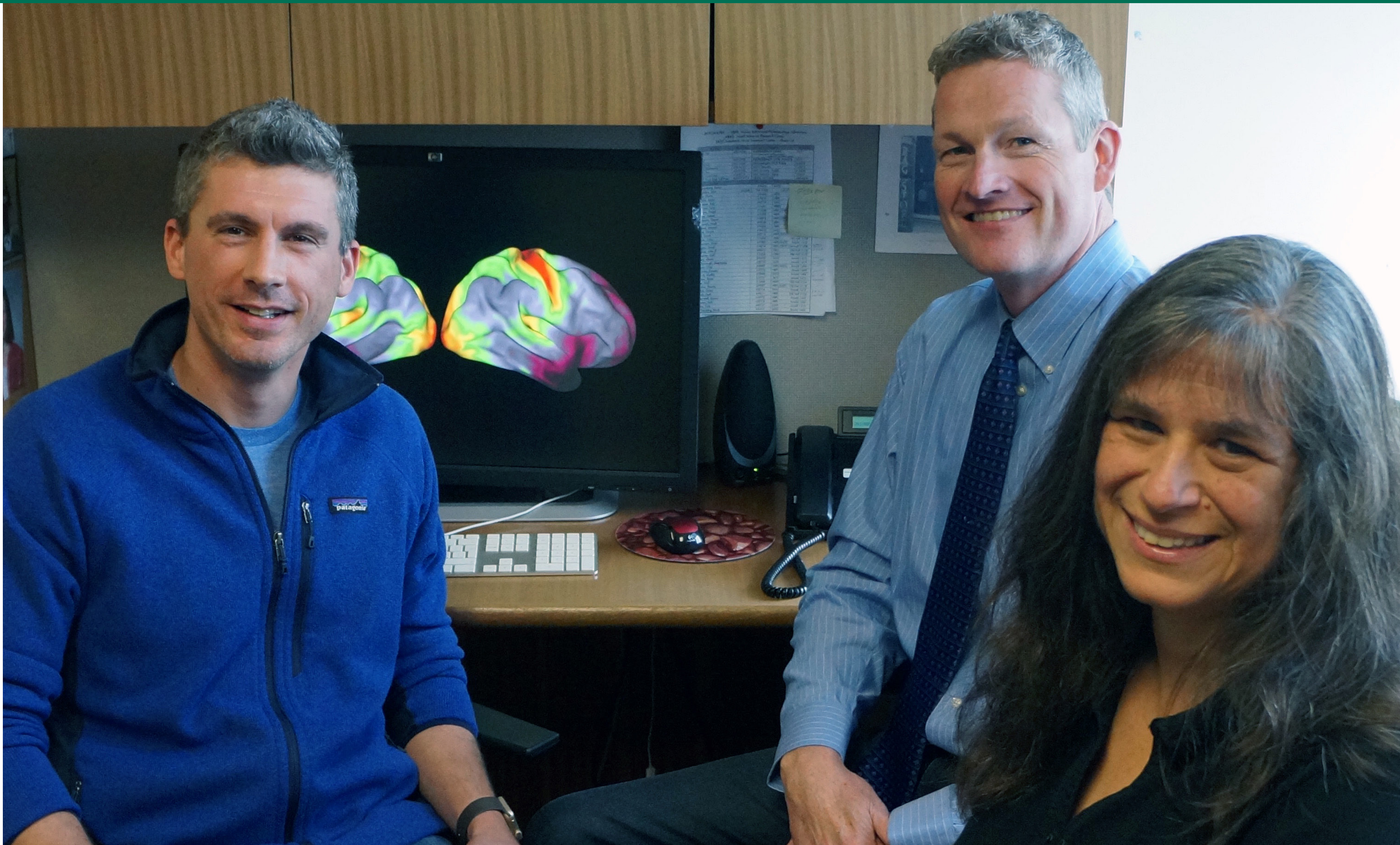


RESEARCH TRAINEE SHOWCASE



MATT ALBAUGH, Ph.D., HUGH GARAVAN, Ph.D., AND ALEXI POTTER, Ph.D.

Department of Psychiatry

Trainee: **Matthew Albaugh, Ph.D.**, Assistant Professor
(formerly Postdoctoral Fellow) Department of Psychiatry

Mentors: **Hugh Garavan, Ph.D.**
Professor, Department of Psychiatry

Alexandra Potter, Ph.D.
Assistant Professor of Psychiatry

Research Area: ADHD Symptomatology and Brain Structure

Paper: "Inattention and Reaction Time Variability are Linked to Ventromedial Prefrontal Volume in Adolescents," published in *Biological Psychiatry*, Nov. 1, 2017

Dr. Albaugh's research, which examined data from the international IMAGEN study, used a multi-informant approach to investigate whether or not dimensional measures of ADHD symptoms and brain imaging data could shed new light on the root source of ADHD's symptoms, including inattention, hyperactivity and impulsivity. This publication represented the largest structural imaging study to date on ADHD symptoms in adolescents and earned him the Trainee Award for Outstanding Research Publication in the Postdoctoral Trainee Research Showcase at the Dean's Excellence in Research Awards event in November 2017.



ADHD SYMPTOMATOLOGY AND VENTROMEDIAL PREFRONTAL STRUCTURE



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Introduction

- In the largest voxel-based morphometry (VBM) study to date on adolescent attention-deficit/hyperactivity disorder (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 (Figures 1 and 2).
- In the largest VBM study to date on adult ADHD, a significant negative correlation was revealed between vmPFC GMV and dimensional measures of inattention (Maier et al., 2015).
- It is possible that vmPFC structure during adolescence is not only related to concomitant symptoms of hyperactivity/inattention, but may also be tied to ADHD symptomatology later in adulthood.
- We employ structural equation modeling (SEM) in order to examine the degree to which adolescent vmPFC volume predicts hyperactive/inattentive symptoms in early adulthood.

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).
- 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 5-year follow-up.

Measures

Psychopathology Assessment

- 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.

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.
- Preprocessing of the structural T1-weighted data was performed with Statistical Parametric Mapping version 8, using standard automated pipelines.
- For 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.

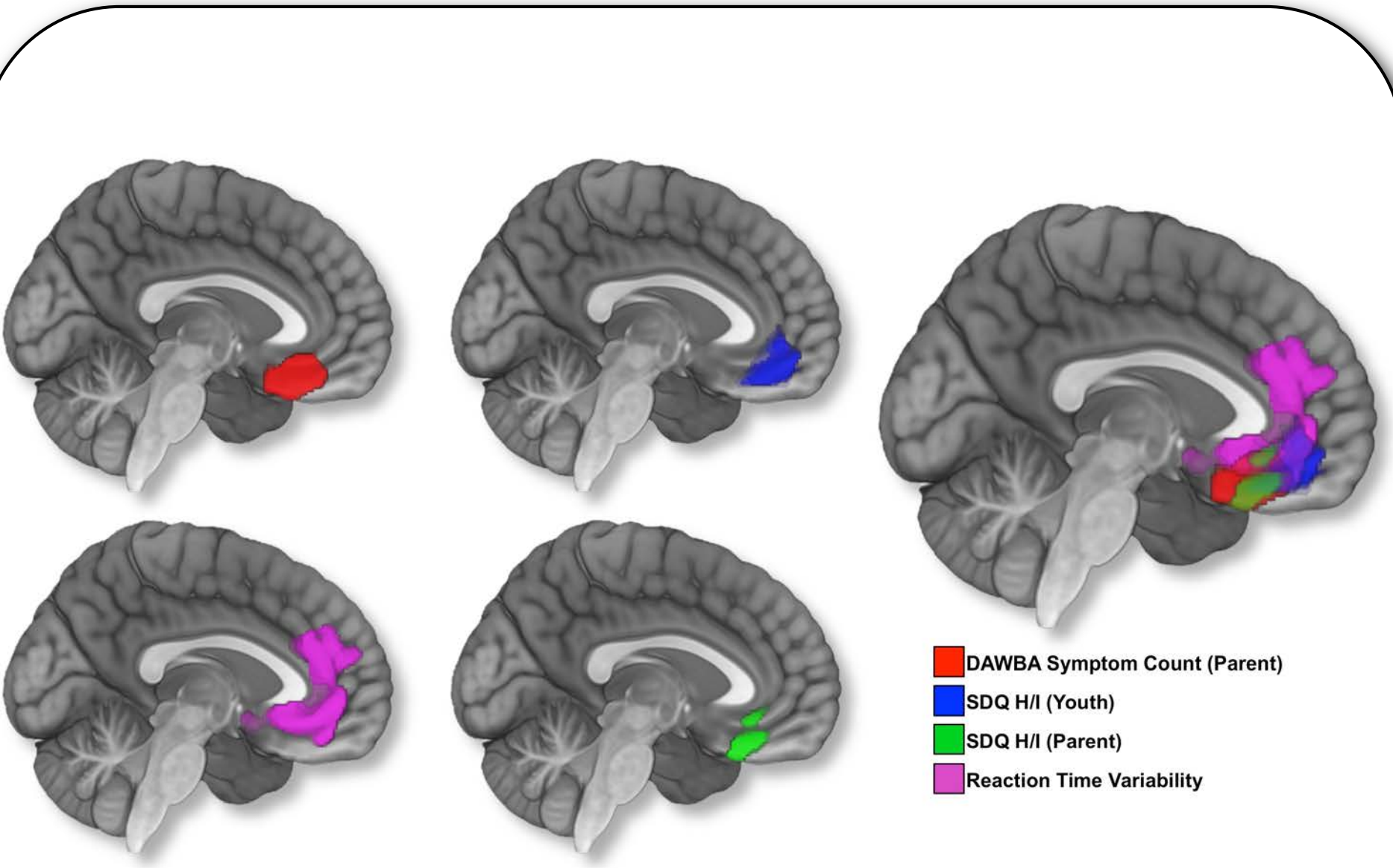


FIGURE 1: Results from whole brain voxel-wise analyses. Age, gender, total gray matter volume (GMV), site, pubertal development, IQ, and SES were controlled for in the analyses. To visualize overlap in findings, the image on the right is a composite of all associations. For details, see Albaugh et al. (2017).

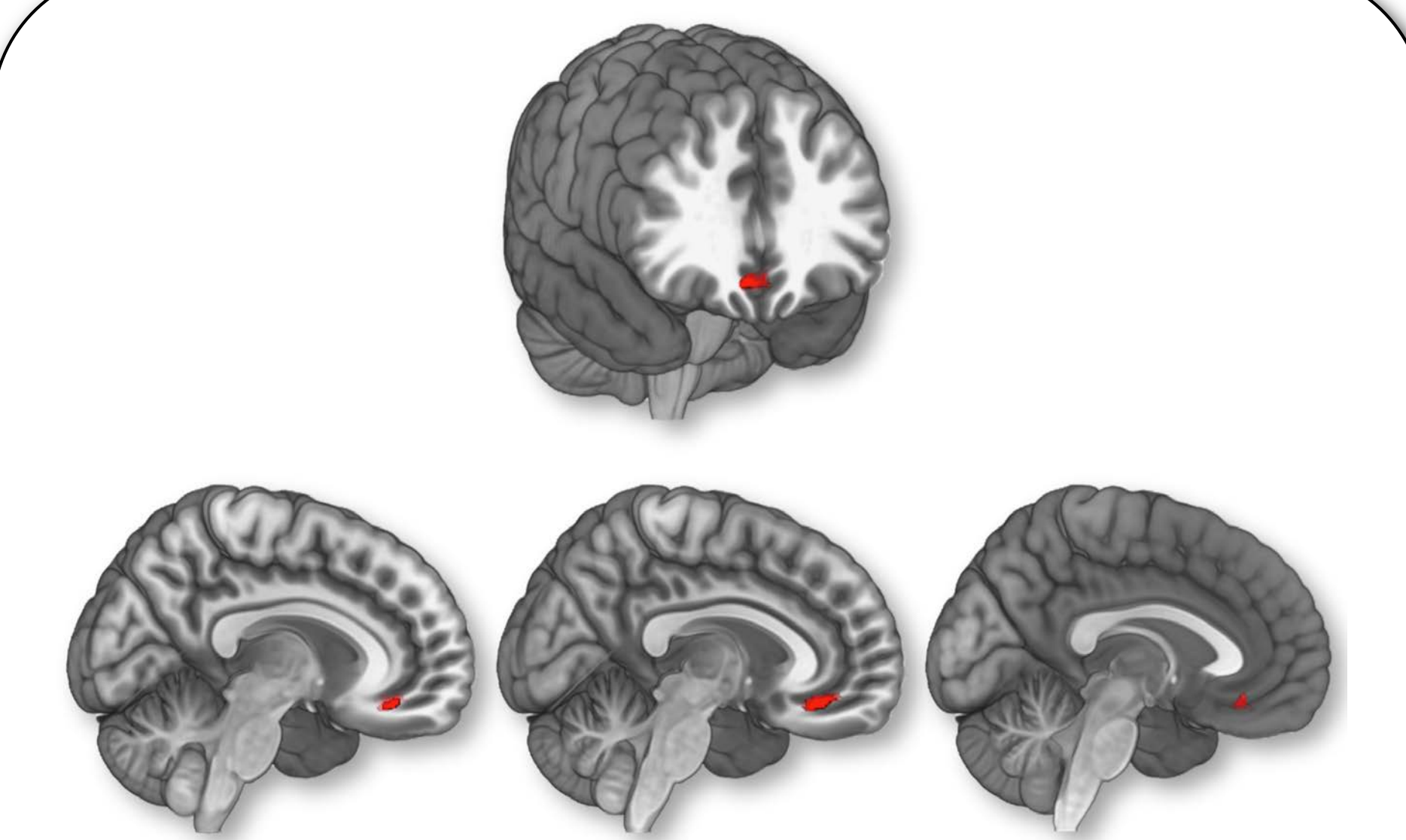


FIGURE 2: Region of overlap between parent DAWBA, parent SDQ, youth SDQ, and reaction time variability. Age, gender, total gray matter volume (GMV), site, pubertal development, Performance IQ, Verbal IQ, and socio-economic status were controlled for in the analyses. An initial height threshold of $p \leq .005$ was implemented at the voxel level, with a corrected family-wise error (FWE; $p \leq .05$) subsequently applied to identify significant clusters.

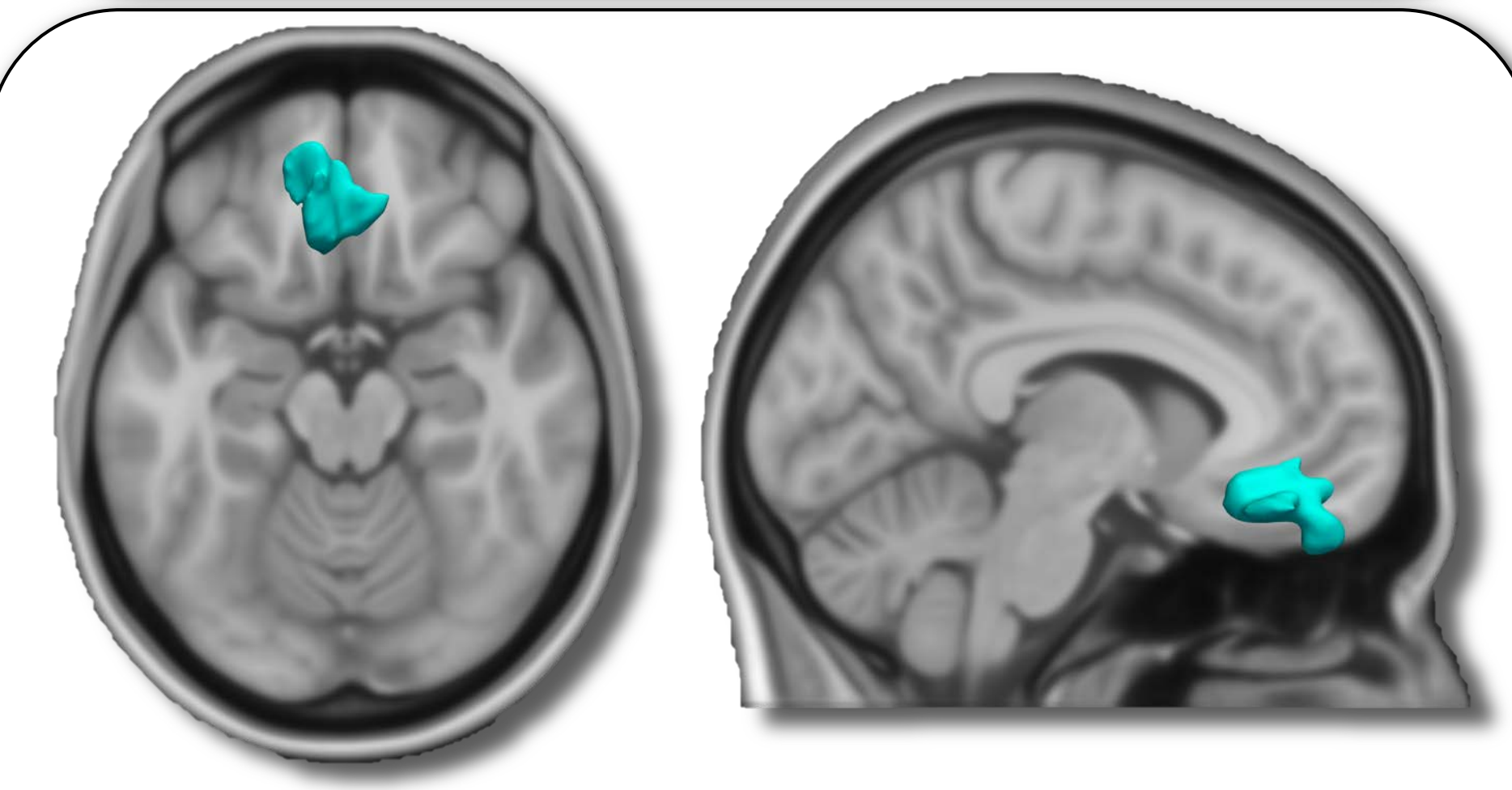


FIGURE 3: Results from regressing baseline regional GMV against SDQ Hyperactive/Inattentive score (assessed approximately 5 years later at follow-up). Age, sex, handedness, total gray matter volume (GMV), site, pubertal development, IQ, and SES were controlled for in the analysis. An initial height threshold of $p \leq .001$ was implemented at the voxel level, with a corrected family-wise error (FWE; $p \leq .05$) applied to identify significant clusters.

Analyses

- Using a brain region previously identified in Albaugh et al. (2017), we conducted a hypothesis-driven, ROI-based analysis.
- SEM was employed to test the extent to which adolescent vmPFC volume was associated with 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 hyperactive/inattentive symptomatology.
- At baseline and follow-up, a hyperactive/inattentive latent variable was derived from items on the youth version of the SDQ. Analysis was carried out using the statistical package Mplus.
- To assess if brain regions during adolescence—other than the vmPFC—might be associated with adult hyperactive/inattentive symptoms, we performed a subsequent whole-brain analysis. A whole-brain voxel-wise analysis was conducted using the GLM. Regional GMV, measured at baseline, was regressed against self-reports of hyperactive/inattentive symptomatology obtained at 5-year follow-up.

Results

- The model showed good fit (RMSEA = 0.048; Comparative fit index = 0.868; Tucker-Lewis Index = 0.834; AIC = 11955; BIC = 12130).
- 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 = -0.205, $p = .001$) where smaller volumes at baseline were associated with higher levels of hyperactive/inattentive symptoms at 5-year follow-up.
- Regressing baseline regional GMV 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 3). No other associations survived correction for multiple comparisons.

Conclusions

- While accounting for baseline symptomatology, smaller ventromedial prefrontal volume during adolescence predicted greater hyperactive/inattentive symptomatology at 5-year follow-up.
- Our findings suggest that vmPFC structure during adolescence may prove to be consequential for the subsequent expression of hyperactive/inattentive symptoms.
- The vmPFC represents a primary hub in the brain's default mode network (DMN)—a network posited to play a central role in mind-wandering and task-unrelated thought. Although speculative, it is possible that volumetric reductions in the vmPFC may be linked to both concomitant and future DMN dysfunction. Future research is needed to test this hypothesis.

REFERENCES

- Albaugh MD, Orr C, Chaarani B, et al. Inattention and Reaction Time Variability Are Linked to Ventromedial Prefrontal Volume in Adolescents. *Biol Psychiatry*. 2017.
- Maier S, Perlov E, Graf E, et al. Discrete Global but No Focal Gray Matter Volume Reductions in Unmedicated Adult Patients with Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry*. 2015.