated with higher ADHD total score at the baseline (r_{1779}=0.14, p<0.001, 95% CI = 0.097 to 0.188), more WM errors (r_{1779}=0.07, p=0.002, 95% CI = 0.026 to 0.121), greater DD rate (r_{1779}=0.06, p=0.007, 95% CI = 0.021 to 0.109), and lower

GMV of the posterior-occipital cluster only (r_{1777}=-0.06, p=0.009, 95% CI = –0.106 to -0.015).

Validation using a clinical cohort of ADHD

In ADHD-200, we confirmed that patients had lower GMVs in both the prefrontal ($3.86 \pm 1.67 ml^3$ vs. $4.40 \pm 1.56 ml^3$, $F_{1,491}$=12.18, p<0.001, $\eta_p^2 = 0.024$; Figure 2A) and the posterior-occipital clusters ($1.21 \pm 0.30 ml^3$ vs. $1.28 \pm 0.29 ml^3$, $F_{1,491}$=9.28, p=0.002, $\eta_p^2 = 0.019$; Figure 2B). These volumetric reductions were non-significant in patients with the combined subtype (n=129) but only significant in patients with the inattentive subtype (n=96; the prefrontal cluster: $F_{1,354}$=12.92, p<0.001, $\eta_p^2 = 0.035$; the posterior-occipital cluster: $F_{1,354}$=7.29, p=0.007, $\eta_p^2 = 0.020$; Figure 2C-D).

Medication effects

In ADHD-200, we found that the TD controls (n=267) had the highest GMVs of both clusters, the medicated patients (n=56) had the intermediate GMVs, and the never-medicated patients (n=99) had the lowest GMVs. Compared with the TD controls, the never-medicated patients had significant group differences in both clusters (the prefrontal cluster: $F_{1,357}$=12.37, p<0.001, $\eta_p^2 = 0.033$; the posterior-occipital cluster: $F_{1,357}$=8.50, p=0.004, $\eta_p^2 = 0.023$; Figure 2E-F). However, the group differences between the TD controls and the medicated patients became nonsignificant. The corresponding effect sizes were significantly decreased compared with that for the never-medicated patients (prefrontal cluster: $\eta_p^2(\text{control vs. medicated}) - \eta_p^2(\text{control vs. never-medicated}) = -0.031$, 95% CI = -0.068 to -0.004; posterior-occipital cluster: -0.022, 95% CI = -0.055 to 0.000 given by 5,000 bootstraps). Therefore, these findings were unlikely to be explained by group differences of either demographics or symptom severity between the medicated and the never-medicated patients (eMethod 1; Table S3).

Discussion

To our knowledge, this is the first study to differentiate the neuroanatomical basis for the cognitive and motivational pathways of ADHD in a large population-based cohort of adolescents. The neuroimaging finding of a common neuroanatomical correlate, namely GMV of the posterior-occipital cluster, shared by both cognitive and motivational deficits suggests an overlapping neuroanatomical basis for the dual pathway model of ADHD. Intriguingly, the study has also revealed associations of GMV of this cluster with both future symptoms of and polygenic risk for ADHD in the population-based cohort. Compared with typically-developed controls, never-medicated patients with ADHD had the lowest GMV of this cluster and medicated patients had an intermediate GMV. These findings demonstrate that such neuroanatomical feature has a potential of serving as an intermediate phenotype of ADHD.

The findings of the current neuroimaging study support an involvement of the visual attention network (VAN) and emphasize the importance of the large-effect cognitive impairment seen in previous behavioral studies in visual attention specifically, as compared with auditory attention (50, 51). First, both identified prefrontal and posterior-occipital clusters are located in VAN; and second, a prospective association of GMV of the posterior-occipital cluster selectively with the inattention score assessed 2 years later. Abnormal brain activities of VAN have been associated with ADHD by functional neuroimaging studies (52), which is complementary to the current structural neuroimaging study. In this functional network, the occipital cortex interacts with the dorsal attention network to maintain visual attention (53) and suppress attention to irrelevant visual stimuli by a top-down modulation of the prefrontal cortex (54). These brain regions are also structurally wired together, particularly the inferior

fronto-occipital fasciculus (IFOF) is a direct pathway that connects the frontal and occipital lobes as well as the parietal and posterior temporal cortices (55). A 2016 meta-analysis of DTI studies on ADHD has reported consistent white matter differences located in the left IFOF (56), and been related to attention (57, 58). The hypothesis is that these regions may be modulated by dopamine activity. In addition to the well-known effect of dopamine on the prefrontal region (59-62), a 2018 study found the dopamine transporter (DAT1)-related reduction of GMV in the left posterior-occipital region may contribute to visual memory performance in children with ADHD (63).

Our comparison between medicated and never-medicated patients with ADHD may suggest a positive effect of medication on gray matter atrophy in patients with ADHD. Stimulant medication for ADHD affects the brain in many aspects, including structure (64, 65), function (66), and neurotransmitter (67). Therefore, lower GMV of the identified clusters in never-medicated patients with ADHD may exclude one alternative explanation that lower GMV was caused secondarily by medication, while comparable GMV between medicated patients and TD controls suggests medication may have a remedial effect for ADHD on brain structure, which provides a possible neuroanatomical basis for the behavioral improvement in visual attention by stimulant treatment for ADHD (68).

The dual pathway model of ADHD has been a very valuable model for our understanding of the neuropsychopathology of this disorder (5-7). Our findings do not support the independent pathways model (i.e. the cognitive circuit between dorsolateral prefrontal cortex and dorsal striatum, and the motivational circuit between orbito-frontal cortex and ventral striatum) (5) but instead demonstrate an interaction between cognition and motivation in ADHD. This interaction is not only supported by the

WM-DD and ISV-DD associations in the IMAGEN sample, but also supported by previous reports of both monetary incentive-enhanced cognition and cognitive biases-enhanced avoidance motivation (69). Our findings further suggest that this interaction may have its neural basis within the VAN, especially the left cuneus in the posterior occipital cortex and the hyperactivation of this region has been previously reported in task-based fMRI experiments (70). Its association with DD is not completely surprising given both the hyperactivation (71, 72) and higher GMV (73) of the posterior occipital cortex have already been associated with choosing delayed gain over immediate reward. Its association with the WM performance (i.e. 2-back accuracy) has also been observed in an fMRI experiment (74). Together, these findings may suggest that the dual pathways in ADHD are likely related to dysfunction of these cognitive and motivational processes, particularly in the visual attentional system, which supports the top-down selection of relevant information from the environment during goal-directed tasks (75).

It has been reported in the literature even a small improvement in memory score (10%) can make a significant difference in school performance (76). The effect sizes of the identified neural associations were small to medium, partially owing to the multifactorial nature of ADHD. However, as shown in the results, these findings were statistically robust and empirically replicable using an independent clinical sample. Therefore, the findings may improve the accuracy of the diagnosis by using GMV of the posterior-occipital cluster as an intermediate phenotype of ADHD, especially the inattention symptoms. This neuroanatomical feature 1) is associated with inattention in the general population; 2) is associated with neuropsychological endophenotypes of ADHD; 3) is associated with genetic risk for ADHD; 4) contributes to the explanation of future inattention symptoms; and 5) is preserved in clinical patients with ADHD, and such a feature cannot be simply explained by a confounding effect of medication. These are

exactly the lines of evidence that are required for the identification of an intermediate phenotype of a mental health disorder (77). The occipital cluster develops early in life and functionally matures during childhood (78), and therefore may also be used as a neuroimaging biomarker of disrupted brain development for the early diagnosis of ADHD. As expected, we also found the ADHD-associated prefrontal cluster was indeed correlated with DD, which is consistent with the frontostriatal model of ADHD (79). However, given this prefrontal area is under significant development during adolescence (80) with a significant individual variation (81), it might be difficult to use GMV of this prefrontal cluster as an imaging trait marker for ADHD.

Limitation

As both parent and teacher ratings are needed for clinical diagnosis, our study using parent ratings may not have fully captured ADHD symptoms. The current study identified a common neural correlate for working memory, attention regulation and delay discounting, which represents particular aspects of the broader cognitive and motivational deficits in ADHD. However, the current study did not identify any significant association of response inhibition with the ADHD symptoms. Our findings are in adolescents, but the development and maturation of the posterior-occipital cortex are believed to be largely completed during childhood. Future longitudinally neuroimaging cohort of ADHD during childhood is necessary to confirm whether there is any abnormal development of this occipital cortex can be observed leading to the manifestation of ADHD symptoms.

Conclusion

In summary, using a comprehensive approach we revealed a common neuroanatomical correlate of both cognitive and motivational pathways for the development of ADHD. Given that the posterior-occipital region developed and matured much earlier than the previously focused prefrontal areas in the frontostriatal model of ADHD, these results might provide new clues to discover novel imaging markers for early diagnosis and pre-emptive intervention strategies for ADHD.

Reference

1. Willcutt EG: The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics 2012; 9:490-499.

2. Barkley RA, Fischer M, Smallish L, et al: The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. J Abnorm Psychol 2002; 111:279-289.

3. Lara C, Fayyad J, De Graaf R, et al: Childhood predictors of adult attention-deficit/hyperactivity disorder: results from the World Health Organization World Mental Health Survey Initiative. Biol Psychiatry 2009; 65:46-54.

4. Wahlstedt C, Thorell LB, Bohlin G: Heterogeneity in ADHD: neuropsychological pathways, comorbidity and symptom domains. J Abnorm Child Psychol 2009; 37:551-564.

5. Sonuga-Barke EJ: The dual pathway model of AD/HD: an elaboration of neuro-developmental characteristics. Neurosci Biobehav Rev 2003; 27:593-604.

6. Sonuga-Barke EJ: Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. Biol Psychiatry 2005; 57:1231-1238.

7. Sonuga-Barke EJS: Psychological heterogeneity in AD/HD - a dual pathway model of behaviour and cognition. Behav Brain Res 2002; 130:29-36.

8. Martinussen R, Hayden J, Hogg-Johnson S, et al: A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2005; 44:377-384.

9. Kofler MJ, Rapport MD, Sarver DE, et al: Reaction time variability in ADHD: a meta-analytic review of 319 studies. Clin Psychol Rev 2013; 33:795-811.

10. Crosbie J, Arnold P, Paterson A, et al: Response inhibition and ADHD traits: correlates and heritability in a community sample. J Abnorm Child Psychol 2013; 41:497-507.

11. Sonuga-Barke EJ, Taylor E, Sembi S, et al: Hyperactivity and delay aversion--I. The effect of delay on choice. J Child Psychol Psychiatry 1992; 33:387-398.

12. Rubia K: “Cool” inferior frontostriatal dysfunction in attention-deficit/hyperactivity disorder versus “hot” ventromedial orbitofrontal-limbic dysfunction in conduct disorder: a review. Biol Psychiatry 2011; 69:e69-e87.

13. Sonuga-Barke EJS, Bitsakou P, Thompson M: Beyond the Dual Pathway Model: Evidence for the Dissociation of Timing, Inhibitory, and Delay-Related Impairments in Attention-Deficit/Hyperactivity

Disorder. J Am Acad Child Adolesc Psychiatry 2010; 49:345-355.

14. Coghill DR, Seth S, Matthews K: A comprehensive assessment of memory, delay aversion, timing, inhibition, decision making and variability in attention deficit hyperactivity disorder: advancing beyond the three-pathway models. Psychol Med 2014; 44:1989-2001.

15. Sonuga-Barke EJ, Dalen L, Remington B: Do executive deficits and delay aversion make independent contributions to preschool attention-deficit/hyperactivity disorder symptoms? J Am Acad Child Adolesc Psychiatry 2003; 42:1335-1342.

16. Yang B-R, Chan R, Gracia N, et al: Cool and hot executive functions in medication-naive attention deficit hyperactivity disorder children. Psychol Med 2011; 41:2593-2602.

17. Thorell LB: Do delay aversion and executive function deficits make distinct contributions to the functional impact of ADHD symptoms? A study of early academic skill deficits. Journal of Child Psychology and Psychiatry 2007; 48:1061-1070.

18. Solanto MV, Abikoff H, Sonuga-Barke E, et al: The ecological validity of delay aversion and response inhibition as measures of impulsivity in AD/HD: a supplement to the NIMH multimodal treatment study of AD/HD. J Abnorm Child Psychol 2001; 29:215-228.

19. Patros CH, L. Sweeney K, Mahone EM, et al: Greater delay discounting among girls, but not boys, with ADHD correlates with cognitive control. Child Neuropsychol 2018; 24:1026-1046.

20. Karalunas SL, Huang-Pollock CL: Examining Relationships Between Executive Functioning and Delay Aversion in Attention Deficit Hyperactivity Disorder. J Clin Child Adolesc Psychol 2011; 40:837-847.

21. Patros CHG, Alderson RM, Lea SE, et al: Visuospatial working memory underlies choice-impulsivity in boys with attention-deficit/hyperactivity disorder. Res Dev Disabil 2015; 38:134-144.

22. Bickel WK, Yi R, Landes RD, et al: Remember the future: working memory training decreases delay discounting among stimulant addicts. Biol Psychiatry 2011; 69:260-265.

23. Wesley MJ, Bickel WK: Remember the future II: meta-analyses and functional overlap of working memory and delay discounting. Biol Psychiatry 2014; 75:435-448.

24. Castellanos FX, Proal E: Large-scale brain systems in ADHD: beyond the prefrontal–striatal model. Trends Cogn Sci 2012; 16:17-26.

25. Norman LJ, Carlisi C, Lukito S, et al: Structural and functional brain abnormalities in attention-deficit/hyperactivity disorder and obsessive-compulsive disorder: a comparative meta-analysis. JAMA psychiatry 2016; 73:815-825.

26. Thapar A: Discoveries on the genetics of ADHD in the 21st century: new findings and their

implications. Am J Psychiatry 2018; 175:943-950.

27. Meyer-Lindenberg A, Weinberger DR: Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nat Rev Neurosci 2006; 7:818-827.

28. Schumann G, Loth E, Banaschewski T, et al: The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. Mol Psychiatry 2010; 15:1128-1139.

29. Milham MP, Fair D, Mennes M, et al: The ADHD-200 consortium: a model to advance the translational potential of neuroimaging in clinical neuroscience. Front Syst Neurosci 2012; 6:62.

30. Goodman R: The strengths and difficulties questionnaire: a research note. Journal of child psychology and psychiatry 1997; 38:581-586.

31. Albaugh MD, Hudziak JJ, Ing A, et al: White matter microstructure is associated with hyperactive/inattentive symptomatology and polygenic risk for attention-deficit/hyperactivity disorder in a population-based sample of adolescents. Neuropsychopharmacology 2019:1.

32. Albaugh MD, Ivanova M, Chaarani B, et al: Ventromedial prefrontal volume in adolescence predicts hyperactive/inattentive symptoms in adulthood. Cereb Cortex 2018.

33. Albaugh MD, Orr C, Chaarani B, et al: Inattention and reaction time variability are linked to ventromedial prefrontal volume in adolescents. Biol Psychiatry 2017; 82:660-668.

34. Bayard F, Thunell CN, Abé C, et al: Distinct brain structure and behavior related to ADHD and conduct disorder traits. Mol Psychiatry 2018:1.

35. Shrout PE: Measurement reliability and agreement in psychiatry. Stat Methods Med Res 1998; 7:301-317.

36. Goodman R: Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry 2001; 40:1337-1345.

37. Kirby KN, Petry NM, Bickel WK: Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. J Exp Psychol Gen 1999; 128:78-87.

38. Duckworth AL, Seligman ME: Self-discipline outdoes IQ in predicting academic performance of adolescents. Psychol Sci 2005; 16:939-944.

39. Sahakian BJ, Owen A: Computerized assessment in neuropsychiatry using CANTAB: discussion paper. J R Soc Med 1992; 85:399-402.

40. Luciana M: Practitioner review: computerized assessment of neuropsychological function in children: clinical and research applications of the Cambridge Neuropsychological Testing Automated

Battery (CANTAB). J Child Psychol Psychiatry 2003; 44:649-663.

41. Kempton S, Vance A, Maruff P, et al: Executive function and attention deficit hyperactivity disorder: stimulant medication and better executive function performance in children. Psychol Med 1999; 29:527-538.

42. D'Alberto N, Chaarani B, Orr CA, et al: Individual differences in stop-related activity are inflated by the adaptive algorithm in the stop signal task. Hum Brain Mapp 2018; 39:3263-3276.

43. Luo Q, Chen Q, Wang W, et al: Association of a Schizophrenia-Risk Nonsynonymous Variant With Putamen Volume in Adolescents: A Voxelwise and Genome-Wide Association Study. JAMA Psychiatry 2019; 76:435-445.

44. Dennis M, Francis DJ, Cirino PT, et al: Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. J Int Neuropsychol Soc 2009; 15:331-343.

45. Eklund A, Nichols TE, Knutsson H: Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. Proc Natl Acad Sci USA 2016; 113:7900-7905.

46. Ho DE, Imai K, King G, et al: MatchIt: Nonparametric Preprocessing for Parametric Causal Inference. J Stat Softw 2011; 42.

47. Demontis D, Walters RK, Martin J, et al: Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet 2018.

48. Riglin L, Collishaw S, Thapar AK, et al: Association of genetic risk variants with attention-deficit/hyperactivity disorder trajectories in the general population. JAMA psychiatry 2016; 73:1285-1292.

49. Euesden J, Lewis CM, O'reilly PF: PRSice: polygenic risk score software. Bioinformatics 2014; 31:1466-1468.

50. Ahrendts J, Rüsch N, Wilke M, et al: Visual cortex abnormalities in adults with ADHD: a structural MRI study. World J Biol Psychiatry 2011; 12:260-270.

51. Lin H-Y, Hsieh H-C, Lee P, et al: Auditory and visual attention performance in children with ADHD: The attentional deficiency of ADHD is modality specific. J Atten Disord 2017; 21:856-864.

52. Xia S, Foxe JJ, Sroubek AE, et al: Topological organization of the "small-world" visual attention network in children with attention deficit/hyperactivity disorder (ADHD). Front Hum Neurosci 2014; 8:162.

53. Shulman GL, Astafiev SV, Franke D, et al: Interaction of stimulus-driven reorienting and expectation in ventral and dorsal frontoparietal and basal ganglia-cortical networks. J Neurosci 2009;

29:4392-4407.

54. Capotosto P, Babiloni C, Romani GL, et al: Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. J Neurosci 2009; 29:5863-5872.

55. Catani M, De Schotten MT: A diffusion tensor imaging tractography atlas for virtual in vivo dissections. Cortex 2008; 44:1105-1132.

56. Chen L, Hu X, Ouyang L, et al: A systematic review and meta-analysis of tract-based spatial statistics studies regarding attention-deficit/hyperactivity disorder. Neurosci Biobehav Rev 2016; 68:838-847.

57. Barkley RA: Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997; 121:65-94.

58. Kvickström P, Eriksson B, van Westen D, et al: Selective frontal neurodegeneration of the inferior fronto-occipital fasciculus in progressive supranuclear palsy (PSP) demonstrated by diffusion tensor tractography. BMC Neurol 2011; 11:13.

59. Brown AB, Biederman J, Valera EM, et al: Effect of dopamine transporter gene (SLC6A3) variation on dorsal anterior cingulate function in attention-deficit/hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 2010; 153:365-375.

60. Floresco SB, Magyar O: Mesocortical dopamine modulation of executive functions: beyond working memory. Psychopharmacology (Berl) 2006; 188:567-585.

61. Durston S, Fossella J, Casey B, et al: Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. Mol Psychiatry 2005; 10:678-685.

62. Berridge CW, Devilbiss DM, Andrzejewski ME, et al: Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. Biol Psychiatry 2006; 60:1111-1120.

63. Shang C, Lin H, Tseng W, et al: A haplotype of the dopamine transporter gene modulates regional homogeneity, gray matter volume, and visual memory in children with attention-deficit/hyperactivity disorder. Psychol Med 2018:1-11.

64. Frodl T, Skokauskas N: Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatr Scand 2012; 125:114-126.

65. Nakao T, Radua J, Rubia K, et al: Gray matter volume abnormalities in ADHD: voxel-based meta-analysis exploring the effects of age and stimulant medication. Am J Psychiatry 2011; 168:1154-1163.

66. Rubia K, Alegria AA, Cubillo AI, et al: Effects of stimulants on brain function in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Biol Psychiatry 2014; 76:616-628.

67. del Campo N, Fryer TD, Hong YT, et al: A positron emission tomography study of nigro-striatal dopaminergic mechanisms underlying attention: implications for ADHD and its treatment. Brain 2013; 136:3252-3270.

68. Low AM, Vangkilde S, le Sommer J, et al: Visual attention in adults with attention-deficit/hyperactivity disorder before and after stimulant treatment. Psychol Med 2018:1-9.

69. Crocker LD, Heller W, Warren SL, et al: Relationships among cognition, emotion, and motivation: implications for intervention and neuroplasticity in psychopathology. Front Hum Neurosci 2013; 7.

70. Hart H, Radua J, Nakao T, et al: Meta-analysis of functional magnetic resonance imaging studies of inhibition and attention in attention-deficit/hyperactivity disorder: exploring task-specific, stimulant medication, and age effects. JAMA Psychiatry 2013; 70:185-198.

71. Wittmann M, Leland DS, Paulus MP: Time and decision making: differential contribution of the posterior insular cortex and the striatum during a delay discounting task. Exp Brain Res 2007; 179:643-653.

72. Hare TA, Hakimi S, Rangel A: Activity in dlPFC and its effective connectivity to vmPFC are associated with temporal discounting. Front Neurosci 2014; 8:50.

73. Owens MM, Gray JC, Amlung MT, et al: Neuroanatomical foundations of delayed reward discounting decision making. Neuroimage 2017; 161:261-270.

74. Owens MM, Duda B, Sweet LH, et al: Distinct functional and structural neural underpinnings of working memory. Neuroimage 2018; 174:463-471.

75. Amso D, Scerif G: The attentive brain: insights from developmental cognitive neuroscience. Nat Rev Neurosci 2015; 16:606-619.

76. Working Group Report Chaired by Professor Sir Gabriel Horn. Brain Science, Addiction and Drugs. , Foresight Brain Science, Addiction and Drugs Project. London: Office of Science and Technology; 2008.

77. Meyer-Lindenberg A, Weinberger DR: Intermediate phenotypes and genetic mechanisms of psychiatric disorders. Nat Rev Neurosci 2006; 7:818-827.

78. Bourne JA: Unravelling the development of the visual cortex: implications for plasticity and repair. J Anat 2010; 217:449-468.

79. Cho SS, Koshimori Y, Aminian K, et al: Investing in the future: stimulation of the medial prefrontal

cortex reduces discounting of delayed rewards. Neuropsychopharmacology 2015; 40:546-553.

80. Caballero A, Granberg R, Tseng KY: Mechanisms contributing to prefrontal cortex maturation during adolescence. Neurosci Biobehav Rev 2016; 70:4-12.

81. Foulkes L, Blakemore S-J: Studying individual differences in human adolescent brain development. Nat Neurosci 2018; 21:315-323.

Author Affiliations: Institute of Science and Technology for Brain-Inspired Intelligence, Ministry of Education-Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence, Fudan University, Shanghai, China (Shen, Luo, Jia, Feng, Sahakian); State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Institute of Brain Science, Fudan University (Luo); Departments of Psychology and Psychiatry and the Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK (Sahakian); Medical Research Council - Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK (Desrivières, Quinlan, Schumann); School of Mathematical Sciences, Fudan University, Shanghai, China (Zhao); Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, Mannheim, Germany (Banaschewski, Millenet, Nees); Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin, Ireland (Bokde); University Medical Centre Hamburg-Eppendorf, Hamburg, Germany (Büchel); Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany (Flor, Nees); Department of Psychology, School of Social Sciences, University of Mannheim, Mannheim, Germany (Flor); NeuroSpin, Commissariat à L'énergie Atomique, Université Paris-Saclay, Gif-sur-Yvette, France (Frouin, Orfanos); Departments of Psychiatry and Psychology, University of Vermont, Burlington, USA (Garavan); Sir Peter Mansfield Imaging Centre School of Physics and Astronomy, University of Nottingham, University Park, Nottingham, UK (Gowland); Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité, Universitätsmedizin Berlin, Germany (Heinz, Walter); Physikalisch-Technische Bundesanstalt Braunschweig and Berlin, Germany (Ittermann); Institut National de la Santé et de la Recherche Médicale Unit 1000, Neuroimaging and Psychiatry, University Paris Sud–Paris Saclay, University Paris Descartes, Paris, France (Martinot, Artiges, Paillère-Martinot); Service Hospitalier Frédéric Joliot, Orsay, France (Martinot, Artiges); Maison de Solenn, Paris, France (Martinot); GH Nord Essonne Psychiatry Department, Orsay, France (Artiges); Assistance Publique–Hôpitaux de Paris, Department of Child and Adolescent Psychiatry, Pitié-Salpêtrière Hospital, Paris, France (Paillère-Martinot); Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, Ontario, Canada (Paus); Departments of Psychology and Psychiatry, University of Toronto, Toronto, Ontario, Canada (Paus); Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Centre Göttingen, Göttingen, Germany (Poustka); Clinic for Child and Adolescent Psychiatry, Medical University of Vienna, Währinger Gürtel, Vienna, Austria (Poustka); Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany (Fröhner, Smolka); School of Psychology and Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland (Whelan); Developmental and Behavioral Pediatric Department and Child Primary Care Department, Ministry of Education-Shanghai Key Lab for Children's Environmental Health, Xinhua Hospital Affiliated to Shanghai Jiaotong University

School of Medicine, Shanghai, China (Li, Sahakian); Department of Computer Science, University of Warwick, Coventry, UK (Feng); Collaborative Innovation Center for Brain Science, Fudan University, Shanghai, China (Feng).

Author Contributions: Mrs. Shen and Dr. Luo have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: Luo, Sahakian.

Acquisition, analysis, or interpretation of data: All authors.

Drafting the manuscript: Luo, Shen, Jia, Sahakian.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Shen, Luo, Jia, Zhao.

Obtained funding: Luo, Li, Feng.

Administrative, technical, or material support: Banaschewski, Bokde, Frouin, Büchel, Flor, Gowland, Ittermann, Martinot, Artiges, Nees, Orfanos, Tzourio, Whelan, Walter, Smolka, Fröhner, Heinz, Li, Paus, Garavan, Feng, Schumann.

Study supervision: Li, Schumann, Feng, Sahakian.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Group Information: The members of the IMAGEN Consortium are as follows: Tobias Banaschewski, MD, PhD, Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; Gareth Barker, PhD, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, England; Arun L.W. Bokde, PhD, Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland; Uli Bromberg, Dipl-Psych, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; Christian Büchel, MD, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany; Erin Burke Quinlan, PhD, Medical Research Council, Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, England; Sylvane Desrivières, PhD, Medical Research Council, Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, England; Herta Flor, PhD, Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, and Department of Psychology, School of Social Sciences, University of Mannheim, Mannheim, Germany; Vincent Frouin, PhD, NeuroSpin, CEA, Université Paris-Saclay, Gif-sur-Yvette, France; Hugh Garavan, PhD, Departments of Psychiatry and Psychology, University of Vermont, Burlington; Penny Gowland, PhD, Sir Peter Mansfield Imaging Centre School of Physics and Astronomy, University of Nottingham, University Park, Nottingham, United Kingdom; Andreas Heinz, MD, PhD, Department of Psychiatry and Psychotherapy, Charité, Universitätsmedizin Berlin, Berlin, Germany; Bernd Ittermann, PhD, Physikalisch-Technische Bundesanstalt, Braunschweig and Berlin, Germany; Jean-Luc Martinot, MD, PhD, Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 Neuroimaging and Psychiatry, University Paris Sud, University Paris Descartes–

Sorbonne Paris Cité and Maison de Solenn, Paris, France; Marie-Laure Paillère Martinot, MD, PhD, Maison de Solenn, Cochin Hospital, Paris, France; Eric Artiges, MD, PhD, Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 Neuroimaging and Psychiatry, University Paris Sud, University Paris Descartes–Sorbonne Paris Cité and Psychiatry Department, Orsay Hospital, Orsay, France; Herve Lemaitre, PhD, Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 Neuroimaging and Psychiatry, Faculté de Médecine, Université Paris-Sud, Le Kremlin-Bicêtre, and Université Paris Descartes, Sorbonne Paris Cité, Paris, France; Frauke Nees, PhD, Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, and Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; Dimitri Papadopoulos Orfanos, PhD, NeuroSpin, CEA, Université Paris-Saclay, Gif-sur-Yvette, France; Tomáš Paus, MD, PhD, Rotman Research Institute, Baycrest and Departments of Psychology and Psychiatry, University of Toronto, Toronto, Ontario, Canada; Luise Poustka, MD, Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Centre Göttingen, Göttingen, Germany, and Clinic for Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria; Sarah Hohmann, MD, Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; Sabina Millenet, Dipl-Psych, Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; Juliane H. Fröhner, Dipl-Psych, Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany; Michael N. Smolka, MD, Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany; Henrik

Walter, MD, PhD, Department of Psychiatry and Psychotherapy, Charité, Universitätsmedizin Berlin, Berlin, Germany; Robert Whelan, PhD, School of Psychology and Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland; and Gunter Schumann, MD, Medical Research Council–Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, England.

Table 1. Characteristics of the study population in the IMAGEN cohort

	Baseline (n=1,963)	2 years' follow-up (n=1,518)
Male	952 (48.5%)	728 (48.0%)
Age (year), mean ± SD	14.43±0.40	16.47±0.57
H-I subscale on parent SDQ		
Total score	2.97±2.29	2.39±2.05
Hyperactivity/impulsivity Score	0.70±1.05	0.47±0.87
Inattention Score	2.27±1.65	1.92±1.57
ADHD categories by H-I total score		
Normal [a]	1,690 (86.1%)	1,394 (91.8%)
Borderline [b]	107 (5.5%)	64 (4.1%)
Abnormal [c]	166 (8.5%)	62 (4.1%)
Delay discounting	-1.98±0.61	-
Working memory	19.45±14.00	-
Intra-subject variability [d]	119.38±30.96	
Stop signal reaction time [d]	186.43±61.90	

Note. H-I = hyperactivity-inattention.

a: Individuals with H-I total score less than 6.

b: Individuals with H-I total score equal to 6.

c: Individuals with H-I total score greater than 6.

d: n=1,846.

Table 2. Associations of neuropsychological variables with ADHD symptoms and GMV of the significant clusters

	ADHD symptom [a]						GMV [b]			
	Total score		Hyperactivity/impulsivity		Inattention		Prefrontal cluster		Posterior-occipital cluster	
	r	95% CI [c]	r	95% CI [c]	r	95% CI [c]	r	95% CI [c]	r	95% CI [c]
WM [d]	0.19***	[0.15,0.24]	0.09***	[0.05,0.14]	0.21***	[0.16,0.25]	-0.04	[-0.08,0.01]	-0.08***	[-0.12,-0.03]
DD [d]	0.13***	[0.08,0.17]	0.06**	[0.02,0.11]	0.14***	[0.09.0.18]	-0.07**	[-0.11,-0.02]	-0.06*	[-0.10,-0.01]
ISV [c]	0.14***	[0.10,0.19]	0.09***	[0.04,0.14]	0.14***	[0.10,0.19]	-0.05*	[-0.10,-0.01]	-0.06**	[-0.11,-0.01]
WM corrected for DD and ISV	0.16***	[0.12,0.21]	0.07**	[0.03,0.12]	0.18***	[0.13,0.22]	-0.04	[-0.09,0.005]	-0.07**	[-0.11,-0.02]
DD corrected for WM and ISV	0.10***	[0.05,0.15]	0.05*	[0.001,0.10]	0.11***	[0.06,0.15]	-0.05*	[-0.09,-0.002]	-0.05*	[-0.09, -3.3e-4]
ISV corrected for WM and DD	0.12***	[0.08,0.17]	0.08**	[0.03,0.13]	0.12***	[0.07,0.16]	-0.04	[-0.09,0.005]	-0.05*	[-0.10,-0.01]

Note. GMV = gray matter volume. WM = working memory. DD = delay discounting. ISV = intra-subject variability. SSRT = stop signal reaction time.

a: Adjusted for age, sex and site.

b: Adjusted for age, sex, handedness, site and TIV.

c: Confidence interval was estimated by bootstrap 5,000 times.

d: n=1,963.

e: n=1,846.

*, p<0.05; **, p<0.01; ***, p<0.001.

Table 3. Hierarchical multiple regression of WM, DD, ISV and GMV of the significant clusters on inattention at age 16 (n=1,421)

		Independent Variables	R^2	ΔR^2	p_e [a]	β_f [b]	t_f [c]	p_f [d]
Step 1	Covariates	Sex	0.412	0.412	<0.001	0.073	2.86	0.004
		Handedness				0.016	0.79	0.430
		TIV				0.010	0.375	0.708
		Inattention at 14				0.608	28.45	<0.001
		Site1				0.018	0.66	0.508
		Site2				0.050	1.80	0.072
		Site3				0.068	2.57	0.010
		Site4				0.065	2.47	0.014
		Site5				0.010	0.36	0.721
		Site6				0.038	1.44	0.151
		Site7				0.036	1.37	0.170
Step 2	Behavior	WM	0.414	0.002	0.017	0.044	2.04	0.042
Step 3		DD	0.414	0.000	0.593	0.007	0.35	0.724
Step 4		IRV	0.415	0.001	0.164	0.028	1.31	0.190
Step 5	Brain structure	GMV in prefrontal	0.415	0.000	0.685	0.047	1.88	0.060
Step 6		GMV in posterior-occipital	0.42	0.005	<0.001	-0.083	-3.55	<0.001

Note. WM = working memory. DD = delay discounting. ISV = intra-subject variability. GMV = gray matter volume.

a: p value of ΔR^2.

b: standardized β in the final model.

c: t value of the regression coefficient in the final model.

d: p value of the regression coefficient in the final model.

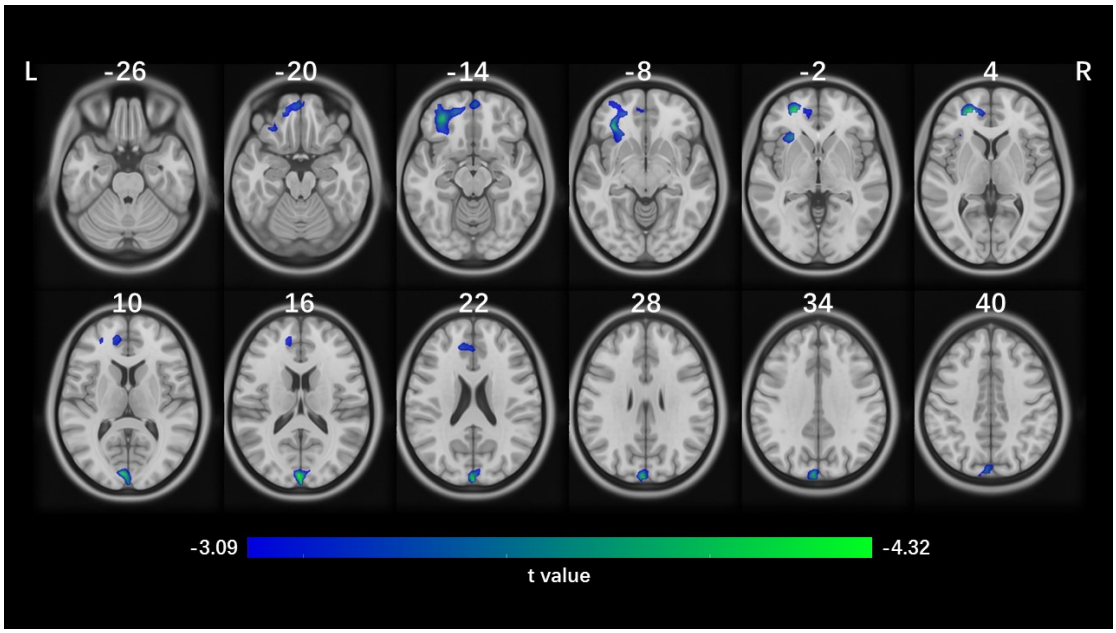

Figure 1. **Significant brain clusters associated with ADHD total score in a population-based cohort.** The results were given by a voxel-wise whole brain analysis using the IMAGEN cohort at the age of 14 years (n=1,963). Age, sex, handedness, TIV and site were used as covariates. An uncorrected $p<0.001$ at voxel-level, with a cluster-level family-wise error (FWE; $p<0.05$) was applied to identify significant clusters. Two clusters were found negatively associated with ADHD total score: the prefrontal cluster (x=-19.5, y=49.5, z=3, 3,357 voxels; peak t_{1950}=-4.29, cluster-level pFWE<0.001), and the posterior-occipital cortex (x=-1.5, y=91.5, z=15, 1,295 voxels; peak t_{1950}=-4.32, cluster-level pFWE=0.025). No clusters were found positively associated with ADHD total score.

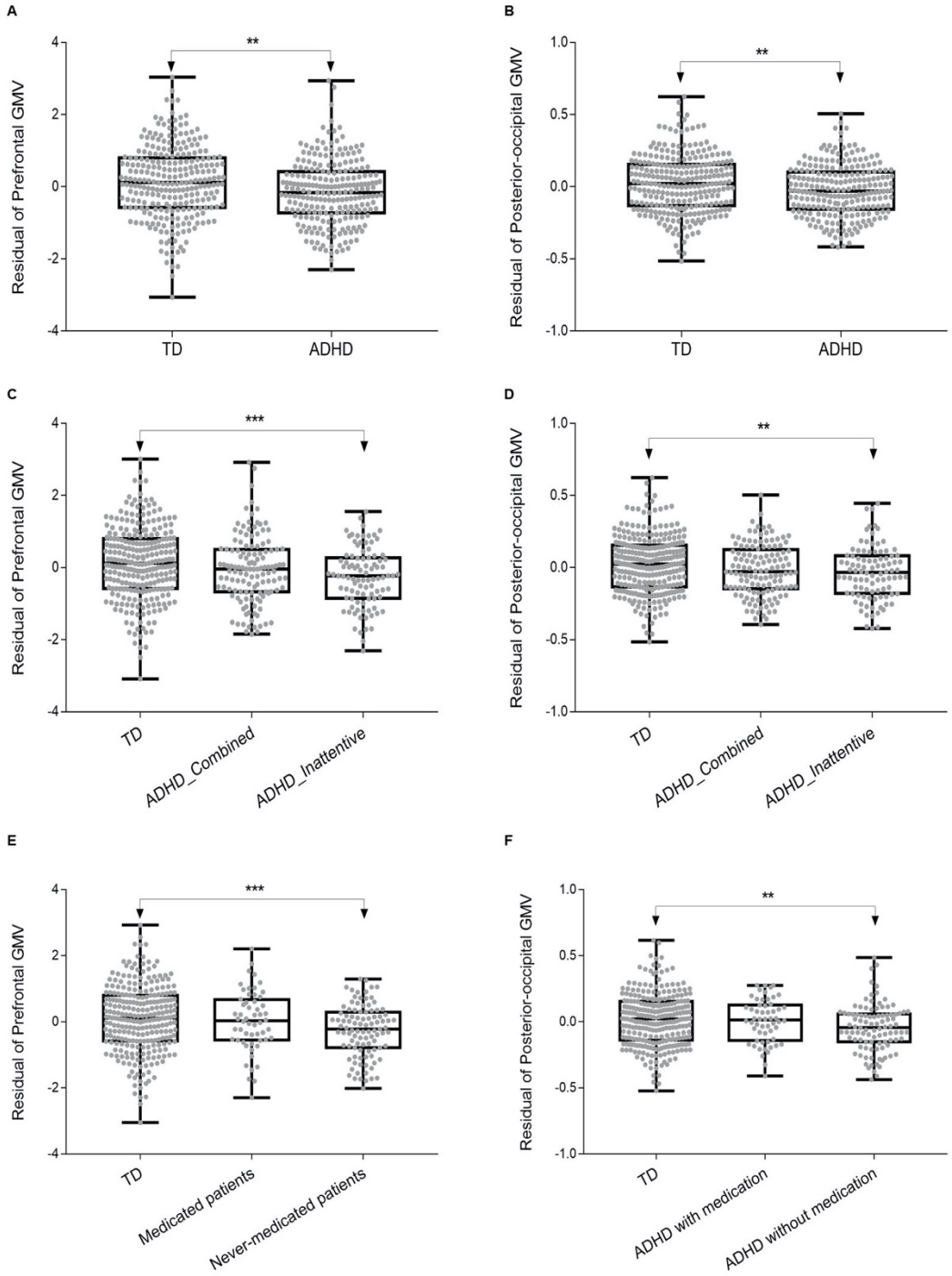

Figure 2. **Group comparison of gray matter volume of the identified clusters in a clinical cohort.** The results were based on the ADHD-200 cohort. Y axis was the residual of gray matter volume (GMV) of the identified clusters regressed on age, sex, handedness, TIV and site. A. Difference of GMV of the prefrontal cluster between controls (n=267) and ADHD patients (n=233). B. Difference of GMV of the posterior-occipital cluster between controls (n=267) and ADHD patients (n=233). C. Difference of GMV

of the prefrontal cluster among controls (n=267), ADHD with combined subtype (n=129) and ADHD with inattentive subtype (n=96). D. Difference of GMV of the posterior-occipital cluster among controls (n=267), ADHD with combined subtype (n=129) and ADHD with inattentive subtype (n=96). E. Difference of GMV of the prefrontal cluster among controls (n=267), medicated patients (n=56) and never-medicated patients (n=99). F. Difference of GMV of the posterior-occipital cluster among controls (n=267), medicated patients (n=56) and never-medicated patients (n=99). Bottom and top of the box are the minimum and maximum, and the band near the middle of the box is the median. **, $p<0.01$; ***, $p<0.001$.