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Complete List of Authors:	Albaugh, Matthew; University of Vermont College of Medicine, Psychiatry Ivanova, Masha; University of Vermont College of Medicine, Psychiatry Chaarani, Bader; University of Vermont College of Medicine, Psychiatry Orr, Catherine; University of Vermont College of Medicine, Psychiatry Allgaier, Nicholas; University of Vermont College of Medicine, Psychiatry Althoff, Robert; University of Vermont College of Medicine, Psychiatry D'Alberto, Nicholas; University of Vermont College of Medicine, Psychiatry Hudson, Kelsey; University of Vermont College of Medicine, Psychiatry Mackey, Scott; University of California, San Diego, Psychiatry Spechler, Philip; University of Vermont College of Medicine, Psychiatry Banaschewski, Tobias; Central Institute of Mental Health, Child and Adolescent Psychiatry Brühl, Rüdiger; Physikalisch-Technische Bundesanstalt in Berlin, Biomedizinische Magnetresonanz Bokde, Arun; Trinity College Dublin, Psychiatry Bromberg, Uli; Universitaetsklinikum Hamburg, Eppendorf Büchel, Christian; NeuroImage Nord, Department for Systems Neuroscience Cattrell, Anna; King's College London, Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience J.Conrod , Patricia ; Universite de Montreal, Department of Psychiatry Desrivières, Sylvane; King's College London, Social, Genetic and Developmental Psychiatry Centre; Sylvane Desrivières, Flor, Herta; Central Institute of Mental Health, Department of Clinical and Cognitive Neuroscience; Frouin, Vincent; CEA, Neurospin Gallinat, Jürgen; University Hospital Hamburg-Eppendorf, Department of Psychiatry and Psychotherapy Goodman, Robert; King's College London , Institute of Psychiatry, Psychology & Neuroscience Gowland, Penny; Peter Mansfield MR Center , School of Physics and Astronomy; Grimmer, Yvonne; Central Institute of Mental Health, Child and Adolescent Psychiatry Heinz, Andreas; Charité - Universitaetsmedizin Berlin, Department of Psychiatry and Psychotherapy Kappel, Viola; Charite - Universitatsmedizin Berlin Institut fur Medizin-Pflegepadagogik und Pflegewissenschaft, Department of Child and

	Adolescent Psychiatry Psychosomatics and Psychotherapy Martinot, Jean-Luc; Service Hospitalier Frederic Joliot, INSERM; Service Hospitalier Frédéric Joliot CEA, Faculté de médecine; University Paris Descartes, Maison de Solenn; Brain & Spine Institute, Center for Neuroimaging Research (CENIR) Paillère Martinot , Marie-Laure; University Paris Sud, University Paris Descartes - Sorbonne Paris Cité, Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 "Neuroimaging & Psychiatry" Nees, Frauke; Central Institute of Mental Health, Department of Cognitive and Clinical Neuroscience Papadopoulos Orfanos, Dimitri; CEA, Neurospin Penttilä, Jani; Tampereen Yliopisto, Adolescent Psychiatry; Poutska, Luise; Central Institute of Mental Health, Child and Adolescent Psychiatry Paus, Tomas; University of Toronto, Rotman Research Institute Smolka, Michael; Technische Universität, Psychiatry Struve, Maren; Central Institute of Mental Health, Department of Clinical and Cognitive Neuroscience Walter, Henrik; Charité University Medicine, Department of Psychiatry and Psychotherapy Whelan , Robert; University College Dublin, Department of Psychology Schumann, Gunter; King's College, Institute of Psychiatry Garavan, Hugh ; University of Vermont, Departments of Psychiatry and Psychology Potter, Alexandra; University of Vermont College of Medicine, Psychiatry
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Author(s):

Matthew D. Albaugh, Ph.D. [1], Masha Ivanova, Ph.D.[1], Bader Chaarani, Ph.D. [1], Catherine Orr, Ph.D. [1], Nicholas Allgaier, Ph.D. [1], Robert R. Althoff, M.D., Ph.D. [1], Nicholas D' Alberto, B.A. [1], Kelsey Hudson, B.A. [1], Scott Mackey, Ph.D. [1], Philip A. Spechler, M.S. [1], Tobias Banaschewski M.D., Ph.D.[2]; Rüdiger Brühl Ph.D.[3]; Arun L.W. Bokde Ph.D.[4]; Uli Bromberg Ph.D.[5]; Christian Büchel M.D.[5]; Anna Cattrell Ph.D.[6]; Patricia J. Conrod Ph.D.[7,8]; Sylvane Desrivières Ph.D.[6]; Herta Flor Ph.D.[9]; Vincent Frouin Ph.D.[10]; Jürgen Gallinat M.D.[11]; Robert Goodman, Ph.D.[12]; Penny Gowland Ph.D.[13]; Yvonne Grimmer, M.D.[9]; Andreas Heinz M.D., Ph.D.[14]; Viola Kappel, Dipl.-Psych.[15]; Jean-Luc Martinot M.D., Ph.D.[16]; Marie-Laure Paillère Martinot M.D., Ph.D.[17]; Frauke Nees Ph.D.[9]; Dimitri Papadopoulos Orfanos Ph.D.[10]; Jani Penttilä, M.D.[18]; Luise Poustka M.D.[2]; Tomáš Paus M.D., Ph.D.[19]; Michael N. Smolka M.D.[20]; Maren Struve, Ph.D.[9]; Henrik Walter M.D., Ph.D.[14]; Robert Whelan Ph.D.[21]; Gunter Schumann M.D.[6]; Hugh Garavan, Ph.D. [1]; & Alexandra S. Potter, Ph.D. [1]

Affiliations:
[1]Department of Psychiatry, University of Vermont College of Medicine, Burlington, VT, USA;
[2]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, 68159 Mannheim, Germany;
[3]Physikalisch-Technische Bundesanstalt (PTB), Braunschweig and Berlin, Germany [or depending on journal requirements can be: Physikalisch-Technische Bundesanstalt (PTB), Abbestr. 2 - 12, Berlin, Germany;
[4]Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neurosciences, Trinity College Dublin;
[5]University Medical Centre Hamburg-Eppendorf, House W34, 3.OG, Martinistr. 52, 20246, Hamburg, Germany;
[6]Medical Research Council - Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom;
[7]Department of Psychiatry, Universite de Montreal, CHU Ste Justine Hospital, Canada;
[8]Department of Psychological Medicine and Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London;
[9]Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, Mannheim, Germany;
[10]Neurospin, Commissariat à l'Energie Atomique, CEA-Saclay Center, Paris, France;
[11]Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf (UKE), Martinistrasse 52, 20246 Hamburg;
[12]King's College London Institute of Psychiatry, Psychology & Neuroscience, London, United Kingdom;
[13]Sir Peter Mansfield Imaging Centre School of Physics and Astronomy, University of Nottingham, University Park, Nottingham, United Kingdom;
[14]Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité, Universitätsmedizin Berlin, Charitéplatz 1, Berlin, Germany;
[15]Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Charité-Universitätsmedizin, Berlin, Germany;
[16]Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 "Neuroimaging & Psychiatry", University Paris Sud, University Paris Descartes - Sorbonne Paris Cité; and Maison de Solenn, Paris, France;
[17]INSERM, UMR 1000, Research Unit NeuroImaging and Psychiatry, Service Hospitalier Frédéric Joliot, Orsay, University Paris-Sud, University Paris Saclay, Orsay, and Maison De Solenn,

University Paris Descartes, Paris, France AP-HP, Department of Adolescent Psychopathology and Medicine, Maison De Solenn, Cochin Hospital, Paris, France;
[18]University of Tampere, Medical School, Tampere, Finland;
[19]Rotman Research Institute, Baycrest and Departments of Psychology and Psychiatry, University of Toronto, Toronto, Ontario, M6A 2E1, Canada;
[20]Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany;
[21]Department of Psychology, University College Dublin.

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Correspondence to Dr. Matthew D. Albaugh, 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

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ABSTRACT

Youths with attention-deficit/hyperactivity disorder symptomatology often exhibit residual inattention and/or hyperactivity in adulthood; however, this is not true for all individuals. We recently reported that dimensional, multi-informant ratings of hyperactive/inattentive symptoms are associated with ventromedial prefrontal cortex (vmPFC) structure. Herein, we investigate the degree to which vmPFC structure during adolescence predicts hyperactive/inattentive symptomatology at 5-year follow-up. Structural equation modeling was used to test the extent to which adolescent vmPFC volume predicts hyperactive/inattentive symptomatology 5 years later in early adulthood. 1,104 participants (M = 14.52 yrs, SD = 0.42; 583 females) possessed hyperactive/inattentive symptom data at 5-year follow-up, as well as quality controlled neuroimaging data and complete psychometric data at baseline. Self-reports of hyperactive/inattentive symptomatology were obtained during adolescence and at 5-year follow-up using the Strengths and Difficulties Questionnaire (SDQ). At baseline and 5-year follow-up, a hyperactive/inattentive latent variable was derived from items on the SDQ. Baseline vmPFC volume predicted adult hyperactive/inattentive symptomatology (standardized coefficient = -.274, $p < .001$) while controlling for baseline hyperactive/inattentive symptomatology. These results are the first to reveal relations between adolescent brain structure and adult hyperactive/inattentive symptomatology, and suggest that early structural development of the vmPFC may be consequential for the subsequent expression of hyperactive/inattentive symptoms.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) symptomatology frequently persists across the span of development. Longitudinal research indicates that functionally impairing symptoms continue into adolescence and adulthood in approximately 60-80% of cases diagnosed during childhood (Barkley RA et al. 1990; McGough JJ and RA Barkley 2004). Despite such findings, longitudinal relations between adolescent brain structure and adult ADHD symptomatology remain virtually unstudied. Prospective longitudinal neuroimaging studies offer an invaluable opportunity to identify early brain-based markers of future emotional and behavioral problems. Investigating links between adolescent brain structure and adult psychopathology may further elucidate the neural underpinnings of adult ADHD symptomatology, as well as help to characterize different disease trajectories. Ultimately, such efforts may inform early intervention and prevention strategies.

The ventromedial prefrontal cortex (vmPFC), comprised of medial portions of the orbitofrontal cortex as well as ventral portions of the medial prefrontal cortex, has long been implicated in ADHD symptomatology and impulse control (Bechara A 2005; Faraone SV et al. 2015). Prior studies demonstrate that the vmPFC is involved in aspects of reward processing, including reward valuation, as well as receipt of reward (Knutson B et al. 2003; Liu X et al. 2011). Indeed, motivation-based dysfunction models of ADHD have been proposed, positing that altered reward processes underpin ADHD behaviors such as hypersensitivity to delay and discounting of future reward (Sonuga-Barke EJ et al. 1994; Sagvolden T et al. 1998; Sonuga-Barke EJ 2005). Portions of the vmPFC also constitute a critical node in the brain's default mode network (DMN)—a functional brain network that, more recently, has been implicated in ADHD

pathophysiology. Specifically, the default-mode interference hypothesis of ADHD postulates that activity in the DMN, which is normally diminished during goal-directed tasks, persists into periods of task-related processing and, consequently, interferes with task-specific processing (Sonuga-Barke EJ and FX Castellanos 2007).

In the largest voxel-based morphometry (VBM) study to date on adolescent ADHD symptomatology, Albaugh et al. (2017) reported that parent and youth ratings of ADHD symptoms were each negatively associated with gray matter volume in an overlapping portion of the vmPFC (Albaugh MD et al. 2017). In particular, reduced GMV in the vmPFC was tied to aspects of inattentive symptomatology in adolescents. Further, Albaugh et al. (2017) found that reaction time variability—posited to reflect attentional lapses—was negatively associated with gray matter volume in an overlapping region of the vmPFC. Similarly, in the largest VBM study to date on adult ADHD, a significant negative correlation was revealed between vmPFC GMV and dimensional measures of inattentive symptomatology (Maier S et al. 2015). Taken together, vmPFC volume may be a critical marker for inattentive symptomatology. It is possible that vmPFC structure during adolescence is not only related to concomitant symptoms of inattention, but may also be tied to the subsequent trajectories of ADHD symptomatology.

When characterizing longitudinal relations between adolescent brain structure and subsequent ADHD psychopathology, it may be beneficial to assess symptomatology in a quantitative fashion. Indeed, empirically based assessment of psychopathology has provided strong support for dimensionality with regard to a number of psychiatric conditions, including ADHD (Hudziak JJ et al. 2007). There have been reports of an association between subclinical symptoms of hyperactivity and impulsivity in typically developing youths and evidence of delayed cortical thickness maturation—interestingly,

delayed thickness maturation was revealed in areas of the cortex that have been previously implicated in clinically significant ADHD symptoms (Shaw P et al. 2011; Ducharme S et al. 2012). Such evidence supports the use of dimensional measures of psychopathology, as emphasized by the National Institute of Mental Health's Research Domain Criteria program (Morris S and B Cuthbert 2012). In addition to assessing psychopathology using dimensional measures, studying large population-based samples affords the opportunity to capture naturally occurring variance in behavioral phenotypes, including psychopathology. Unfortunately, few studies have examined the neural correlates of hyperactivity/inattention in population-based samples.

In the present study, we employ structural equation modeling (SEM) in order to examine the degree to which adolescent vmPFC volume predicts hyperactive/inattentive symptoms during early adulthood in a large, population-based sample of 1,104 youths. In a subset of participants, we also test the degree to which hyperactive/inattentive symptoms and vmPFC structure are related at study follow-up, during early adulthood.

MATERIALS AND METHODS

Sample

Neuroimaging and behavioral data were obtained from the IMAGEN study conducted across eight European sites, which includes 2,223 adolescents recruited from schools at age 14 years (SD = 0.41 year; age range = 12.9–15.7 years). A description of recruitment and assessment procedures, as well as study exclusion and inclusion criteria, has been published elsewhere (Schumann G et al. 2010). In the present study, a total of 1,104 participants possessed ADHD symptom data at the 5-year follow-up, as

well as quality controlled neuroimaging data and complete psychometric and demographic data at baseline. Of these 1,104 participants, 976 (88.4%) possessed quality controlled neuroimaging data at the 5-year follow-up as well as complete psychometric and demographic data at baseline.

Assessment of Hyperactivity and Inattention

The Development and Well-Being Assessment (DAWBA) is a computer-based package of questionnaires, interviews, and rating techniques used to assess adolescent psychopathology (Goodman R et al. 2000). In the present study, ADHD symptom counts were derived from the parent version of the DAWBA administered at baseline and were used solely in defining the vmPFC ROI (see below for further details) used in SEM analysis.

At baseline and 5-year follow-up, the self-report version of the Strengths and Difficulties Questionnaire (SDQ) was used to assess symptoms of hyperactivity and inattention (Goodman R 1997). 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 have retest stability over 4-6 months (Goodman R 2001). Importantly, concurrent validity has been established between the Child Behavior Checklist Attention Problems subscale—arguably the most widely accepted dimensional measure of hyperactive/inattentive symptomatology in youths—and the SDQ Hyperactive/Inattentive scale (r = .75) (Mieloo C et al. 2012).

Demographic Measures

The puberty development scale (PDS) was used to assess the pubertal status of participants (Petersen AC et al. 1988). The socioeconomic status (SES) 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 (Whelan R et al. 2014).

MRI acquisition

MRI scanning was conducted at the eight IMAGEN assessment sites using 3T whole body MRI systems. Image-acquisition utilized a set of parameters that were compatible with all scanners in order to ensure comparability of data across the different scanners. Details surrounding image acquisition protocols and quality checks have been described elsewhere, including extensive standardization across MRI scanners (Schumann G *et al.* 2010).

Structural MRI

High-resolution anatomical MRIs were acquired with a three-dimensional T1-weighted magnetization prepared gradient echo sequence (MPRAGE) based on the ADNI protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/).

MRI data preprocessing

Preprocessing of the structural T1-weighted data was performed with Statistical Parametric Mapping version 8 (Wellcome Department of Neuroimaging, London, United

Kingdom, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), using standard automated pipelines (Schumann G *et al.* 2010). T1-weighted MRI processing included image segmentation into gray matter, white matter and cerebrospinal fluid tissue classes, preceded by an iterative registration to the Montreal Neurological Institute template space, using SPM's optimized normalization routine (Ashburner J and KJ Friston 2005). For voxel-based morphometry (VBM), gray matter images were smoothed with a Full Width at Half Maximum Gaussian kernel of 8 mm, warped to standard MNI space and modulated by multiplying the linear and non-linear component of the Jacobian determinants generated during spatial normalization (Ashburner J and KJ Friston 2000).

ROI Definition

Parent reports of ADHD symptoms (obtained at baseline) were used to define the vmPFC ROI (shown in Supplemental Figure 1). Specifically, baseline regional GMV was regressed against baseline total ADHD symptom count—using parent reports on the DAWBA—while controlling for age, sex, total gray matter volume, site, pubertal development, Performance IQ, Verbal IQ, and SES. As outlined in Albaugh et al. (2017), this regression analysis included 1,538 adolescents and revealed a negative association in bilateral vmPFC (3424 voxels, x = -4, y = 30, z = -20; peak Z score = 4.12).

Although the spatial resolution of MRI does not allow for reliable identification of cytoarchitectonic areas in humans, we have attempted to apply the cytoarchitectonic scheme of Ongur et al. (2003) using anatomical landmarks. Moving in the caudal to rostral direction along the gyrus rectus, the ROI likely includes areas 32pl, 14c, 14r, and 11m, as well as areas 10m and 10r along the medial wall (Ongur D et al. 2003). The lateral extent of the ROI likely includes portions of area 13.

Statistical Analyses

Structural equation modeling (SEM) was employed to test the extent to which adolescent vmPFC volume was associated with self-reported hyperactive/inattentive symptomatology at 5-year follow-up, while accounting for the effects of sex, age, pubertal status, IQ, handedness, site, SES, and total gray matter volume, as well as baseline self-reports of hyperactive/inattentive symptomatology. By controlling for baseline symptoms, we tested the extent to which baseline vmPFC structure accounted for unique variance in follow-up H/I symptoms—independent of baseline symptomatology. At baseline and follow-up, a hyperactive/inattentive latent variable was derived from items on the youth version of the SDQ. Three SDQ items from the hyperactive/inattentive subscale were used to indicate the latent variable ("*I am restless, I cannot stay still for long*", "*I am constantly fidgeting or squirming*", "*I am easily distracted, I find it difficult to concentrate*"). This was due to the fact that the two positively coded items ("*I think before I do things*", "*I finish the work I'm doing. My attention is good*") did not covary with the other items, likely reflecting their positive scaling. The tendency for positively worded items on the SDQ to cluster together, irrespective of the subscale they belong to, has been previously reported by other groups (DiStefano C and RW Motl 2006; Palmieri PA and GC Smith 2007; Van Roy B et al. 2008). Analysis was carried out using the statistical package Mplus (http://www.statmodel.com). We utilized the Weighted Least Squares with Mean and Variance Adjusted Chi Square Test Statistic estimator (WLSMV), which is robust to violations of multivariate normality (Muthén LK and BO Muthén 2001-2016). We also repeated our analysis using standard multiple linear regression, utilizing the 5-item SDQ

Hyperactive/Inattentive summary scores at baseline and follow-up (rather than indicating latent variables).

In order to assess if brain regions during adolescence—other than the vmPFC—might be associated with adult hyperactive/inattentive symptoms, we performed a subsequent exploratory whole-brain analysis. Specifically, a whole-brain voxel-wise analysis was conducted using the general linear model, performed with the VBM toolbox of SPM8. Regional GMV, measured at baseline, was regressed against self-reports of hyperactive/inattentive symptomatology obtained at 5-year follow-up. Age at baseline, sex, handedness, total gray matter volume (GMV), site, pubertal development, Performance IQ, Verbal IQ, and SES were controlled for in the analysis. An initial height threshold of $p \leq .001$ was implemented at the voxel level, with a corrected family-wise error (FWE; $p \leq .05$) subsequently applied to identify significant clusters.

RESULTS

Demographic and Behavioral Measures

Demographic and psychometric information for participants is provided in Table 1. For the 1104 participants included in the main SEM analysis, self-report ratings of hyperactive/inattentive symptomatology at follow-up were inversely correlated with SES ($r = -0.114$, $p < .001$) and Verbal IQ ($r = -0.068$, $p = .023$). In addition, self-reported SDQ H/I scores at follow-up were positively correlated with self-reported SDQ H/I scores at baseline ($r = 0.434$, $p < .001$). Baseline parent-reported DAWBA symptom counts were correlated with baseline self-reported SDQ H/I scores ($r = 0.345$, $p < .001$) as well as follow-up self-reported SDQ H/I scores ($r = 0.235$, $p < .001$) (Supplemental Table 1).

Imaging Analyses

ROI-based Analysis. Table 2 displays results from the ROI-based SEM analysis. The model (Figure 1) showed good fit (Root Mean Square Error of Approximation = 0.030; Comparative fit index = 0.941; Tucker-Lewis Index = 0.925). Our analysis revealed that there was a significant direct effect of baseline vmPFC volume on hyperactive/inattentive symptoms at 5-year follow-up (standardized coefficient = -0.274, $p < .001$) where smaller volumes at baseline were associated with higher levels of hyperactive/inattentive symptoms at 5-year follow-up—independent of baseline self-reports of hyperactive/inattentive symptoms. Results were not meaningfully altered when age and pubertal stage at time of MRI scan were removed from the model, or while controlling for other SDQ subscales (including mood and anxiety symptoms captured on the Emotion subscale, as well as oppositional/rule-breaking behaviors captured on the Conduct subscale). These latter findings suggest that co-occurring psychopathology was not confounding our results.

It is noteworthy that very similar results were obtained when standard multiple linear regression analysis was performed in which SDQ Hyperactive/Inattentive summary scores (using all five items) were used rather than latent variables (Supplemental Table 2). More specifically, follow-up SDQ Hyperactive/Inattentive summary scores were regressed on sex, age, pubertal status, Performance IQ, Verbal IQ, handedness, site, SES, baseline total gray matter volume, baseline SDQ Hyperactive/Inattentive summary score, and baseline vmPFC ROI volume.

Using only the 976 participants with available follow-up imaging data, we attempted to include vmPFC volume (assessed at 5-year follow-up) into the structural equation model—in particular, as a mediating variable in between baseline vmPFC and follow-up hyperactive/inattentive symptoms. This resulted in a lack of model convergence. Upon further investigation, this reflected the fact that follow-up vmPFC volume was not significantly correlated with hyperactive/inattentive symptoms at baseline or 5-year follow-up (See Supplemental Tables 3-5). Baseline vmPFC volume, however, was significantly correlated with follow-up vmPFC volume (r = 0.846, p < .001). *Post hoc* partial correlation analysis revealed a significant association between baseline vmPFC volume and follow-up hyperactive/inattentive SDQ summary score while controlling for follow-up vmPFC volume, baseline hyperactive/inattentive SDQ summary score, as well as sex, handedness, site, SES, age at baseline, pubertal development at baseline, baseline total GMV, and follow-up total GMV (r = -.084, p = .009).

Whole-brain Analysis. Regressing baseline regional gray matter volume against follow-up hyperactive/inattentive SDQ summary scores revealed a negative association in the vmPFC (1351 voxels, x = -12, y = 46, z = -17; peak Z value = 5.04) (Figure 2). No other associations survived correction for multiple comparisons. Figure 3 depicts the spatial overlap between the parent-defined ROI used for the *a priori* analyses above and the results from this whole-brain analysis.

When controlling for baseline H/I self-report scores in the above VBM analysis, findings hold when an initial height threshold of p ≤ .005 is implemented at the voxel level, with a corrected family-wise error (FWE; p ≤ .05) subsequently applied to identify significant clusters.

DISCUSSION

To our knowledge, this is the first report of a longitudinal association between adolescent brain structure and hyperactive/inattentive symptomatology in early adulthood. Critically, vmPFC structure during adolescence was linked to hyperactive/inattentive symptomatology in early adulthood. In our SEM and standard multiple linear regression analyses, smaller ventromedial prefrontal volume at baseline predicted greater hyperactive/inattentive symptomatology at 5-year follow-up. It is important to note that, in these analyses, we controlled for baseline symptomatology. Further, covarying for mood and anxiety psychopathology, as well as conduct problems, did not meaningfully alter our results. Thus, our findings indicate that adolescent vmPFC volume accounts for unique variance in self-reported hyperactive/inattentive symptoms at 5-year follow-up—independent of self-reported baseline symptomatology. Taken together, vmPFC morphology during adolescence may possess predictive utility with regard to future symptoms of hyperactivity/inattention in early adulthood.

The vmPFC has been previously associated with concomitant ADHD symptomatology in adolescents and adults. In recent work by Albaugh et al. (2017), it was found that vmPFC gray matter volume during adolescence was negatively associated with concomitant parent and youth reports of inattention. In this same study, it was also reported that reaction time variability was negatively associated with gray matter volume in an overlapping region of the vmPFC. Similar results were obtained in the largest brain structural imaging study to date on adult ADHD, where a significant negative correlation was revealed between vmPFC gray matter volume and a dimensional measure of inattentive symptomatology (Maier S *et al.* 2015). Taken together, these previous studies further implicate the vmPFC in the pathophysiology of inattention. The present study

extends findings from these previous reports, demonstrating that adolescent vmPFC structure is associated with hyperactive/inattentive symptomatology approximately five years later in early adulthood, independent of baseline symptomatology.

Interestingly, the vmPFC represents a central node in the brain's default-mode network, a brain network that has been hypothesized to play a role in the pathophysiology of ADHD symptoms. Specifically, 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 (Sonuga-Barke EJ and FX Castellanos 2007). The ventromedial prefrontal cortex represents a primary hub in the brain's default mode network (DMN)—a network believed 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 both concomitant and future DMN dysfunction. In a recent study by Salavert et al. (2015), ADHD participants exhibited reduced deactivation of the ventromedial prefrontal cortex during a working memory task. The authors suggest that failure to deactivate the medial prefrontal cortex is tied to lapses of attention, and that this may be a central feature of ADHD symptomatology (Salavert J et al. 2015). In the context of the present study, reduced vmPFC volume during adolescence may serve as a marker for increased vulnerability to future DMN dysfunction—more specifically, an impaired ability to deactivate portions of the DMN. Future studies are needed to test this hypothesis.

In the context of the DMN, it is noteworthy that mind-wandering—or the drifting of attention away from external, task-related activities towards self-generated cognitions—has been previously tied to the vmPFC. Numerous functional imaging studies have implicated the vmPFC in mind-wandering (Andrews-Hanna JR, JS Reidler, C Huang, et

al. 2010; Fox KC et al. 2015). Bertossi and Ciaramelli (2016) recently found that patients with vmPFC damage reported significantly reduced off-task thoughts and less frequent daydreaming when compared to controls. The extent and overlap of patients' brain lesions studied by Bertossi and Ciaramelli (2016) share a striking resemblance to the ROI used in the present study. As noted by others, the vmPFC belongs to the "medial temporal lobe (MTL)-subsystem" of the DMN (Andrews-Hanna JR, JS Reidler, J Sepulcre, et al. 2010). As hypothesized by Bertossi and Ciaramelli, the vmPFC—and its shared connections with MTL structures—may be central to the mental construction of past events, or possible future scenarios (Bertossi E and E Ciaramelli 2016). According to their hypothesis, vmPFC patients may experience a relative dearth of internally generated thoughts about the past and future, and there is little competition from the internal milieu with regard to the allocation of attentional resources (Bertossi E and E Ciaramelli 2016). Although speculative, it is plausible that aberrant functioning and/or connectivity of the vmPFC could also lead to an abundance of internally generated stimuli that outcompete external stimuli for attentional resources. Interestingly, this aberrant functioning and/or connectivity of the vmPFC may underpin aspects of normative, as well as clinically significant, inattention. It is also worth mentioning that over-activation of the subcallosal cingulate area (Brodmann Area 25)—an area closely neighboring the caudal extent of the ROI used in the present study—has been tied to the shifting of attention away from external stimuli and towards negative, self-referential thoughts (Choi KS et al. 2015).

Findings from the present study may also reflect altered maturation of neural pathways involved in reward processing. A number of functional neuroimaging studies have found evidence of hypo-responsiveness during reward anticipation in adolescent and adult ADHD samples (Scheres A et al. 2007; Strohle A et al. 2008). It was recently reported

that vmPFC-lesioned neurosurgical patients exhibited reduced ventral striatal activity during the anticipation of reward, as well as decreased nucleus accumbens volumes, relative to neurologically healthy controls (Pujara MS et al. 2016). Intriguingly, in the context of the present study, structural alterations in the vmPFC during adolescence may be related to enduring functional deficits in reward processing.

Few imaging studies have attempted to test longitudinal associations between brain metrics and ADHD-related outcomes. In a seminal longitudinal study by Shaw et al. (2006), 163 children with ADHD (mean age at study entry, 8.9 years) and 166 controls underwent MRI scanning, with the majority of participants undergoing MRI scanning two times or more. Clinical evaluations were conducted at follow-up (mean follow-up, 5.7 years). In brief, children with worse clinical outcome possessed thinner left medial prefrontal cortex at baseline relative to controls and ADHD participants with better outcomes. This finding appears in line with results from the present study indicating that reduced ventromedial prefrontal volume during adolescence is associated with greater ADHD symptomatology in early adulthood. Mattfeld et al. (2014) recently used resting state MRI to characterize patterns of functional connectivity within three groups: I) patients with persistent ADHD diagnoses in both childhood and adulthood, II) patients who had met criteria for ADHD diagnosis in childhood but not during adulthood, and III) controls who did not meet criteria for ADHD diagnosis during childhood or adulthood (Mattfeld AT et al. 2014). Importantly, participants were scanned as adults. Positive functional correlation between two major midline nodes of the DMN—the vmPFC and posterior cingulate— was reduced in patients with a persistent ADHD diagnosis, but not in remitted patients or controls. Furthermore, whereas control participants exhibited significant negative correlations between resting state activity in medial prefrontal and bilateral dorsolateral prefrontal regions, these regions were not significantly anti-

correlated in participants with persistent or remitted ADHD. These findings suggest that DMN dysfunction may indeed be related to trajectories of ADHD symptomatology.

It is noteworthy that baseline vmPFC volume was associated with hyperactive/inattentive symptoms at follow-up; however, follow-up vmPFC volume was not significantly associated with baseline or follow-up symptomatology. Although seemingly at odds with Maier et al. (2015), this finding appears in line with several morphometric studies of adult ADHD in which volumetric reductions were limited to the dorsal anterior cingulate and areas comprising the dorsal attention network (Seidman LJ et al. 2006; Makris N et al. 2007). Given the relatively protracted structural development of the vmPFC—particularly with regard to cortical surface expansion (Sowell ER et al. 2004)—it may be a region where delayed brain maturation could still be observed at time of baseline assessment. Interestingly, results from the present study appear to dovetail with findings of Ducharme et al. (2012). Studying a large population-based sample of typically developing youths, Ducharme et al. (2012) revealed negative associations between Child Behavior Checklist Attention Problems score and orbitofrontal (including portions of the vmPFC) cortical thickness early on in development; however, this relation was not observed in older youths. Thus, our results appear to support previous reports of clinical and subclinical ADHD symptoms being associated with reduced rates of brain structural change. Moreover, it is notable that self-reported hyperactive/inattentive symptoms at follow-up were related to vmPFC structure five years earlier even when partialling out the influence of this region's volume at follow-up. This suggests that the earlier developmental trajectory of this region may prove to be consequential for the subsequent expression of hyperactive/inattentive symptoms.

We have demonstrated anatomical convergence with regard to the association between baseline brain structure and baseline parent-reports of ADHD symptoms, and the longitudinal association between baseline brain structure and subsequent self-reported hyperactive/inattentive symptomatology in early adulthood (controlling for baseline self-reports of hyperactive/inattentive symptomatology). Given that this anatomical overlap was observed primarily in ventromedial prefrontal cortices, these results further implicate this brain region in the pathophysiology of ADHD symptomatology. Thus, vmPFC structure during adolescence is not only related to concomitant hyperactivity/inattention, but also future hyperactivity/inattention in adulthood—with smaller volumes during adolescence being associated, on average, with greater hyperactive/inattentive symptomatology in adulthood.

Intriguingly, findings from the present study suggest that aspects of prefrontal structure during adolescence may, ultimately, be of clinical significance in the context of adult ADHD. Although speculative, it is possible that more refined assessments of orbital and ventromedial prefrontal morphology during adolescence may help to identify youths at greatest risk for clinically significant symptom change. It is possible that youth with aberrant vmPFC volume during adolescence, when coupled with particular genetic and/or environmental factors, may increase likelihood of clinically significant symptomatology in adulthood. Future studies may benefit from investigating the extent to which environmental and genetic factors may serve to moderate the relationship between adolescent prefrontal structure and adult hyperactive/inattentive symptomatology.

Finally, it should be noted that aspects of the vmPFC have been implicated in a number of different psychopathologies and behaviors, including anxiety, depression, impulse

control, psychopathy, and reward valuation (Hiser J and M Koenigs 2017). This observation likely reflects several important points. First, the majority of previous neuroimaging studies have utilized relatively simple approaches to characterizing psychopathology. With the advent of more sophisticated statistical approaches, such as bifactor models of psychopathology (Lahey BB et al. 2017), it is possible that a more general psychopathology factor—a factor that cuts across different classes of psychopathology and accounts for observed correlations across different symptom domains—may help to elucidate why particular brain areas are implicated in numerous psychopathologies. Second, the vmPFC has been identified as a hub node in the brain's "rich club" network—a constellation of brain regions that possess rich connections and are densely interconnected (van den Heuvel MP and O Sporns 2013). Thus, the vmPFC is ideally situated to exert influence on numerous brain networks; its rich connectivity may account for the vmPFC's putative role in numerous psychopathologies and behaviors.

The present study possesses a number of methodological strengths. We utilized a large longitudinal, population-based sample, capturing naturally occurring variation in ADHD symptomatology. We also assessed hyperactive/inattentive symptoms as a quantitative trait rather than following a strict categorical approach. These methodological approaches serve to greatly bolster statistical power. Nonetheless, given that we have focused on regional GMV in our analyses, we are unable to definitively comment on the neurophysiological underpinnings of the VBM findings. Similarly, we are unable to comment on possible ties to aberrant structural and/or functional connectivity. Future studies are needed to address these issues. We were limited by the fact that only self-reports of ADHD symptomatology were obtained at follow-up. Thus, our SEM analysis rested solely upon self-reports of hyperactive/inattentive symptoms using the SDQ.

Lastly, we did not have information with regard to prescription stimulant usage, which may have qualified the relationship between brain structure and hyperactive/inattentive symptoms over the developmental window studied.

In conclusion, vmPFC structure, which has been previously linked to concomitant ADHD symptomatology, also informs ADHD symptom trajectories from adolescence into early adulthood. These findings suggest that vmPFC structure in adolescence may have clinical utility by informing ADHD symptom trajectories. More granular assessment of adolescent vmPFC morphology may increase predictive utility in future studies.

Table 1. Summary Statistics for Demographic and Psychometric Variables

	N = 1,104	N = 976 (Available Follow-up Imaging)
Age at baseline (in years) (Mean ± SD)	14.52 ± 0.42	14.52 ± 0.42
Sex	52.8% F (583), 47.2% M (521)	53.0% F (517), 47.0% M (459)
SES (Mean ± SD)	18.28 ± 3.92	18.37 ± 3.88
Verbal IQ (Mean ± SD)	112.75 ± 14.00	112.76 ± 13.99
Performance IQ (Mean ± SD)	109.83 ± 14.61	109.88 ± 14.59
Baseline H/I Score on Youth SDQ (Mean ± SD)	3.80 ± 2.11	3.82 ± 2.10
Baseline DAWBA Symptom Count (Mean ± SD)	3.59 ± 5.32	3.54 ± 5.32
Follow-up H/I Score on Youth SDQ (Mean ± SD)	3.41 ± 2.14	3.39 ± 2.13
Participants scoring at, or above, Youth SDQ H/I cut-off of 7 at follow-up	93	82

H/I=Hyperactive/Inattentive scale

Table 2. Summary of ROI-based Structural Equation Modeling Analysis

Direct effects on Latent H/I Variable at 5-Year Follow-Up

	Std. beta	Sig.
Baseline ROI GMV	-0.274	**<0.001**
Sex	0.065	0.224
Hand	0.006	0.871
Site1	0.104	0.036
Site2	0.155	**0.003**
Site3	0.159	**0.001**
Site4	-0.024	0.593
Site5	-0.049	0.328
Site6	-0.010	0.835
Site7	-0.025	0.630
SES	-0.123	**0.002**
Age	-0.002	0.959
Puberty	-0.048	0.303
IQ PR	0.008	0.845
IQ VC	0.029	0.505
Baseline Total GMV	0.188	**0.014**
Baseline Latent H/I Variable	0.535	**<0.001**

SES = socioeconomic status; Puberty = pubertal development scale; IQ PR = Perceptual IQ; IQ VC = Verbal IQ; H/I = Hyperactive/Inattentive; ROI = Region of interest; GMV = Gray matter volume (N = 1,104)

Figure 1:

The model used to study the relationship between baseline vmPFC GMV and follow-up hyperactive/inattentive symptomatology (N = 1,104). Only statistically significant parameters are reported. A range of parameters is reported for site because it was coded via seven binary dummy-variables. All covariates were assessed at baseline.

Figure 2:

Results from whole brain voxel-wise analyses regressing baseline regional gray matter volume against SDQ Hyperactive/Inattentive score (assessed approximately 5 years later at follow-up). Age, sex, handedness, total gray matter volume (GMV), site, pubertal development, Performance IQ, Verbal IQ, and socio-economic status were controlled for in the analysis. An initial height threshold of $p \leq .001$ was implemented at the voxel level, with a corrected family-wise error (FWE; $p \leq .05$) subsequently applied to identify significant clusters (N = 1,104). In axial view, left is left.

Figure 3:

(A) Blue depicts baseline regional GMV related to parent-reported hyperactive/inattentive symptomatology (assessed at baseline) (see Albaugh et al., in press, for further details; N = 1538). Red depicts baseline regional GMV related to self-reported hyperactive/inattentive summary score (assessed approximately 5 years later at follow-up) on the Strengths and Difficulties Questionnaire (N = 1,104). Pink represents overlap in results. Age, sex, handedness, total gray matter volume (GMV), site, pubertal development, Performance IQ, Verbal IQ, and socio-economic status were controlled for in the analysis. An initial height threshold of $p \leq .001$ was implemented at the voxel level, with a corrected family-wise error (FWE; $p \leq .05$) subsequently applied to identify significant clusters. (B) Three-dimensional reconstruction of results. Blue depicts baseline regional GMV related to parent-reported ADHD symptomatology (assessed at baseline) (see Albaugh et al., in press, for further details; N = 1,538). Red depicts baseline regional GMV related to self-reported ADHD symptoms (assessed approximately 5 years later at follow-up) on the Strengths and Difficulties Questionnaire (N = 1,104). Results shown in axial view.

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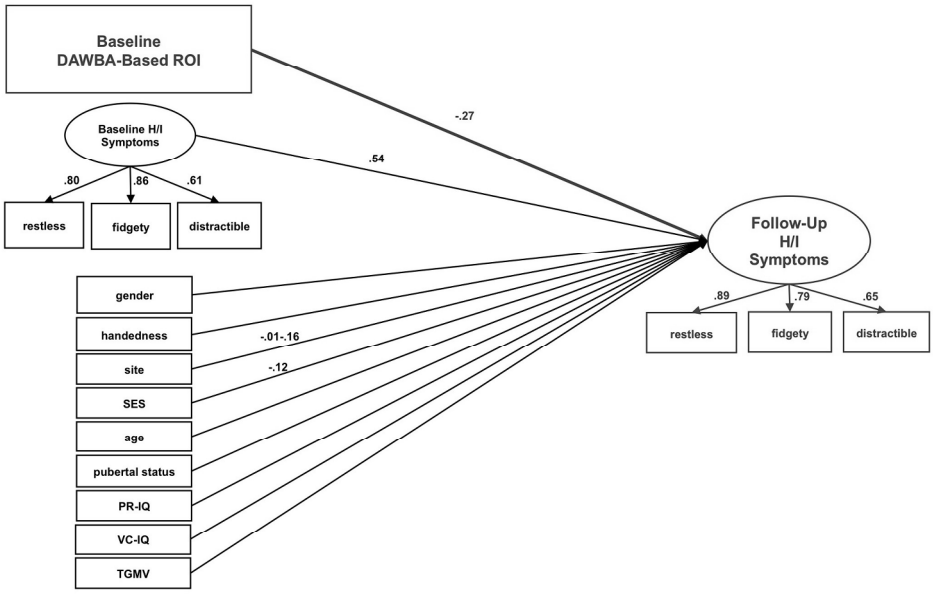

Figure 1: The model used to study the relationship between baseline vmPFC GMV and follow-up hyperactive/inattentive symptomatology (N = 1,104). Only statistically significant parameters are reported. A range of parameters is reported for site because it was coded via seven binary dummy-variables. All covariates were assessed at baseline.

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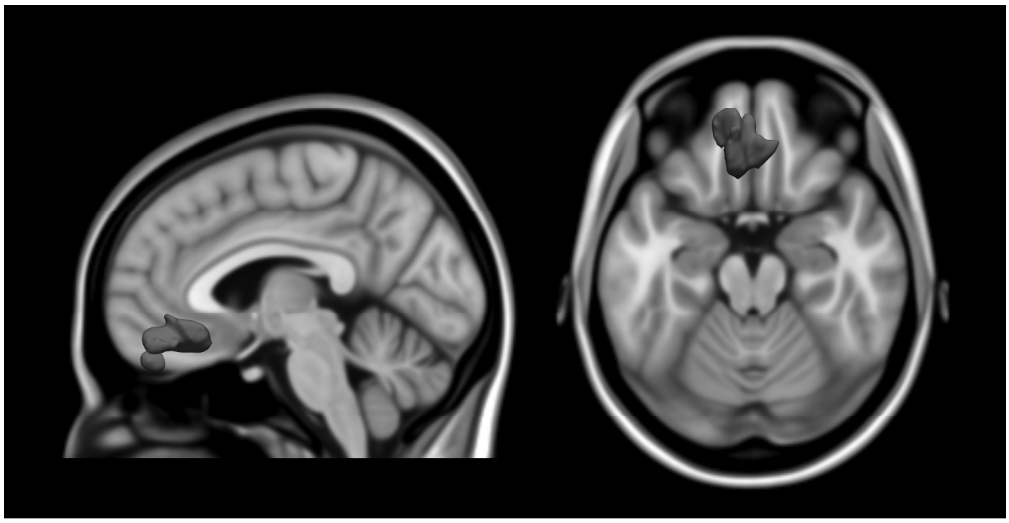

Figure 2: Results from whole brain voxel-wise analyses regressing baseline regional gray matter volume against SDQ Hyperactive/Inattentive score (assessed approximately 5 years later at follow-up). Age, sex, handedness, total gray matter volume (GMV), site, pubertal development, Performance IQ, Verbal IQ, and socio-economic status were controlled for in the analysis. An initial height threshold of $p \leq .001$ was implemented at the voxel level, with a corrected family-wise error (FWE; $p \leq .05$) subsequently applied to identify significant clusters (N = 1,104). In axial view, left is left.

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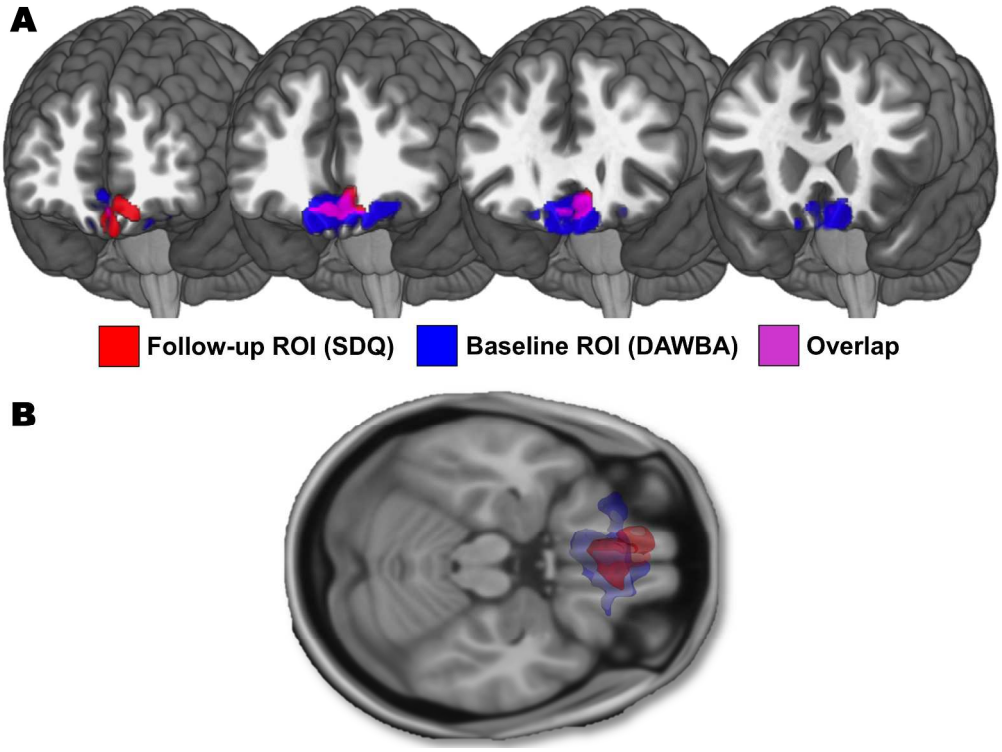

Figure 3: (A) Blue depicts baseline regional GMV related to parent-reported hyperactive/inattentive symptomatology (assessed at baseline) (see Albaugh et al., in press, for further details; N = 1538). Red depicts baseline regional GMV related to self-reported hyperactive/inattentive summary score (assessed approximately 5 years later at follow-up) on the Strengths and Difficulties Questionnaire (N = 1,104). Pink represents overlap in results. Age, sex, handedness, total gray matter volume (GMV), site, pubertal development, Performance IQ, Verbal IQ, and socio-economic status were controlled for in the analysis. An initial height threshold of $p \leq .001$ was implemented at the voxel level, with a corrected family-wise error (FWE; $p \leq .05$) subsequently applied to identify significant clusters. (B) Three-dimensional reconstruction of results. Blue depicts baseline regional GMV related to parent-reported ADHD symptomatology (assessed at baseline) (see Albaugh et al., in press, for further details; N = 1,538). Red depicts baseline regional GMV related to self-reported ADHD symptoms (assessed approximately 5 years later at follow-up) on the Strengths and Difficulties Questionnaire (N = 1,104). Results shown in axial view.

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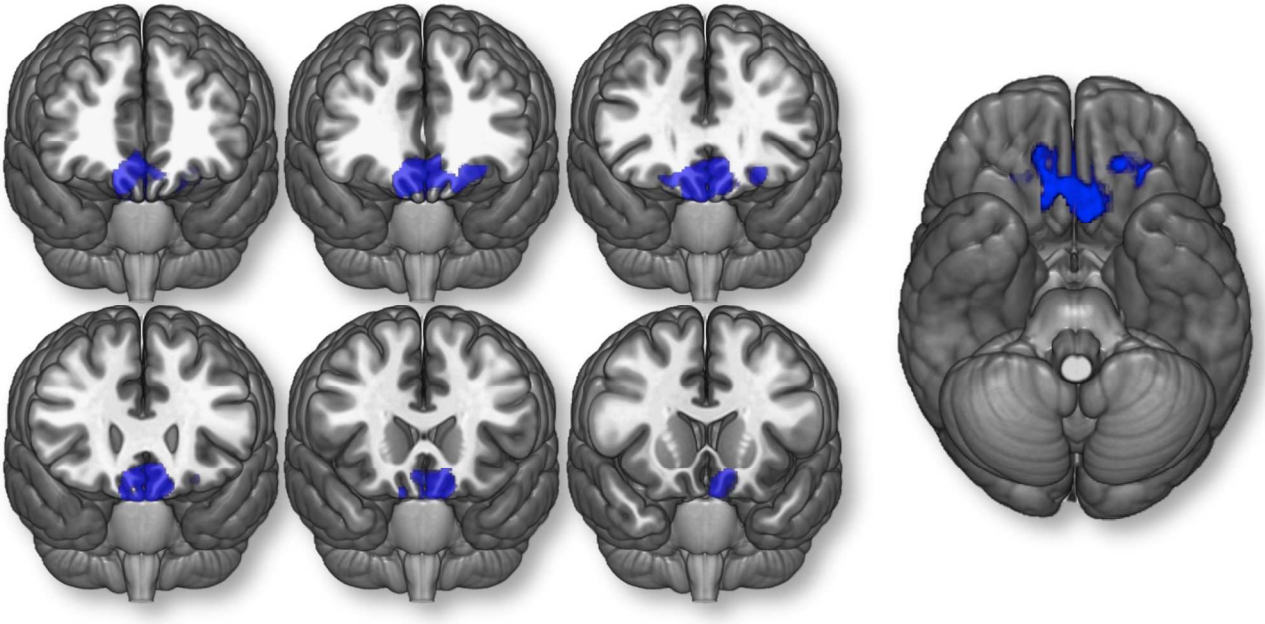
Supplemental Figure 1:



On left, coronal cross-sections of the ventromedial prefrontal cortex region of interest used in the structural equation model (SEM) analysis. Blue depicts baseline regional GMV related to parent-reported ADHD symptom counts (assessed at baseline). Age, sex, 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 family-wise error ($p \leq .05$) subsequently applied to identify significant clusters. On right, region of interest depicted on the orbital surface.

Supplemental Table 1. Correlations between ADHD Measures

	Baseline DAWBA	Baseline SDQ H/I	Follow-up SDQ H/I
Baseline DAWBA (parent)	1		
Baseline SDQ H/I (self-report)	.345	1	
Follow-up SDQ H/I (self-report)	.235	.434	1

N= 1104; all correlations are significant at $p < .001$

Supplemental Table 2. Summary of ROI-based Multiple Linear Regression Analysis

Standard Multiple Linear Regression

	Std. beta	Sig.
Baseline ROI GMV	-0.135	**0.009**
Sex	0.028	0.476
Hand	0.038	0.162
Site1	0.054	0.134
Site2	0.097	**0.009**
Site3	0.135	**<0.001**
Site4	-0.022	0.499
Site5	-0.017	0.640
Site6	0.009	0.785
Site7	0.028	0.448
SES	-0.083	**0.006**
Age	0.004	0.902
Puberty	-0.012	0.712
IQ PR	0.028	0.362
IQ VC	0.025	0.446
Baseline Total GMV	0.085	0.131
Baseline SDQ Hyperactive/Inattentive	0.407	**<0.001**

SES = socioeconomic status; Puberty = pubertal development scale; IQ PR = Perceptual IQ; IQ VC = Verbal IQ; H/I = Hyperactive/Inattentive; ROI = Region of interest; GMV = Gray matter volume.

Supplemental Table 3. Partial Correlations between ADHD Measures and Baseline ROI.

Correlations

Control Variables			Baseline ROI
Sex, Hand, Site, SES, Age, PDS, IQPR, IQVC, Baseline Total GMV	Baseline SDQ H/I (self-report)	Correlation	-.080
		Significance (2-tailed)	.008
		df	1087
	Baseline DAWBA symptom count (parent)	Correlation	-.138
		Significance (2-tailed)	.000
		df	1087
	Follow-up SDQ H/I (self-report)	Correlation	-.105
		Significance (2-tailed)	.001
		df	1087

SES = socioeconomic status; Puberty = pubertal development scale; IQ PR = Perceptual IQ; IQ VC = Verbal IQ; H/I = Hyperactive/Inattentive; ROI = Region of interest; GMV = Gray matter volume.

Supplemental Table 4. Partial Correlations between ADHD Measures and Follow-up ROI.

Correlations

Control Variables			Follow-up ROI
Sex, Hand, Site, SES, Age, PDS, IQPR, IQVC, Follow-up Total GMV	Baseline SDQ H/I (self-report)	Correlation	-0.005
		Significance (2-tailed)	0.867
		df	959
	Baseline DAWBA (parent)	Correlation	0.017
		Significance (2-tailed)	0.595
		df	959
	Follow-up SDQ H/I (self-report)	Correlation	-0.050
		Significance (2-tailed)	0.125
		df	959

SES = socioeconomic status; Puberty = pubertal development scale; IQ PR = Perceptual IQ; IQ VC = Verbal IQ; H/I = Hyperactive/Inattentive; ROI = Region of interest; GMV = Gray matter volume.

Supplemental Table 5. Multiple Linear Regression Testing Concurrent Association between ROI and Hyperactive/Inattentive Score at Follow-up.

Standard Multiple Linear Regression

	Std. beta	Sig.
Follow-up ROI GMV	-.132	.125
Sex	-.012	.788
Hand	.040	.207
Site1	.105	.015
Site2	.096	.028
Site3	.147	.000
Site4	-.007	.861
Site5	-.042	.319
Site6	.004	.926
Site7	.028	.529
SES	-.120	.001
Age	-.009	.793
Puberty	.012	.767
IQ PR	.032	.371
IQ VC	-.019	.612
Follow-up Total GMV	.088	.300

SES = socioeconomic status; Puberty = pubertal development scale; IQ PR = Perceptual IQ; IQ VC = Verbal IQ; ROI = Region of interest; GMV = Gray matter volume.