Archival Report

Biological Psychiatry

Inattention and Reaction Time Variability Are Linked to Ventromedial Prefrontal Volume in Adolescents

Matthew D. Albaugh, Catherine Orr, Bader Chaarani, Robert R. Althoff, Nicholas Allgaier, Nicholas D'Alberto, Kelsey Hudson, Scott Mackey, Philip A. Spechler, Tobias Banaschewski, Rüdiger Brühl, Arun L.W. Bokde, Uli Bromberg, Christian Büchel, Anna Cattrell, Patricia J. Conrod, Sylvane Desrivières, Herta Flor, Vincent Frouin, Jürgen Gallinat, Robert Goodman, Penny Gowland, Yvonne Grimmer, Andreas Heinz, Viola Kappel, Jean-Luc Martinot, Marie-Laure Paillère Martinot, Frauke Nees, Dimitri Papadopoulos Orfanos, Jani Penttilä, Luise Poustka, Tomáš Paus, Michael N. Smolka, Maren Struve, Henrik Walter, Robert Whelan, Gunter Schumann, Hugh Garavan, and Alexandra S. Potter

ABSTRACT

BACKGROUND: Neuroimaging studies of attention-deficit/hyperactivity disorder (ADHD) have most commonly reported volumetric abnormalities in the basal ganglia, cerebellum, and prefrontal cortices. Few studies have examined the relationship between ADHD symptomatology and brain structure in population-based samples. We investigated the relationship between dimensional measures of ADHD symptomatology, brain structure, and reaction time variability—an index of lapses in attention. We also tested for associations between brain structural correlates of ADHD symptomatology and maps of dopaminergic gene expression.

METHODS: Psychopathology and imaging data were available for 1538 youths. Parent ratings of ADHD symptoms were obtained using the Development and Well-Being Assessment and the Strengths and Difficulties Questionnaire (SDQ). Self-reports of ADHD symptoms were assessed using the youth version of the SDQ. Reaction time variability was available in a subset of participants. For each measure, whole-brain voxelwise regressions with gray matter volume were calculated.

RESULTS: Parent ratings of ADHD symptoms (Development and Well-Being Assessment and SDQ), adolescent self-reports of ADHD symptoms on the SDQ, and reaction time variability were each negatively associated with gray matter volume in an overlapping region of the ventromedial prefrontal cortex. Maps of *DRD1* and *DRD2* gene expression were associated with brain structural correlates of ADHD symptomatology.

CONCLUSIONS: This is the first study to reveal relationships between ventromedial prefrontal cortex structure and multi-informant measures of ADHD symptoms in a large population-based sample of adolescents. Our results indicate that ventromedial prefrontal cortex structure is a biomarker for ADHD symptomatology. These findings extend previous research implicating the default mode network and dopaminergic dysfunction in ADHD.

Keywords: Attention-deficit/hyperactivity disorder, Inattention, Multi-informant, Neuroimaging, Reaction time variability, Ventromedial prefrontal cortex

http://dx.doi.org/10.1016/j.biopsych.2017.01.003

Attention-deficit/hyperactivity disorder (ADHD) is among the most prevalent neuropsychiatric disorders in youths, with approximately 3% to 7% of school-aged children meeting diagnostic criteria (1). Longitudinal studies indicate that functionally impairing symptoms continue into adolescence and adulthood in approximately 60% to 80% of cases diagnosed during childhood (2,3). Extant morphometry studies on ADHD have implicated a number of anatomically related brain areas; however, findings have been inconsistent, with no common structural abnormality emerging across studies. In adults and youths, structural abnormalities have been reported in the basal ganglia (4–10), prefrontal cortex (PFC) (10–12), cerebellum (5,10,13,14), and anterior cingulate cortex (15) and less frequently reported in the hippocampus, amygdala, and thalamus (16,17). Several factors, however, may obscure underlying brain-behavior relationships in the study of ADHD symptomatology, including the use of categorical diagnoses, the lack of multi-informant behavioral ratings, and small sample sizes. To aptly characterize the neuroanatomical substrates of ADHD symptomatology, it is critical to demonstrate convergence across dimensional,

ISSN: 0006-3223

multi-informant behavioral data using large population-based samples. If possible, findings should also demonstrate convergence with other established features of ADHD symptomatology across different domains, including measures of cognition as well as neurochemistry.

Over the last few decades, empirically based assessment of psychopathology has revealed aspects of dimensionality with regard to many psychiatric conditions, including ADHD (18). Such findings have been difficult to reconcile with the categorical taxonomy espoused by DSM. Although numerous studies have tested for brain differences between ADHD patients and typically developing control subjects, few studies have investigated brain correlates of attention problems in the general population. Following from a dimensional conceptualization of psychopathology, it is reasonable to postulate that both clinical and normative levels of a given psychiatric syndrome will be underpinned by overlapping neural substrates. Mous *et al.* (19) recently reported that cortical thickness in bilateral postcentral gyri was negatively associated with parent-reported attention problems in a population-based sample of 444 6- to 8-year-old children. Ducharme *et al.* (20) found that subclinical attention problems in typically developing youths 6 to 18 years old were associated with a decreased rate of cerebral cortical thinning within prefrontal and parietal cortical regions—brain areas that have been implicated in the pathophysiology of clinically significant attention problems (i.e., ADHD) (21,22). Similarly, Shaw *et al.* (23) reported an association between subclinical symptoms of hyperactivity and impulsivity in typically developing youths and delayed cortical thickness maturation. Such evidence supports the use of dimensional measures of psychopathology, as emphasized by the National Institute of Mental Health Research Domain Criteria program (24). Taken together, there is compelling evidence that subclinical variation in ADHD symptoms is tied to brain structure and development and that these associations may be obfuscated by a strict categorical DSM approach.

In the assessment of developmental psychopathology, informants represent an important source of variance (18). The current DSM taxonomy does not offer clear, standardized methods for synthesizing reports from multiple informants. Martel *et al.* (25) recently reported that information from multiple informants increases the validity of assessing ADHD and that averaging ratings is the optimal method for integrating multi-informant data. Dimensional ratings from multiple informants also allow for more sophisticated methods of integrating data, such as latent variable approaches. Unfortunately, few neuroimaging studies have used dimensional assessments of ADHD symptoms from multiple informants.

In addition to using quantitative, multi-informant behavioral ratings, we aimed to demonstrate convergence across different domains with measures previously associated with ADHD symptomatology. Reaction time variability refers to the degree of intraindividual variation in responding to a target stimulus, and increased reaction time variability on attention tasks has been commonly reported in youths with ADHD (26,27). Lesion studies indicate that frontal lobe damage is accompanied by increased reaction time variability (28). There is also evidence that individual differences in reaction time variability predict inhibitory success (29). Furthermore, subjects with increased reaction time variability exhibit greater activation within inhibitory regions of the brain during tasks of response inhibition (29). Thus, reaction time variability may serve as an objective neurocognitive marker for ADHD symptomatology. However, it remains unclear the extent to which such cognitive measures are related to parent and self-report ratings of ADHD symptoms as well as brain structure in the general population.

Finally, patterns of gene expression may provide additional support in identifying potential brain-based markers for ADHD symptomatology. The brain's dopaminergic system has been strongly implicated in a wide variety of cognitive functions, including attention, and repeatedly linked to the pathophysiology of ADHD symptomatology. Indeed, some medications that have proven efficacious in the treatment of ADHD work by blocking dopamine reuptake and/or stimulating dopamine release, increasing extracellular dopamine levels. It is reasonable to postulate that regions of the brain that are volumetrically related to ADHD symptomatology will be tied to the expression of genes encoding for dopaminergic receptors.

In this article, we investigate the relationship between dimensional measures of ADHD symptomatology and brain structure in a large population-based sample of adolescents, using multi-informant behavioral ratings. In a subset of participants, we also investigate relationships between reaction time variability, measures of ADHD symptomatology, and brain structure. Finally, using publicly available gene expression data collected as part of the Allen Human Brain Atlas (30), we test the extent to which the relationship between brain structure and ADHD symptomatology is correlated with patterns of dopaminergic gene expression. To our knowledge, this study represents the first voxel-based morphometry (VBM) of ADHD symptomatology using a population-based sample of youths.

METHODS AND MATERIALS

Sample

Neuroimaging and behavioral data were obtained from the IMAGEN study conducted across eight European sites in France, the United Kingdom, and Germany, which includes 2223 adolescents recruited from schools at 14 years of age (SD 0.41 year; age range, 12.9–15.7 years). A detailed description of recruitment and assessment procedures has been published elsewhere (31). The present study included 1538 participants with multi-informant psychopathology data, quality-controlled neuroimaging data, and complete demographic data (Table 1). Behavioral data for the stop signal task (SST) were available in only a subset of participants (n = 767).

Psychopathology Assessment

The Development and Well-Being Assessment (DAWBA) (32) is a computer-based package of questionnaires, interviews, and rating techniques used to assess adolescent psychopathology. In the present study, ADHD symptom counts were derived from the parent version of the DAWBA—youths did not complete the DAWBA ADHD module. In addition to total symptom count, the parent version of the DAWBA yielded separate symptom counts for both hyperactivity/impulsivity and inattention.

Table 1. Summary of Statistics for Predictor Variables

Variable	Value
Age, Years, Mean (SD)	14.53 (0.41)
Gender, F/M, *n* (%)	785 (51%)/753 (49%)
SES, Mean (SD)	17.80 (4.06)
Verbal IQ, Mean (SD)	110.94 (14.88)
Performance IQ, Mean (SD)	108.16 (14.87)
DAWBA Symptom Count, Mean (SD)	4.05 (5.79)
H/I Score on Parent SDQ, Mean (SD)	2.94 (2.27)
H/I Score on Youth SDQ, Mean (SD)	3.94 (2.15)
Reaction Time Variability, Mean (SD)	101.49 (24.96) (n = 767)

N = 1538 unless otherwise noted.

DAWBA, Development and Well-Being Assessment; F, female; H/I, hyperactive/inattentive scale; M, male; SDQ, Strengths and Difficulties Questionnaire; SES, socioeconomic status.

Self-report and parent report versions of the Strengths and Difficulties Questionnaire (SDQ) were also used to assess symptoms of hyperactivity and inattention (33). In addition to the hyperactive/inattentive scale, the emotional scale on the youth SDQ was used to assess mood and anxiety symptoms. The SDQ is a reliable and valid measure of youth emotional and behavior symptoms, on which scores are predictive of increased probability of clinician-rated psychiatric disorders and retest stability over 4 to 6 months (34).

Behavioral Measures

Behavioral data from the functional imaging SST were used in the present study. Associations were tested between ADHD symptom scores (DAWBA and SDQ) and several SST measures, including mean reaction time, stop signal reaction time, and reaction time variability. SD of "Go" reaction time on the SST was used to assess reaction time variability in participants.

Demographic Measures

The Puberty Development Scale was used to assess the pubertal status of participants (35). The socioeconomic status score was derived by summing the following variables: mother's education score, father's education score, family stress unemployment score, financial difficulties score, home inadequacy score, neighborhood score, financial crisis score, mother employed score, and father employed score (36).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was conducted at the eight IMAGEN assessment sites using 3T whole-body MRI systems (31). See the Supplement for further details.

Structural MRI

High-resolution anatomical MRI scans were acquired with a three-dimensional T1-weighted magnetization prepared rapid acquisition gradient-echo sequence based on the Alzheimer's Disease Neuroimaging Initiative protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/).

MRI Data Preprocessing

Preprocessing of the structural T1-weighted data was performed with SPM8 (Wellcome Department of Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), using standard automated pipelines (31). See the Supplement for details.

Statistical Analyses

Whole-brain voxelwise analyses were conducted using the general linear model performed with the VBM toolbox of SPM8. Age, gender, total gray matter volume (GMV), site, pubertal development, performance IQ, verbal IQ, and socioeconomic status were controlled for in each model. For all analyses, an initial height threshold of $p \leq .005$ was implemented at the voxel level, with a corrected familywise error ($p \leq .05$) subsequently applied to identify significant clusters. For the VBM analyses outlined below, results were not meaningfully altered when adopting an initial height threshold of $p \leq .001$.

Latent Variable Analysis

Latent variable analysis has been proposed as a powerful method for incorporating multi-informant reports of psychopathology as predictor variables in regression modeling (37). In the present study, confirmatory factor analysis was carried out using the package lavaan in R (38). In particular, a latent ADHD symptom variable was derived from the observed multi-informant measures. Observed measures included parent reports and self-reports of ADHD symptoms on the SDQ and ADHD symptom counts based on the parent version of the DAWBA.

Gene Expression

Relationships between the structural correlates of ADHD symptomatology and gene expression were examined. To test for associations between gene expression and brain structural correlates of ADHD symptoms, we used a brain map derived from regressions between GMV and the mean composite of multi-informant behavioral ratings. This decision was based on previous research indicating that averaging symptom ratings across multiple informants appears optimal relative to other approaches such as structural equation modeling (25). The unthresholded t statistic map, resulting from regressing regional GMV against the mean composite of multi-informant ratings, was subsequently tested for associations with patterns of gene expression. Using the alleninf toolbox (39) and gene expression data collected for the Allen Human Brain Atlas (30), we tested for an association with several dopaminergic genes that have been previously implicated in ADHD symptomatology: *DRD1*, *DRD2*, and *DRD4*. In brief, the toolbox extracts the Montreal Neurological Institute coordinates of each gene expression sampling site, draws a spherical region of interest (r = 4 mm), and averages values of the statistical map within each spherical region of interest. Average region of interest values are then correlated with normalized gene expression values. Further details can be found elsewhere (39).

Table 2. Bivariate Correlations Between Behavioral and Cognitive Measures of ADHD Symptoms

Measure		Parent SDQ	DAWBA	Reaction Time Variability	Composite ADHD	Latent Variable
Youth SDQ	Pearson correlation	.430	.359	.139	.736	.518
	sig (two-tailed)	$p < .001$	$p < .001$	$p < .001$	$p < .001$	$p < .001$
	n	1538	1538	767	1538	1538
Parent SDQ	Pearson correlation		.661	.139	.861	.973
	sig (two-tailed)		$p < .001$	$p < .001$	$p < .001$	$p < .001$
	n		1538	767	1538	1538
DAWBA	Pearson correlation			.108	.832	.802
	sig (two-tailed)			$p < .005$	$p < .001$	$p < .001$
	n			767	1538	1538
Reaction Time Variability	Pearson correlation				.159	.149
	sig (two-tailed)				$p < .001$	$p < .001$
	n				767	767
Composite ADHD	Pearson correlation					.944
	sig (two-tailed)					$p < .001$
	n					1538

Table displays Pearson correlation values and respective significance levels.

ADHD, attention-deficit/hyperactivity disorder; DAWBA, Development and Well-Being Assessment; SDQ, Strengths and Difficulties Questionnaire; sig, significance.

RESULTS

Demographic and Behavioral Measures

Demographic information for participants is provided in Table 1. Correlations between multi-informant ratings (including mean composite and latent ADHD measures) and reaction time variability are listed in Table 2.

Both parent and youth ratings of ADHD symptoms were inversely correlated with socioeconomic status (range, $r = -.095$ to $-.193$) as well as performance and verbal IQ (range, $r = -.107$ to $-.231$). In addition, parent ADHD ratings on the DAWBA and SDQ were inversely correlated with pubertal stage (range, $r = -.107$ to $-.112$). Boys, on average, possessed significantly higher ADHD symptom ratings on the DAWBA ($t = 5.86$, $p < .001$) and parent SDQ ($t = 6.66$, $p < .001$).

Imaging Analyses

DAWBA Symptom Count. Regressing regional GMV against total ADHD symptom count—based on parent reporting on the DAWBA—revealed a negative association in bilateral ventromedial PFCs (vmPFCs) and orbital lateral PFC (3424 voxels, x = −4, y = 30, z = −20; peak *Z* score = 4.12) (Figures 1 and 2). The effect size for this association was $f^2 = 0.01$. No other associations survived correction for multiple comparisons.

Follow-up analyses were conducted using hyperactive/impulsive and inattentive symptom counts on the DAWBA. Hyperactive/impulsive and inattentive symptom counts on the DAWBA were positively correlated ($r = .57$, $p = 2.93 \times 10^{-130}$). When analyzed separately, inattentive symptoms were negatively associated with GMV in bilateral vmPFCs and left orbital lateral PFC (2906 voxels, x = −4, y = 28, z = −20; peak *Z* score = 4.58), and hyperactive/impulsive symptoms were negatively associated with gray matter in the left superior temporal gyrus, left posterior insula, and left parietal operculum (2006 voxels, x = −63, y = −16, z = 4; peak *Z* score = 4.16) (Figure 2). No other associations survived correction for multiple comparisons. Results were not altered when covarying for self-reported mood and anxiety symptoms on the SDQ.

Parent SDQ. Regression analysis revealed a negative association between the hyperactivity/inattention subscale score on the parent version of the SDQ and GMV in bilateral vmPFCs (1887 voxels, x = 10, y = 38, z = −15; peak *Z* score = 4.86) (Figures 1 and 2). The effect size for this association was $f^2 = 0.01$. No other associations survived correction for multiple comparisons. Again, results were not changed when controlling for self-reported mood and anxiety symptoms on the SDQ.

Youth SDQ. Regressing regional GVM against the hyperactivity/inattention subscale score on the youth self-report version of the SDQ revealed a negative association in bilateral vmPFCs and right orbital lateral PFC (2576 voxels, x = 9, y = 33, z = −15; peak *Z* score = 3.73) (Figure 1). The effect size for this association was $f^2 = 0.02$. No other associations survived correction for multiple comparisons. Results were not changed when controlling for self-reported mood and anxiety symptoms on the SDQ.

Latent Variable. Regional GMV was regressed against factor loadings on the latent ADHD symptom variable, derived using confirmatory factor analysis. Factor loadings on the latent variable were negatively associated with GMV in bilateral vmPFCs (3210 voxels, x = 9, y = 33, z = −17; peak *Z* score = 4.96) (Supplemental Figure S1). The effect size for this association was $f^2 = 0.01$. The Dice similarity coefficient (DSC) was calculated to quantify the spatial overlap between results obtained using the latent ADHD variable and each of the three

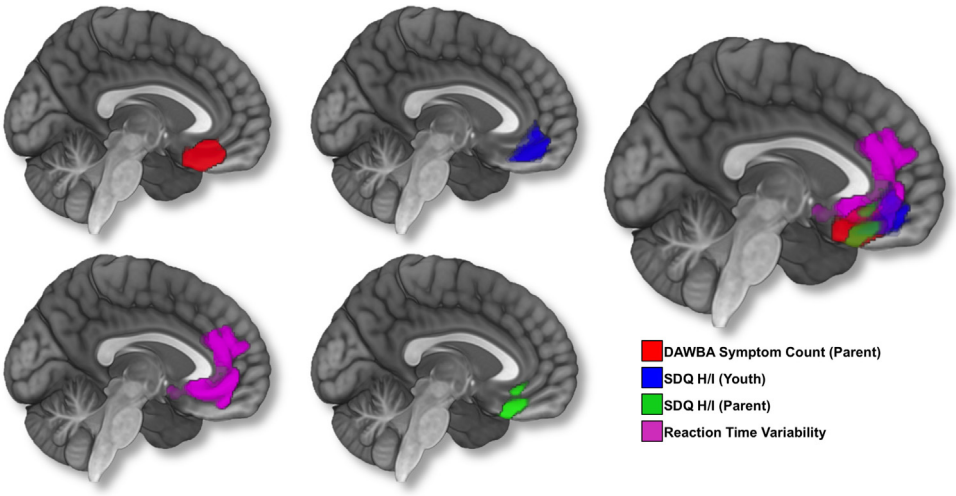

Figure 1. Results from whole-brain voxelwise analyses. Age, gender, total gray matter volume, site, pubertal development, performance IQ, verbal IQ, and socioeconomic status were controlled for in the analyses. An initial height threshold of $p \leq .005$ was implemented at the voxel level, with a corrected familywise error ($p \leq .05$) subsequently applied to identify significant clusters. To visualize overlap in findings, the image on the right is a composite of all associations. DAWBA, Development and Well-Being Assessment; H/I, hyperactive/inattentive scale; SDQ, Strengths and Difficulties Questionnaire.

ADHD behavioral rating measures described above (DAWBA, parent SDQ, youth SDQ). Based on image validation literature, a good overlap occurs with a DSC >0.70 (40). The DSC was high when comparing results obtained with the latent ADHD variable and both the DAWBA and the parent SDQ (0.72 and 0.73, respectively); however, the DSC was considerably lower when comparing with the youth SDQ (0.29).

Supplemental Figure S1 depicts the relationship between regional GMV and the confirmatory factor analysis–derived latent ADHD variable as well as a composite ADHD score calculated by averaging across multi-informant data on the SDQ and DAWBA. The correlation between the confirmatory factor analysis–derived latent ADHD variable and the composite ADHD score was very high ($r = .94$, $p < .001$). Again, the DSC was calculated to quantify the spatial overlap between the multi-informant averaging method and the latent variable approach. The DSC for the two maps was equal to 0.71.

SST. Mean reaction time and stop signal reaction time were not related to measures of ADHD symptomatology. However, each measure of ADHD symptomatology was positively correlated with reaction time variability ($r = .11$ to $.14$) (Table 2). Regressing regional GMV against reaction time variability in a subset of participants with available behavioral data ($n = 767$) revealed a negative association in bilateral medial PFCs, including dorsal portions of the anterior cingulate gyrus (5007 voxels, x = 9, y = 50, z = 12; peak Z score = 3.85). The effect size for this association was $f^2 = 0.03$. No other associations survived correction for multiple comparisons (Figure 1). Figure 3 depicts the region in which GMV was negatively associated with reaction time variability as well as all three of the behavioral rating measures (center of gravity for region of overlap, x = 3.13, y = 34.42, z = −14.84).

Gene Expression

The statistical map resulting from regressing regional GMV against the mean composite of multi-informant ratings (Supplemental Figure S2) was associated with *DRD1* ($r = -.27$, $p = 2.0 \times 10^{-54}$) and *DRD2* ($r = .09$, $p = 1.9 \times 10^{-7}$) expression (Figures 4 and 5). *DRD4* expression was not associated with brain areas that were related to ADHD symptomatology.

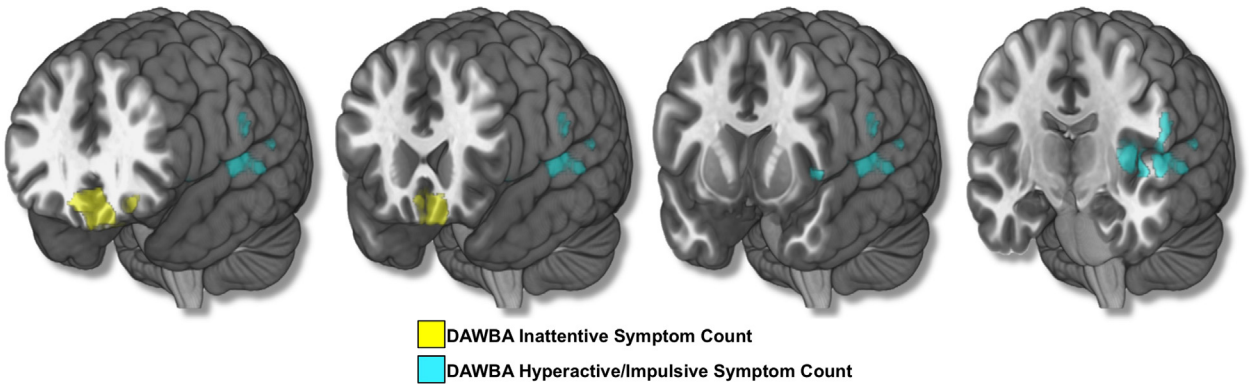

Figure 2. Results from whole-brain voxelwise analyses using hyperactive/impulsive and inattentive symptom counts. Age, gender, total gray matter volume, site, pubertal development, performance IQ, verbal IQ, and socioeconomic status were controlled for in the analyses. An initial height threshold of $p \leq .005$ was implemented at the voxel level, with a corrected familywise error ($p \leq .05$) subsequently applied to identify significant clusters. DAWBA, Development and Well-Being Assessment.

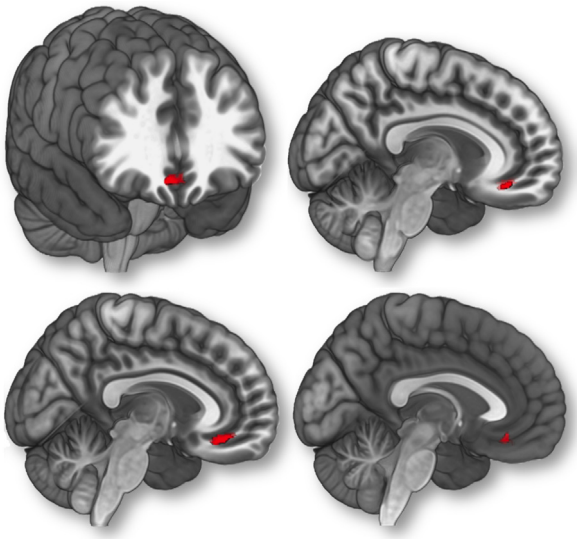

Figure 3. Region of overlap between parent Development and Well-Being Assessment, parent Strengths and Difficulties Questionnaire, youth Strengths and Difficulties Questionnaire, and reaction time variability is illustrated. Age, gender, total gray matter volume, site, pubertal development, performance IQ, verbal IQ, and socioeconomic status were controlled for in the analyses. An initial height threshold of $p \leq .005$ was implemented at the voxel level, with a corrected familywise error ($p \leq .05$) subsequently applied to identify significant clusters.

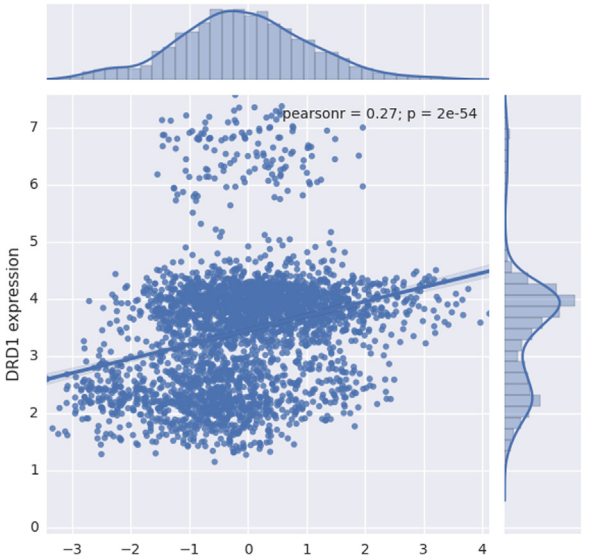

Figure 4. Scatterplot depicting the relationship between normalized gene expression values (y axis) and *t* statistic value (x axis) corresponding to the association between gray matter volume and multi-informant average of attention-deficit/hyperactivity disorder symptoms. Positive *t* values indicate an inverse association between gray matter volume and symptoms, whereas negative *t* values represent a positive association between gray matter volume and attention-deficit/hyperactivity disorder symptomatology.

DISCUSSION

To our knowledge, this is the largest population-based structural imaging study on ADHD symptomatology to date. Parent and youth ratings of ADHD symptoms all were negatively associated with GMV in an overlapping portion of the vmPFC. Critically, our findings were not changed when measures of mood and anxiety symptoms were controlled for in analyses. When analyzing hyperactivity/impulsivity and inattention symptom counts separately, we found that inattention symptoms were associated with reduced volume in bilateral vmPFCs, whereas hyperactive/impulsive symptoms were related to reduced GMV in the left superior temporal gyrus, parietal operculum, and posterior insula. Thus, reduced GMV in vmPFCs appears to be particularly tied to aspects of inattentive symptoms in adolescents. In line with this interpretation, we found that reaction time variability—posited to reflect lapses in attention as opposed to hyperactivity—was negatively associated with GMV in an overlapping region of the vmPFC. Given convergence across dimensional, multi-informant behavioral ratings and a measure of neurocognitive functioning that has been previously tied to ADHD, our findings indicate that vmPFC structure is a brain-based marker for attention problems in adolescents.

In the largest VBM study to date on adult ADHD, a significant negative correlation was revealed between vmPFC GMV and dimensional measures of ADHD symptomatology (41). Specifically, when analyzing patients and control subjects together, the authors found an inverse relationship between dimensional measures of ADHD symptomatology and vmPFC GMV. Inattentive symptoms, in particular, were negatively correlated with GMV in the vmPFC (41). Strikingly, the findings of Maier *et al.* (41) largely overlap with the results of the present study. Taken together, reduced GMV in the vmPFC may serve as a marker for attention problems in both adolescent and adult populations.

Increased reaction time variability on tasks of vigilant attention has been a common finding when comparing children with ADHD with typically developing control subjects (26,27). This finding has led other authors to hypothesize that increased reaction time variability is tied to aberrant default mode network (DMN) activity (42). In particular, the default mode interference hypothesis posits that activity in the DMN, which is typically attenuated during goal-directed tasks, can persist into periods of task-related processing and, as a result, compete with task-specific neural processing (42). The vmPFC represents a primary hub in the DMN of the brain—a network posited to play a central role in mind wandering and task-unrelated thought. Although speculative, it is possible that the volumetric reductions in the vmPFC may be linked to DMN dysfunction. In a recent study by Salavert *et al.* (43), participants with ADHD exhibited reduced deactivation of the medial PFC during a working memory task. The authors suggest that failure to deactivate the medial PFC is tied to lapses of attention and that this may be a central feature of ADHD symptomatology. It is possible that findings in the present study are tied to DMN dysfunction, and, more specifically, reduced vmPFC GMV may be related to an impaired ability to deactivate portions of the DMN. Future studies are needed to test this possibility.

It is noteworthy that despite modest correlations between multi-informant behavioral ratings ($r = .36$ to $.66$), we observed striking convergence with regard to brain structural correlates. Similarly, reaction time variability was modestly correlated with

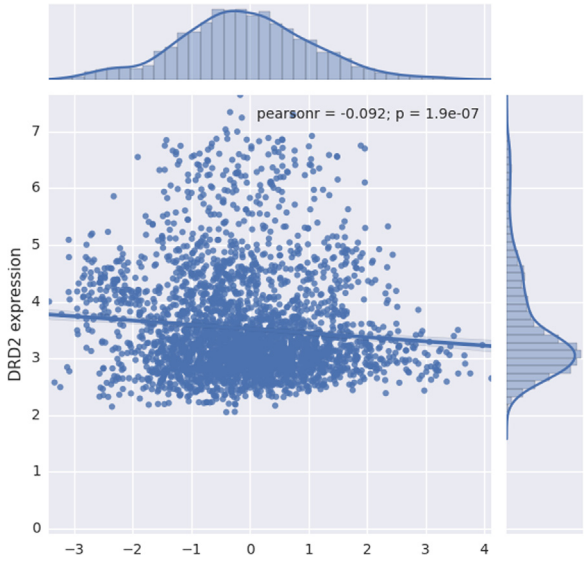

Figure 5. Scatterplot depicting the relationship between normalized gene expression values (y axis) and *t* statistic value (x axis) corresponding to the association between gray matter volume and multi-informant average of attention-deficit/hyperactivity disorder symptoms. Positive *t* values indicate an inverse association between gray matter volume and symptoms, whereas negative *t* values represent a positive association between gray matter volume and attention-deficit/hyperactivity disorder symptoms.

behavioral ratings of ADHD symptomatology (r = .11 to .14), and, again, we observed considerable overlap with regard to anatomical correlates. These findings suggest that the vmPFC is tied to parental and youth self-reports of ADHD symptomology, as well as to an objective behavioral measure of ADHD symptomology (i.e., reaction time variability).

In the present study, two different methods were used to analyze multi-informant ratings of adolescent attention problems. First, a composite ADHD symptom score was created by averaging multi-informant behavioral ratings. Averaging multi-informant ratings of ADHD symptomatology has been found by others to be the optimal method for integrating multi-informant data (25). Second, confirmatory factor analysis was used to derive a latent ADHD symptom variable based on multi-informant DAWBA and SDQ data. To our knowledge, this is the first neuroimaging study to directly compare these two methods of handling multiple-informant behavioral data. In short, we found that these two methods yielded very similar results when relating to regional GMV, producing statistical maps with a high degree of spatial overlap.

We found that the statistical map representing the relationship between GMV and ADHD symptomatology was significantly correlated with patterns of dopaminergic gene expression. More specifically, areas of the brain in which ADHD symptomatology was inversely associated with GMV tended to be regions that expressed the gene that encodes for the dopamine D_1 receptor, *DRD1*. This finding is particularly intriguing given that dopamine D_1 receptor density in the cortex has been recently linked to the functional decoupling of DMN and task-positive networks in humans (44). Thus, dopamine D_1 receptor density in the vmPFC—a major hub of the DMN—may be particularly relevant with regard to ADHD symptomatology, affecting the dynamic interplay between task-negative and task-positive networks. Candidate gene studies have also tied *DRD1* to symptoms of inattention (45). Brain areas showing reduced volume at higher levels of ADHD symptomatology were characterized by relatively low *DRD2* expression. It is unclear why *DRD1* and *DRD2* expression patterns were differentially associated with our VBM results. It is possible that these findings can be explained, in part, by the differential distribution of D_1 and D_2 receptors in the human brain (46). Previous research indicates a dorsolateral-ventromedial gradient with regard to the respective distribution of D_1 and D_2 receptors, with D_1 receptors being more prevalent in ventromedial regions of the striatum and cortex (46,47). This differential distribution of D_1 and D_2 receptors is also believed to reflect a distinction between "direct" and "indirect" corticostriatal-thalamic-cortical circuits—with D_1 receptors playing a more important role in "direct" circuits that serve to disinhibit thalamic activity and initiate behavior, and D_2 receptors playing a greater role in "indirect" circuits that serve to inhibit neuronal activity (47–49). Although speculative, the results of our follow-up gene expression analyses may reflect a relative imbalance between D_1 and D_2 systems. However, it is important to emphasize that these gene expression analyses are meant to be hypothesis generating in nature. It is critical that future studies more directly test these possibilities.

It is important to address limitations of the present study. First, given that we have focused on regional GMV in our analyses, we are unable to definitively comment on the neurophysiological underpinnings of our VBM findings. Similarly, we are unable to comment on possible ties to aberrant structural and/or functional connectivity. Second, patterns of gene expression are related to age and developmental stage, and our gene expression analyses do not capture these age-related influences. Third, it is worth noting that across all analyses, observed effect sizes were small. This may reflect that the vmPFC findings in the present study constitute one part in the full elucidation of brain-based correlates of ADHD. Fourth, we observed an apparent dissociation with regard to the neuroanatomical correlates of hyperactive/impulsive and inattentive symptoms. However, it is possible that differences in statistical power may have influenced these results—in particular, more variance was observed in inattentive symptoms (mean 2.64, SD 3.86) relative to hyperactive/impulsive symptoms (mean 1.42, SD 2.65).

In conclusion, reduced volume in the vmPFC may serve as a relatively stable biomarker for inattention. The present study lays the foundation for informing early intervention and prevention efforts. One exciting future direction will be to examine the extent to which vmPFC structure during adolescence predicts subsequent symptom trajectories into adulthood. This work has the potential to identify brain-based markers for future outcomes, helping to target youths at greatest risk for poor outcomes.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the European Union–funded FP6 Integrated Project IMAGEN "Reinforcement-related behaviour in normal brain function and psychopathology" Grant No. LSHM-CT-2007-037286; FP7 projects

IMAging GEnetics for MENtal Disorders Grant No. 602450, AGGRESSOTYPE Grant No. 602805, and MATRICS Grant No. 603016; Innovative Medicine Initiative Project EU-AIMS Grant No. 115300-2; Medical Research Council Grants "Developmental pathways into adolescent substance abuse" Grant No. 93558 and Consortium on Vulnerability to Externalizing Disorders and Addictions Grant No. MR/N000390/1; Swedish funding agencies VR, FORTE, and FORMAS; Medical Research Council and Wellcome Trust Behavioural and Clinical Neuroscience Institute, University of Cambridge, National Institute for Health Research Biomedical Research Centre at South London, and Maudsley National Health Service Foundation Trust and King's College London; Bundesministeriumfür Bildung und Forschung Grant Nos. 01GS08152, 01EV0711, eMED SysAlc01ZX1311A, and Forschungsnetz AERIAL; Deutsche Forschungsgemeinschaft Grant Nos. SM 80/7-1, SM 80/7-2, and SFB 940/1; National Institutes of Health "Axon, Testosterone and Mental Health During Adolescence" Grant No. RO1 MH085772-01A1; National Institutes of Health Consortium Grant No. U54 EB020403, supported by a National Institutes of Health cross-alliance that funds Big Data to Knowledge Centres of Excellence; and Tobacco Centers of Regulatory Science Grant No. P50DA036114 (to HG). This research was supported by Center of Biomedical Research Excellence award P20GM103644-01A1 from the National Institute of General Medical Sciences (to AP, HG, RA, BC, PS).

TB has served as an advisor or consultant to Bristol-Myers Squibb, Desitin Arzneimittel, Eli Lilly and Company, Medice, Novartis International, Pfizer Inc., Shire, UCB, and Vifor Pharma; has received conference attendance support, conference support, or speaking fees from Eli Lilly and Company, Janssen-McNeil, Medice, Novartis International, Shire, and UCB; and is involved in clinical trials conducted by Eli Lilly and Company, Novartis International, and Shire; the present work is unrelated to these relationships. JG has received research funding from the German Federal Ministry of Education and Research, AstraZeneca, Eli Lilly and Company, Janssen-Cilag, and Bristol-Myers Squibb and has received speaking fees from AstraZeneca, Janssen-Cilag, and Bristol-Myers Squibb. The other authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry (MDA, CO, BC, RRA, NA, ND, KH, SM, PAS, HG, ASP), University of Vermont College of Medicine, Burlington, Vermont; Departments of Child and Adolescent Psychiatry and Psychotherapy (TB, LP) and Cognitive and Clinical Neuroscience (HF, YG, FN, MS), Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim; Physikalisch-Technische Bundesanstalt (RB); Departments of Psychiatry and Psychotherapy (AH, HW) and Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (VK), Charité-Universitätsmedizin Berlin, Berlin; Department of Psychiatry and Psychotherapy (JG), University Medical Center Hamburg-Eppendorf (UB, CB), Hamburg; Department of Psychiatry and Neuroimaging Center (MNS), Technische Universität Dresden, Dresden, Germany; Discipline of Psychiatry (ALWB), School of Medicine and Trinity College Institute of Neurosciences, Trinity College Dublin; Department of Psychology (RW), University College Dublin, Dublin; Medical Research Council Social, Genetic and Developmental Psychiatry Centre (AC, SD, GS) and Department of Psychological Medicine and Psychiatry (PJC), Institute of Psychiatry, Psychology and Neuroscience (RG), King's College London; Sir Peter Mansfield Imaging Centre School of Physics and Astronomy (PG), University of Nottingham, Nottingham, United Kingdom; Department of Psychiatry (PJC), Université de Montréal, Centre Hospitalier Universitaire Sainte-Justine Hospital, Montreal, Quebec; Rotman Research Institute, Baycrest, and Departments of Psychology and Psychiatry (TP), University of Toronto, Toronto, Ontario, Canada; Neurospin (VF, DPO), Commissariat à l'Energie Atomique, CEA Saclay Center; Institut National de la Santé et de la Recherche Médicale Unit 1000 Neuroimaging and Psychiatry (J-LM), University Paris Sud, University Paris Descartes-Sorbonne Paris Cité and Maison de Solenn; Institut National de la Santé et de la Recherche Médicale Unit 1000 Neuroimaging and Psychiatry (M-LPM), Service Hospitalier Frédéric Joliot, Orsay, University Paris Sud, University Paris Saclay, Orsay, and Maison De Solenn, University Paris Descartes; Department of Adolescent Psychopathology and Medicine (M-LPM), Maison De Solenn, Cochin Hospital, Paris, France; and Medical School (JP), University of Tampere, Tampere, Finland.

Address correspondence to Matthew D. Albaugh, Ph.D., Department of Psychiatry, University of Vermont College of Medicine, University Health Center campus, 1 South Prospect Street, Burlington, VT 05401; E-mail: malbaugh@uvm.edu.

Received Oct 20, 2016; revised Dec 13, 2016; accepted Jan 4, 2017.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2017.01.003.

REFERENCES

1. American Psychiatric Association (2000): Diagnostic and Statistical Manual of Mental Disorders, 4th ed rev. Washington, DC: American Psychiatric Association.
2. Barkley RA, Fischer M, Edelbrock CS, Smallish L (1990): The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study. J Am Acad Child Adolesc Psychiatry 29:546–557.
3. McGough JJ, Barkley RA (2004): Diagnostic controversies in adult attention deficit hyperactivity disorder. Am J Psychiatry 161: 1948–1956.
4. Almeida Montes LG, Ricardo-Garcell J, Barajas De La Torre LB, Prado Alcantara H, Martinez Garcia RB, Fernandez-Bouzas A, *et al*. (2010): Clinical correlations of grey matter reductions in the caudate nucleus of adults with attention deficit hyperactivity disorder. J Psychiatry Neurosci 35:238–246.
5. Proal E, Reiss PT, Klein RG, Mannuzza S, Gotimer K, Ramos-Olazagasti MA, *et al*. (2011): Brain gray matter deficits at 33-year follow-up in adults with attention-deficit/hyperactivity disorder established in childhood. Arch Gen Psychiatry 68:1122–1134.
6. Seidman LJ, Biederman J, Liang L, Valera EM, Monuteaux MC, Brown A, *et al*. (2011): Gray matter alterations in adults with attention-deficit/hyperactivity disorder identified by voxel based morphometry. Biol Psychiatry 69:857–866.
7. Onnink AM, Zwiers MP, Hoogman M, Mostert JC, Kan CC, Buitelaar J, *et al*. (2014): Brain alterations in adult ADHD: Effects of gender, treatment and comorbid depression. Eur Neuropsychopharmacol 24:397–409.
8. Ellison-Wright I, Ellison-Wright Z, Bullmore E (2008): Structural brain change in attention deficit hyperactivity disorder identified by meta-analysis. BMC Psychiatry 8:51.
9. Frodl T, Skokauskas N (2012): Meta-analysis of structural MRI studies in children and adults with attention deficit hyperactivity disorder indicates treatment effects. Acta Psychiatr Scand 125:114–126.
10. Valera EM, Faraone SV, Murray KE, Seidman LJ (2007): Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. Biol Psychiatry 61:1361–1369.
11. Depue BE, Burgess GC, Bidwell LC, Willcutt EG, Banich MT (2010): Behavioral performance predicts grey matter reductions in the right inferior frontal gyrus in young adults with combined type ADHD. Psychiatry Res 182:231–237.
12. Pironti VA, Lai MC, Muller U, Dodds CM, Suckling J, Bullmore ET, *et al*. (2014): Neuroanatomical abnormalities and cognitive impairments are shared by adults with attention-deficit/hyperactivity disorder and their unaffected first-degree relatives. Biol Psychiatry 76: 639–647.
13. Montes LG, Ricardo-Garcell J, De la Torre LB, Alcantara HP, Garcia RB, Acosta DA, *et al*. (2011): Cerebellar gray matter density in females with ADHD combined type: A cross-sectional voxel-based morphometry study. J Atten Disord 15:368–381.
14. Makris N, Liang L, Biederman J, Valera EM, Brown AB, Petty C, *et al*. (2015): Toward defining the neural substrates of ADHD: A controlled structural MRI study in medication-naive adults. J Atten Disord 19: 944–953.
15. Amico F, Stauber J, Koutsouleris N, Frodl T (2011): Anterior cingulate cortex gray matter abnormalities in adults with attention deficit hyperactivity disorder: A voxel-based morphometry study. Psychiatry Res 191:31–35.

16. Bonath B, Tegelbeckers J, Wilke M, Flechtner HH, Krauel K (2016): Regional gray matter volume differences between adolescents with ADHD and typically developing controls: Further evidence for anterior cingulate involvement [published online ahead of print Jan 8]. J Atten Disord.
17. Batty MJ, Palaniyappan L, Scerif G, Groom MJ, Liddle EB, Liddle PF, *et al*. (2015): Morphological abnormalities in prefrontal surface area and thalamic volume in attention deficit/hyperactivity disorder. Psychiatry Res 233:225–232.
18. Hudziak JJ, Achenbach TM, Althoff RR, Pine DS (2007): A dimensional approach to developmental psychopathology. Int J Methods Psychiatr Res 16(suppl 1):S16–S23.
19. Mous SE, White T, Muetzel RL, El Marroun H, Rijlaarsdam J, Polderman TJ, *et al*. (2016): Cortical morphology as a shared neurobiological substrate of attention-deficit/hyperactivity symptoms and executive functioning: A population-based pediatric neuroimaging study. J Psychiatry Neurosci 41:150371.
20. Ducharme S, Hudziak JJ, Botteron KN, Albaugh MD, Nguyen TV, Karama S, *et al*. (2012): Decreased regional cortical thickness and thinning rate are associated with inattention symptoms in healthy children. J Am Acad Child Adolesc Psychiatry 51:18–27; e12.
21. Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, *et al*. (2007): Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci U S A 104: 19649–19654.
22. Shaw P, Lerch J, Greenstein D, Sharp W, Clasen L, Evans A, *et al*. (2006): Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 63:540–549.
23. Shaw P, Gilliam M, Liverpool M, Weddle C, Malek M, Sharp W, *et al*. (2011): Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: Support for a dimensional view of attention deficit hyperactivity disorder. Am J Psychiatry 168:143–151.
24. Morris SE, Cuthbert BN (2012): Research Domain Criteria: Cognitive systems, neural circuits, and dimensions of behavior. Dialogues Clin Neurosci 14:29–37.
25. Martel MM, Schimmack U, Nikolas M, Nigg JT (2015): Integration of symptom ratings from multiple informants in ADHD diagnosis: A psychometric model with clinical utility. Psychol Assess 27:1060–1071.
26. Hart H, Radua J, Nakao T, Mataix-Cols D, Rubia K (2013): 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 70:185–198.
27. Kofler MJ, Rapport MD, Sarver DE, Raiker JS, Orban SA, Friedman LM, *et al*. (2013): Reaction time variability in ADHD: A meta-analytic review of 319 studies. Clin Psychol Rev 33:795–811.
28. Stuss DT, Murphy KJ, Binns MA, Alexander MP (2003): Staying on the job: The frontal lobes control individual performance variability. Brain 126:2363–2380.
29. Bellgrove MA, Hester R, Garavan H (2004): The functional neuroanatomical correlates of response variability: Evidence from a response inhibition task. Neuropsychologia 42:1910–1916.
30. Hawrylycz MJ, Lein ES, Guillozet-Bongaarts AL, Shen EH, Ng L, Miller JA, *et al*. (2012): An anatomically comprehensive atlas of the adult human brain transcriptome. Nature 489:391–399.
31. Schumann G, Loth E, Banaschewski T, Barbot A, Barker G, Buchel C, *et al*. (2010): The IMAGEN study: Reinforcement-related behaviour in normal brain function and psychopathology. Mol Psychiatry 15: 1128–1139.
32. Goodman R, Ford T, Richards H, Gatward R, Meltzer H (2000): The Development and Well-Being Assessment: Description and initial validation of an integrated assessment of child and adolescent psychopathology. J Child Psychol Psychiatry 41:645–655.
33. Goodman R (1997): The Strengths and Difficulties Questionnaire: A research note. J Child Psychol Psychiatry 38:581–586.
34. Goodman R (2001): Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry 40: 1337–1345.
35. Petersen AC, Crockett L, Richards M, Boxer A (1988): A self-report measure of pubertal status: Reliability, validity, and initial norms. J Youth Adolesc 17:117–133.
36. Whelan R, Watts R, Orr CA, Althoff RR, Artiges E, Banaschewski T, *et al*. (2014): Neuropsychosocial profiles of current and future adolescent alcohol misusers. Nature 512:185–189.
37. Horton NJ, Laird NM, Zahner GEP (1999): Use of multiple informant data as a predictor in psychiatric epidemiology. Int J Methods Psychiatr Res 8:6–18.
38. Rosseel Y (2012): lavaan: An R package for structural equation modeling. J Stat Softw 48:1–36.
39. Gorgolewski KJ, Fox AS, Chang L, Schafer A, Arelin K, Burmann I, *et al*. (2014): Tight Fitting Genes: Finding Relations Between Statistical Maps and Gene Expression Patterns. Hamburg, Germany: Organization for Human Brain Mapping.
40. Zijdenbos AP, Dawant BM, Margolin RA, Palmer AC (1994): Morphometric analysis of white matter lesions in MR images: Method and validation. IEEE Trans Med Imaging 13:716–724.
41. Maier S, Perlov E, Graf E, Dieter E, Sobanski E, Rump M, *et al*. (2016): Discrete global but no focal gray matter volume reductions in unmedicated adult patients with attention-deficit/hyperactivity disorder. Biol Psychiatry 80:905–915.
42. Sonuga-Barke EJ, Castellanos FX (2007): Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. Neurosci Biobehav Rev 31:977–986.
43. Salavert J, Ramos-Quiroga JA, Moreno-Alcázar A, Caseras X, Palomar G, Radua J, *et al.* (2015): Functional imaging changes in the medial prefrontal cortex in adult ADHD [published online ahead of print Oct 29.] J Atten Disord.
44. Roffman JL, Tanner AS, Eryilmaz H, Rodriguez-Thompson A, Silverstein NJ, Ho NF, *et al*. (2016): Dopamine D1 signaling organizes network dynamics underlying working memory. Sci Adv 2:e1501672.
45. Luca P, Laurin N, Misener VL, Wigg KG, Anderson B, Cate-Carter T, *et al*. (2007): Association of the dopamine receptor D1 gene, DRD1, with inattention symptoms in families selected for reading problems. Mol Psychiatry 12:776–785.
46. Hall H, Sedvall G, Magnusson O, Kopp J, Halldin C, Farde L (1994): Distribution of D1- and D2-dopamine receptors, and dopamine and its metabolites in the human brain. Neuropsychopharmacology 11: 245–256.
47. Lichter DG, Cummings JL (2001): Frontal-Subcortical Circuits in Psychiatric and Neurological Disorders. New York, NY: Guilford Press.
48. Parent A, Hazrati LN (1995): Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Brain Res Rev 20:91–127.
49. Parent A, Hazrati LN (1995): Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Brain Res Rev 20:128–154.