Biological Psychiatry: CNNI

Archival Report

Sulcal Depth and Genetic Susceptibility Influence Initial Treatment Response in Adults With Attention-Deficit/Hyperactivity Disorder

Jonathan Laatsch, Friederike S. David, Frederike Stein, Carlo Maj, Andreas J. Forstner, Simon Maier, Swantje Matthies, Esther Sobanski, Barbara Alm, Ludger Tebartz van Elst, Axel Krug, and Alexandra Philipsen

ABSTRACT

BACKGROUND: As neurobiological markers gain prominence in guiding personalized treatments, sulcal depth (SD) remains an underexplored yet pivotal factor in neural processing and therapeutic efficacy. While genetic influences shape cortical architecture, their role in modulating the relationship between SD and treatment outcomes remains unclear. In this study, we investigated whether pretreatment SD predicts symptom alleviation in adults with attention-deficit/hyperactivity disorder (ADHD) and explored moderating effects of genetic susceptibility for ADHD and cross-disorder influences.

METHODS: Using structural neuroimaging data from COMPAS (Comparison of Methylphenidate and Psychotherapy in Adult ADHD Study), we examined associations between SD and treatment response following a 12-week intervention involving either group psychotherapy or clinical management with methylphenidate or placebo. Pretreatment SD was derived from 119 T1-weighted anatomical scans and analyzed using linear regression models to assess its predictive value for posttreatment symptom severity. Subsequently, we explored the moderating role of polygenic scores for ADHD and cross-disorder susceptibility. Structural analyses were performed using the threshold-free cluster enhancement approach in CAT, with moderation analyses conducted in SPSS.

RESULTS: Results revealed that SD in parietal, temporal, and occipital regions significantly predicted symptom alleviation, linking deeper sulci with greater treatment efficacy. Moreover, genetic predisposition to ADHD and cross-disorder traits influenced these relationships, highlighting an interaction between cortical structure and genetic susceptibility in determining treatment outcomes.

CONCLUSIONS: These findings highlight SD as a promising neurobiological marker of ADHD treatment response and emphasize the importance of integrating neurobiological and genetic factors into predictive models of therapeutic efficacy in psychiatry.

https://doi.org/10.1016/j.bpsc.2025.09.012

With up to 60% of individuals experiencing persistent symptoms of attention-deficit/hyperactivity disorder (ADHD) into adulthood, the disorder manifests itself across a spectrum of severity, with diverse manifestations of symptoms, etiological factors, developmental trajectories, and responses to treatment (1–4). Given this complexity, accurately forecasting individual-level treatment trajectories and outcomes poses major challenges given the substantial complexity and variability inherent in ADHD (5). Recognizing this challenge, several research groups have investigated potential biological predictors of psychostimulant treatment response in adults with ADHD (6–9). Key predictors included genetic markers (10) and task-based (11) and structural (8,12) neuroimaging findings, as well as neurophysiological (13) and electrophysiological (14) indicators, emphasizing the diverse and complex neurobiological landscape of ADHD. While these discoveries offer promising implications for improving diagnostic precision, the multifaceted nature of ADHD underscores the ongoing need for research into biological markers.

In this context, there has been increasing interest toward exploring the brain surface and cortical folding as predictors of treatment outcomes across a variety of psychiatric conditions (15–19). Our research group recently showed that baseline cortical gyrification significantly predicted overall ADHD symptom alleviation across 3 symptom dimensions (12). Extending this line of research, one emerging area of focus is sulcal morphology that assesses the morphology of the cortex by estimating the width and depth of several major sulci of the brain (20). The development of sulcal depth (SD) is tightly regulated by genetic factors that shape the functional

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organization of the cortex (21). Advances in computational modeling, such as sulcal graph analysis, highlight the high heritability of sulcal pits that form early in gestation and exhibit robust correspondence with functional topographies (21,22). In the case of the central sulcus, heritability estimates are approximately 56% for depth and 66% for length, pointing to the influence of genetically programmed developmental trajectories (21). These insights reflect a broader understanding of genetically guided cortical maturation, whereby sulcation unfolds along a central-to-frontal axis, shaping structural complexity and surface morphology (23–25). As cortical folding advances, sulcal pits anchor functional territories, with structure-function coupling strengthening throughout development (26) closely related to functional areas (22). For example, depth variations in prefrontal sulci predict verbal working memory performance (27). Despite its conceptual relevance, SD has attracted comparatively little empirical attention, despite a growing body of evidence associating it with a range of neurodevelopmental disorders (28,29).

While research on SD in relation to ADHD in adults remains predominantly confined to our research group (30,31), studies in pediatric populations have revealed distinct atypical sulcal patterns in patients with ADHD, contrasting with those observed in healthy control participants. Li *et al.* (28) found that the average and maximum depths of the left central sulcus, as well as the average cortical thickness of the bilateral central sulci, were larger in the ADHD group compared with the control group. Building on this, Li *et al.* (29) revealed significant dissimilarities in sulcal patterns, particularly in the left frontal, right parietal, and temporal lobes, along with increased within-group variability and reduced interhemispheric similarity in the frontal lobe in individuals with ADHD.

Given ADHD's strong genetic basis, it is plausible that variations in SD reflect underlying neurodevelopmental mechanisms contributing to the disorder. ADHD shares complex genetic architecture across multiple psychiatric conditions (32) with pleiotropic variants, suggesting that persistent ADHD symptoms may arise from broader heritable influences. In fact, the Cross-Disorder Group of the Psychiatric Genomics Consortium (PGC) (32) identified disorder clusters shaped by pleiotropic loci, whose expression peaks during midfetal development and continues into adulthood (32). In a related advancement, Demontis *et al.* (33) identified 32 independent lead variants located in 27 genome-wide significant loci significantly associated with ADHD heritability, explaining around 14% of the variance in the phenotype attributable to common genetic variants. These findings are consistent with previous studies suggesting that genetic risk for ADHD contributes to a progressive manifestation of clinical symptoms beyond childhood (34–36).

Genetic influences on brain morphology are well established (37), and widespread structural brain abnormalities have consistently been implicated in the pathophysiology of ADHD (38–41). Furthermore, there is compelling evidence suggesting that the influence of genetic predisposition for ADHD on the manifestation of ADHD symptoms may be intricately linked to changes in brain structure (42–44). For example, Sudre *et al.* (42) showed that on a population level, axial diffusivity of the right corona radiata and thickness of the left dorsomedial prefrontal and area of the right lateral temporal cortex mediated the relationship between polygenic risk for ADHD and symptoms of hyperactivity/impulsivity. These findings underscore the value of neuroimaging biomarkers in elucidating genetically driven symptom expression. Consistent with this, polygenic scores (PGSs) have shown early promise in predicting treatment response in disorders such as major depression and schizophrenia (45), although their use in ADHD remains scarcely applied.

Collectively, the studies mentioned above highlight the significance of cortical structural alterations and genetic liability in the expression of ADHD symptoms. These genetic underpinnings and structural alterations not only correlate with symptom severity (30,35) but may also offer valuable insights into predicting treatment response (8,12,35,45). In this context, the interplay between genetic liability and brain structure strengthens the notion that genetic factors are integral to neuroanatomical substrates underlying symptom manifestation. Although genetic influences on ADHD have been well documented in pediatric populations, adult-focused research remains limited, particularly in relation to structural brain correlates and therapeutic response. This gap is especially salient given that despite advances in neuroimaging, the potential links between SD, genetic liability, and therapeutic outcomes remain unexplored.

Extending the rationale presented above, in the current study, we explored whether alterations in SD hold prognostic value in predicting treatment response in adults with ADHD. Expanding on our previous work (12,30) within the context of the COMPAS (Comparison of Methylphenidate and Psychotherapy in Adult ADHD Study) cohort, we investigated pretreatment SD in relation to treatment response following a 12-week intervention period, both across the entire sample and within each treatment group. Additionally, we explored the potential moderating effect of genetic influences on the relationship between SD and treatment response, considering both ADHD-related genetic liability and cross-disorder vulnerability. As the first and largest multicenter randomized clinical trial of its kind, COMPAS assessed the efficacy of group psychotherapy (GPT) in comparison to clinical management (CM), each paired with either methylphenidate (MPH) or placebo (PLA) in adults with ADHD (46–48). To account for the subtle neuroanatomical variability, we applied threshold-free cluster enhancement (TFCE), which offers superior sensitivity over conventional voxel-based morphometry for detecting both focal and distributed effects in neurodevelopmental contexts, while controlling for familywise error (FWE) (49,50).

Building on our previous research, we anticipated that independent of treatment, pretreatment SD would be positively associated with overall ADHD symptom alleviation in predominantly frontal structures. In the context of psychostimulant efficacy, we predicted that shallower SD in prefrontal structures would be positively correlated with greater reductions in hyperactivity symptoms. Similarly, reduced SD in parietal regions was anticipated to be linked to treatment response to GPT in reducing symptoms of inattention. Building on the findings of Sudre *et al.* (42), we also anticipated that ADHD-related genetic liability would moderate the relationship between SD and treatment efficacy, specifically in relation to hyperactivity and impulsivity. Given the complex genetic

architecture of cross-disorder susceptibility, the effects were expected to be pleiotropic and were explored without predefined hypotheses.

METHODS AND MATERIALS

All participants provided written informed consent, and the study was approved by the appropriate ethics and regulatory bodies in accordance with the Declaration of Helsinki (see the Supplement for full details).

Participants

Extending the line of our research (12), we conducted this study with the identical cohort of research participants previously outlined in detail. The final imaging sample comprised 119 individuals with high-quality pretreatment T1-weighted magnetic resonance imaging (MRI) scans, all of whom were scanned exclusively at the Freiburg study center. Participants were evenly distributed across 4 treatment arms: 26 received GPT with MPH, 32 received GPT with PLA, 32 underwent CM with MPH, and 29 underwent CM with PLA. This resulted in balanced allocation across both pharmacological and psychotherapeutic conditions (MPH: n = 58; PLA: n = 61; GPT: n = 58; CM: n = 61). Detailed information on recruitment procedures, exclusion criteria (Table S1), participant flow (Figure S1), and the structure and delivery of each treatment modality is provided in the Supplement. Table 1 summarizes the demographic and psychometric data for the full sample and for each treatment modality. Tables S2 to S4 present baseline group comparisons and longitudinal treatment effects (see the Supplement).

Assessment of Symptomatology

ADHD symptomatology was assessed using the German version of the Conners Adult ADHD Rating Scale (CAARS) (51), a 66-item questionnaire designed to evaluate 4 core symptom domains across 8 subscales: inattention/cognitive problems, hyperactivity/restlessness, impulsivity/emotional lability, issues with self-concept, and 3 DSM-based indices (inattention, hyperactivity/impulsivity, and DSM total score), as well as a global ADHD total score (52). Responses are rated on a Likert scale from 0 (not at all) to 3 (severely), with the questionnaire being available in both a self-report (CAARS S:L) and observer-rated form. For more information regarding the CAARS questionnaire, cf. (52–54). For this study, we primarily focused on the CAARS S:L to assess treatment response, emphasizing self-perceived changes in ADHD symptoms as the key outcome.

PGS Calculation

PGSs were calculated using summary statistics from a genome-wide association study (GWAS) of ADHD (33) and from the Psychiatric Genomics Consortium's Cross-Disorder Group (CDG) GWAS meta-analysis of genetic susceptibility across 8 psychiatric disorders (32). ADHD PGS weights were

Table 1. Demographic and Psychometric Data for the Full Patient Sample (N = 119) and for Each Treatment Modality

	Total Sample, N = 119	MPH, n = 58	PLA, n = 61	GPT, n = 58	CM, n = 61
Age, Years	35 ± 9.9 [19–58]	35 ± 10.7 [19–57]	36 ± 9.1 [20–58]	35 ± 10.7 [19–57]	35 ± 9.84 [19–52]
Sex					
Female	48.7%	50%	47.5%	50%	54.1%
Male	51.3%	50%	52.5%	50%	45.9%
Verbal IQ	113 ± 14.9 [88–145]	113 ± 15.1 [88–143]	112 ± 14.8 [89–145]	111 ± 14.3 [88–143]	114 ± 15.5 [89–145]
TIV, mm^3	1456.42 ± 136.93	1447.98 ± 141.84	1464.44 ± 132.78	1459.91 ± 139.39	1453.1 ± 135.63
Education, University Entrance Diploma	51.3%	55%	47.5%	41%	61%
WURS-k Score	39.87 ± 8.74	39.93 ± 9.56	39.82 ± 7.97	40.5 ± 7.98	40.23 ± 9.41
ADHD Subtype					
Combined	53%	50%	56%	43%	62%
Inattentive	44%	50%	39%	54%	36%
Hyperactive-impulsive	3%	0%	5%	3%	2%
Previous Psychopharmacological Treatment					
≥1 Previous psychopharmacological medication	48%	55%	41%	47%	49%
Antidepressants	32%	33%	31%	29%	34%
Methylphenidate, amphetamine, or other psychostimulants	24%	29.3%	18%	28%	20%
Sedatives, neuroleptics, atomoxetine hydrochloride, mood stabilizers, or others	10%	12%	8%	7%	13%

Values are presented as mean ± SD [range], %, or mean ± SD.
CM, clinical management; GPT, group psychotherapy; MPH, methylphenidate; PLA, placebo; TIV, total intracranial volume; WURS-k, Wender-Utah Rating Scale.

derived from the most recent large-scale meta-GWAS comprising 38,691 cases and 186,843 controls of European (EUR) ancestry, integrating data from iPSYCH, deCODE, and PGC. Fixed-effects meta-analysis, fine-mapping, and functional annotation were used to identify and prioritize putative risk loci. CDG PGS weights were based on a transdiagnostic GWAS meta-analysis including 232,964 cases and 494,162 controls spanning ADHD, anxiety, autism spectrum disorder, major depressive disorder, generalized anxiety disorder, bipolar disorder, schizophrenia, obsessive-compulsive disorder, and Tourette syndrome. Shared genetic architecture across these conditions was characterized using linkage disequilibrium (LD) score regression and cross-trait meta-analysis, identifying pleiotropic loci that contribute to transdiagnostic vulnerability and general psychopathology.

Weights were derived from respective GWAS summary statistics using PGS-CS-auto (55) with the 1000 Genomes (phase 3) (56) EUR data as LD reference panel. PGSs were then calculated within the COMPAS sample using PLINK 2.0 (57). PGSs were *z* scored to have a mean of 0 and a standard deviation of 1. Detailed information about genotyping, quality control, and imputation can be found in the Supplement.

MRI Data Acquisition and Preprocessing

MRI data acquisition and preprocessing followed the same procedure as outlined in our previous publication (30). Detailed information about MRI data acquisition and preprocessing can be found in the Supplement.

Statistical Analyses

Demographic and psychometric data were analyzed using SPSS version 30.0.0 (IBM Corp.). Baseline symptomatology was assessed through separate 1-way multivariate analyses of covariance, with CAARS S:L subscales as dependent variables and treatment condition (e.g., GPT/CM; MPH/PLA) as the independent variable. Group and time effects were examined through separate general linear model repeated-measures analyses of covariance, incorporating time as the within-subject factor and treatment as the between-subjects factor. The CAARS S:L subscales served as dependent variables, with treatment representing specific therapeutic conditions and time capturing changes from baseline to posttreatment at 12 weeks. Age and sex were included as covariates in all analyses. Post hoc analyses were conducted as appropriate. Bonferroni adjustments were applied to account for multiple comparisons, with significance set at $p < .05$.

All brain structural analyses using T1-weighted images were performed using the CAT12 toolbox for SPM12 (version 7771) in MATLAB (version R2021a; The MathWorks, Inc.). Linear regression models assessed correlations between SD and treatment response, both in the full sample and within treatment-specific subgroups. Treatment response was defined as the change in CAARS S:L subscale scores from baseline (week 0) to postintervention (week 13), with positive values indicating greater symptom improvement. In subgroup analyses, participants were stratified into active treatment groups (MPH or GPT), which mitigated the influence of nonprimary variables by balancing their potential confounding impact. Age and sex were controlled for as covariates of no interest, and absolute threshold masking was set to 0.1. TFCE with 5000 permutations for generalized linear model contrast generation was applied for subsequent analysis, testing for both positive and negative correlations. Identified clusters in the surface parameter analyses were annotated using the Desikan-Killiany atlas (58). Statistical significance was defined by a cluster extent threshold of $k > 35$ and $p < .05$ FWE-corrected (combined peak-cluster level), controlling for multiple comparisons.

Moderation Analyses

We performed moderation analyses using the PROCESS macro (version 4.2.1.4) in SPSS version 30.0.0 to investigate whether main effects or interactions between the ADHD or CDG PGS and identified clusters (raw or adjusted beta estimates) significantly predicted changes in ADHD-related psychopathology after 12 weeks of treatment. In these models, the identified clusters served as predictors, the ADHD or CDG PGS served as moderators, and changes in psychopathology over 12 weeks was the outcome. PGSs were standardized to *z* scores by mean centering and scaling to unit variance. Age, sex, and 3 ancestry components were included as covariates to control for potential confounding effects. Significance of moderation effects was assessed using bootstrapping with 10,000 resamples and heteroscedasticity-consistent standard errors (HC3) (59). Effects were considered significant if the 95% CI did not include 0.

RESULTS

Baseline comparisons revealed no significant group differences in SD after FWE correction (all associated FWE-corrected cluster-level *p*s $> .30$). Similarly, baseline symptomatology showed no significant association with pretreatment SD (all associated TFCE values <9806.16, FWE-corrected peak-cluster level $p > .083$) (see Table S5).

Total Sample

Independent of treatment modality, pretreatment SD was positively associated with posttreatment reductions in impulsivity symptoms. The effect centered on the right lingual gyrus (Montreal Neurological Institute [MNI] x/y/z = 16/−9/10, $k = 337$, TFCE = 15,190.52, $p = .039$) (Figure 1), accounting for approximately 8.2% of the variance in symptom change (adjusted $R^2 = 0.082$). In contrast, no significant associations emerged for changes in total score severity, inattention, hyperactivity, self-concept, or related DSM indices (all associated TFCE values $<11,986.18$, FWE-corrected peak-cluster level $p > .063$).

Total Sample Moderation

Neither the ADHD PGS (B = 3.77; SE = 4.16; $t = 0.91$; $p = .37$; 95% CI, −4.49 to 12.04) nor the cross-disorder PGS (B = 5.50; SE = 5.44; $t = 1.01$; $p = .32$; 95% CI, −5.32 to 16.33) showed a significant main effect on changes in impulsivity symptoms following 12 weeks of therapy, irrespective of the treatment modality. Furthermore, neither PGS moderated the association between pretreatment SD in the right lingual cortex and posttreatment impulsivity change. Specifically, the interaction

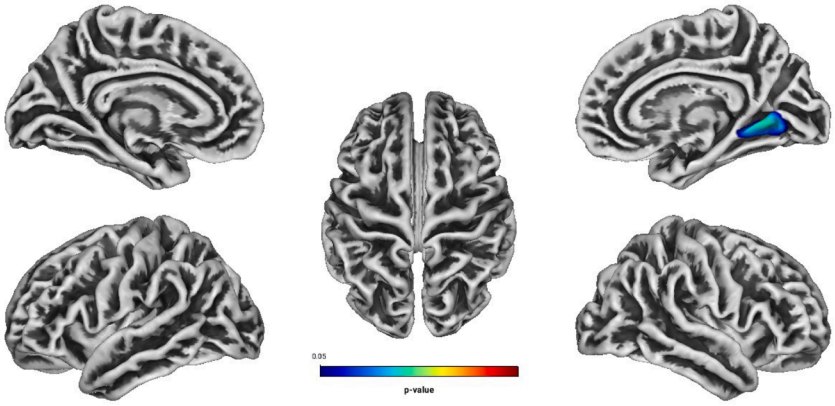

Figure 1. Positive association between sulcal depth and Conners Adult ADHD Rating Scale, self-report impulsivity change (weeks 0–13). Cluster of significant positive correlation at $p < .05$ after threshold-free cluster enhancement, familywise error–corrected combined peak-cluster level.

between SD and the ADHD PGS was nonsignificant (ΔR^2 = 0.01, $F_{HC3\ 1,85}$ = 0.93, p = .34), as was the interaction with cross-disorder genetic liability (ΔR^2 = 0.01, $F_{HC3\ 1,85}$ = 0.93, p = .34) (Table 2).

MPH Group

Pretreatment SD was negatively associated with posttreatment symptom improvement as measured by both hyperactivity and DSM total score change. In patients treated with

Table 2. Summary Statistics for Moderation Models Examining the Influence of PGS on the Relationship Between Adjusted SD Estimates and Changes in ADHD-Related Psychopathology (n = 94)

Factor	Brain Region (Hemisphere)	Cluster Size	Interaction	B	SE	t	ΔR^2	p	95% CI
Treatment Independent									
Impulsivity	Lingual (R)	337	Lingual (R) × ADHD PGS	−0.32	0.33	−0.96	0.008	.338	−0.98 to 0.34
			Lingual (R) × CDG PGS	−0.40	0.42	−0.96	0.008	.338	−1.24 to 0.43
Methylphenidate									
Hyperactivity	SM (L)	76	SM (L) × ADHD PGS	0.79	0.39	2.04	0.047*	.045*	0.02 to 1.57
			SM (L) × CDG PGS	0.59	0.60	0.98	0.022	.329	−0.61 to 1.79
DSM Total Score	SM/postcentral (L)	158	SM/postcentral (L) × ADHD PGS	0.83	0.49	1.71	0.025	.092	−0.14 to 1.8
			SM/postcentral (L) × CDG PGS	−0.02	0.69	−0.03	<0.001	.974	−1.4 to 1.35
Group Psychotherapy									
Total Score	Lingual/PH (R)	1656	Lingual/PH (R) × ADHD PGS	−2.98	3.05	−0.98	0.015	.331	−9.05 to 3.08
			Lingual/PH (R) × CDG PGS	−0.56	3.86	−0.14	<0.001	.886	−8.24 to 7.12
Inattention	Lingual/PH (R)	1947	Lingual/PH (R) × ADHD PGS	0.83	0.52	1.6	0.038	.116	−0.21 to 1.86
			Lingual/PH (R) × CDG PGS	0.92	0.54	1.71	0.046	.091	−0.15 to 2
	PC/lingual (L)	2377	PC/lingual (L) × ADHD PGS	1.38	0.71	1.95	0.03	.054	−0.02 to 2.79
			PC/lingual (L) × CDG PGS	0.49	0.82	0.60	0.004	.552	−1.13 to 2.11
	SF/precentral (L)	1851	SF/precentral (L) × ADHD PGS	0.81	1.5	0.54	0.005	.592	−2.17 to 3.78
			SF/precentral (L) × CDG PGS	1.12	1.43	0.78	0.008	.437	−1.72 to 3.95
	SP/IP (L)	544	SP/IP (L) × ADHD PGS	−0.65	0.46	−1.42	0.029	.161	−1.55 to 0.26
			SP/IP (L) × CDG PGS	−0.89	0.32	−2.79	0.066*	.007*	−1.53 to −0.26
Impulsivity	Precuneus (R)	56	Precuneus (R) × ADHD PGS	−0.14	0.77	−0.18	<0.001	.858	−1.67 to 1.4
			Precuneus (R) × CDG PGS	−1.61	0.77	−2.08	0.046*	.04*	−3.15 to −0.07
Self-Concept	Precentral (L)	150	Precentral (L) × ADHD PGS	−0.72	0.57	−1.25	0.024	.216	−1.85 to 0.43
			Precentral (L) × CDG PGS	0.77	0.60	1.28	0.025	.205	−0.43 to 1.97
DSM Total Score	PH/lingual (R)	407	PH/lingual (R) × ADHD PGS	−0.48	0.72	−0.66	0.008	.511	−1.92 to 0.96
			PH/lingual (R) × CDG PGS	0.83	0.88	0.94	0.018	.349	−0.92 to 2.59

Moderation models accounted for the effect of age, sex, and 3 ancestry principal components. Heteroskedasticity-robust standard errors were used to calculated CIs [HC3 (60)].

*$p < .05$.

ADHD, attention-deficit/hyperactivity disorder; CDG, Cross-Disorder Group; IP, inferior parietal cortex; L, left; PC, posterior cingulate cortex; PGS, polygenic score; PH, parahippocampal gyrus; R, right; SD, sulcal depth; SF, superior frontal gyrus; SM, supramarginal gyrus; SP, superior parietal cortex.

Table 3. Associations of Sulcal Depth and CAARS S:L in ADHD-Related Psychopathology Change (Weeks 0–13) in the Methylphenidate Subgroup (*N* = 119)

Factor	Correlation	Coordinates of the Maximum Intensity Voxel, x/y/z, MNI	Anatomical Labeling	Hemisphere	*k*	*p*	TFCE
Hyperactivity	Negative	−46/−4/38	100% supramarginal	Left	76	.047	14,340.49
DSM Total Score	Negative	−34/0/40	53% supramarginal 47% postcentral	Left	158	.046	14,013.91

Table shows associations at $p < .05$, TFCE, FWE-corrected combined peak-cluster level. *k* represents the cluster extent size.
CAARS S:L, Conners Adult ADHD Rating Scale, self-report; FWE, familywise error; MNI, Montreal Neurological Institute; TFCE, threshold-free cluster enhancement.

MPH, reduced SD in the left supramarginal gyrus (SMG) predicted greater reductions in hyperactivity posttreatment (see Table 3 and Figure 2), whereas a similar association with DSM total score change was also linked to pretreatment SD in the left SMG and postcentral gyrus (Table 3 and Figure 3). The directionality of effects illustrated by trend lines is depicted in Figures S2 and S3 (see Supplement).

No additional significant associations were found between any subscale and pretreatment SD (all associated TFCE values <13,695.86, FWE-corrected peak-cluster level $p > .05$). Similarly, treatment effects on ADHD-related symptom alleviation were not statistically significant ($F_{7,109} = 1.26$, $p = .28$, $\eta_p^2 = 0.08$, Wilk's $\Lambda = 0.93$) (see Table S4).

MPH Group Moderation

There was a significant moderation effect of ADHD PGS on the relationship between pretreatment SD in the left SMG and hyperactivity change after 12 weeks of therapy with MPH ($\Delta R^2 = 0.047$; $F_{HC3\ 1,87} = 4.14$; $p = .045$; 95% CI, 0.02 to 1.57).

Conditional effects modeling demonstrated that although the association between SD and hyperactivity change shifted in magnitude and direction across levels of the ADHD PGS, Johnson-Neyman analysis yielded no significant transition points. At a low level of ADHD PGS (−2.23), the effect of SD on hyperactivity change was negative (B = −1.59; SE = 0.97; $t = -1.65$; $p = .10$; 95% CI, −3.52 to 0.33), whereas at a high level of ADHD PGS (2.28), the effect was positive but marginally nonsignificant (B = 1.98; SE = 1.02; $t = 1.95$; $p = .06$; 95% CI, −0.04 to 4.01). Neither the ADHD PGS (B = −0.48; SE = 0.57; $t = -0.84$; $p = .41$; 95% CI, −1.61 to 0.66) nor the cross-disorder PGS (B = 1.4; SE = 0.53; $t = 0.26$; $p = .79$; 95% CI, −0.92 to 1.2) exhibited significant main effects on changes in posttreatment hyperactivity symptoms. All remaining moderation analyses were also statistically nonsignificant (all associated *p* values > .092).

GPT Group

Among patients undergoing GPT, pretreatment SD was positively associated with posttreatment total score change, primarily in the right lingual and the parahippocampal gyri (see Table 4 and Figure 4). Improvements in inattention were similarly linked to increased pretreatment SD in 4 distributed clusters across both hemispheres (see Table 4 and Figure 5). In addition, greater SD in the right precuneus predicted posttreatment reductions in impulsivity (see Table 4 and Figure 6), while posttreatment improvement in self-concept was positively associated with SD in the left precentral gyrus (see Table 4 and Figure 7). Consistent with these results, posttreatment DSM total score change also showed a positive relationship with pretreatment SD in the right parahippocampal gyrus and right lingual cortex (see Table 4 and Figure 8). Figures S4 to S11 illustrate these effects through trend lines, visualizing interactions between SD and both treatment groups.

In contrast, no statistically significant relationships between hyperactivity change or its DSM index and SD were observed (all associated TFCE values <7456.89, FWE-corrected peak-cluster level $p > .15$). However, there was a significant group effect on overall symptom reduction ($F_{7,109} = 3.09$, $p = .01$, $\eta_p^2 = 0.17$, Wilk's $\Lambda = 0.84$)

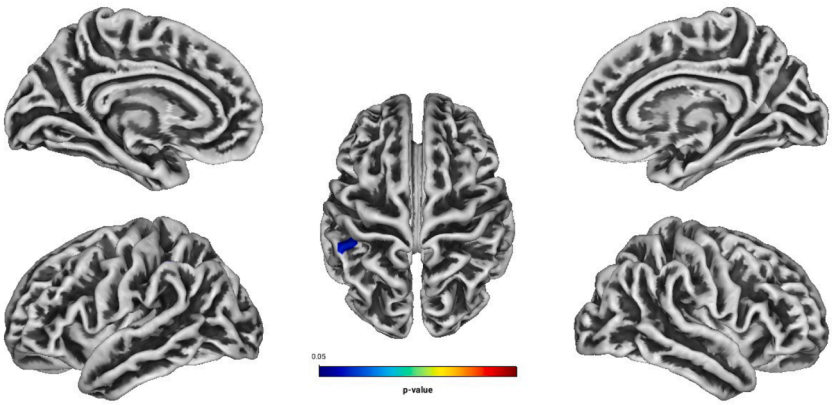

Figure 2. Negative association between sulcal depth and Conners Adult ADHD Rating Scale, self-report hyperactivity change (weeks 0–13) for methylphenidate treatment. Cluster of significant positive correlation at $p < .05$ after threshold-free cluster enhancement, familywise error–corrected combined peak-cluster level.

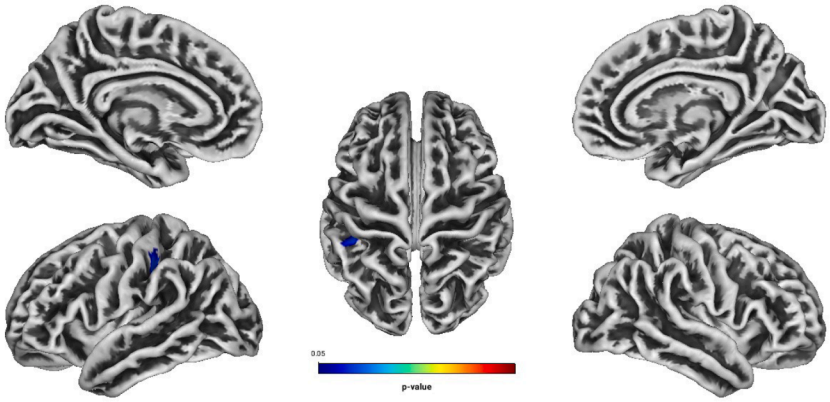

Figure 3. Negative association between sulcal depth and Conners Adult ADHD Rating Scale, self-report DSM total score change (weeks 0–13) for methylphenidate treatment. Cluster of significant positive correlation at $p < .05$ after threshold-free cluster enhancement, familywise–corrected combined peak-cluster level.

(see Table S4). Notably, CM showed superior efficacy compared with GPT in reducing total ADHD symptoms, symptoms of inattention, and symptoms of impulsivity after 12 weeks of therapy.

GPT Group Moderation

Neither the ADHD PGS (B = −3.15; SE = 2.76; t = −1.14; p = .26; 95% CI, −8.63 to 2.33) nor the cross-disorder PGS (B = 0.58; SE = 3.33; t = 0.17; p = .87; 95% CI, −6.04 to 7.2) demonstrated significant main effects on posttreatment total symptom change after 12 weeks of GPT. Similarly, neither the interaction between SD and the ADHD PGS (ΔR^2 = 0.015, $F_{HC3\ 1,87}$ = 0.96, p = .33) nor SD and the CDG PGS ($\Delta R^2 <$ 0.001, $F_{HC3\ 1,87}$ = 0.02, p = .89) significantly predicted the posttreatment total score change after 12 weeks of GPT treatment.

Nevertheless, the interaction between the CDG PGS and SD in the superior and parietal cortex significantly predicted inattention change after 12 weeks of GPT treatment (ΔR^2 = 0.066; $F_{HC3\ 1,87}$ = 7.76; p = .01; 95% CI, −1.53 to −0.26). The Johnson-Neyman method identified significance regions for PGS values <−1.1 and >1.15. An ADHD PGS load <−1.1 yielded positive PGS effects on the association between SD and inattention score changes (all associated B values >0.93, $p < .05$), while an ADHD PGS load >1.15 demonstrated

Table 4. Associations of Sulcal Depth and CAARS S:L in ADHD-Related Psychopathology (Weeks 0–13) in the Psychotherapy Subgroup (*N* = 119)

Factor	Correlation	Coordinates of the Maximum Intensity Voxel, x/y/z MNI	Anatomical Labeling	Hemisphere	*k*	*p*	TFCE
Total Score	Positive	8/−37/1	33% lingual 23% parahippocampal 21% fusiform	Right	1656	.03	16,743.54
Inattention	Positive	6/−42/7	33% lingual 15% parahippocampal 13% pericalcarine 11% precuneus 11% isthmus cingulate	Right	1947	.02	20,077.26
	Positive	−2/7/34	20% posterior cingulate 19% lingual 16% isthmus cingulate 11% parahippocampal 10% pericalcarine 10% paracentral	Left	2377	.04	15,330.48
	Positive	−35/14/64	46% superior frontal 27% precentral 14% caudal middle frontal	Left	1851	.036	15,908.19
	Positive	−25/−37/41	69% superior parietal 31% inferior parietal	Left	544	.044	14,623.47
Impulsivity	Positive	12/−17/30	100% precuneus	Right	56	.049	13,348.92
Self-Concept	Positive	−42/13/49	100% precentral	Left	150	.043	14,144.07
DSM Total Score	Positive	23/1/−7	73% parahippocampal 14% lingual	Right	407	.041	15,102.7

Table shows associations at $p < .05$, TFCE, FWE-corrected combined peak-cluster level. *k* represents the cluster extent size.
CAARS S:L, Conners Adult ADHD Rating Scale, self-report; FWE, familywise error; MNI, Montreal Neurological Institute; TFCE, threshold-free cluster enhancement.

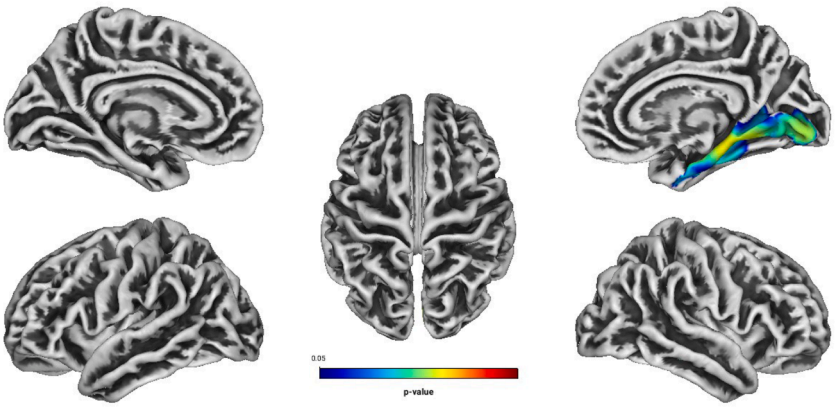

Figure 4. Positive association between sulcal depth and Conners Adult ADHD Rating Scale, self-report total score change (weeks 0–13) for the psychotherapy subgroup. Cluster of significant positive correlation at $p < .05$ after threshold-free cluster enhancement, familywise error–corrected combined peak-cluster level.

negative effects on the relationship (all associated B values <-1.07, $p < .05$). All remaining analyses assessing the main effects of either the ADHD or the cross-disorder PGS on inattention change yielded nonsignificant results ($p > .16$). Likewise, none of the interaction terms evaluating whether ADHD- or cross-disorder genetic liability moderated the association between pretreatment SD and inattention score change reached statistical significance ($p > .054$).

The CDG PGS significantly moderated the relationship between the right precuneus and impulsivity change after 12 weeks of GPT ($\Delta R^2 = 0.046$, $F_{HC3\ 1,87} = 4.34$, $p = .04$). The Johnson-Neyman method revealed a statistically significant region of negative effect for PGS values >0.49 (all associated B values <-1.31, $p < .05$).

There was also no significant main effect of either the ADHD PGS (B = −0.34; SE = 0.67; $t = -0.52$; $p = .61$; 95% CI, −1.67 to 0.98) or the CDG PGS (B = 0.28; SE = 0.70; $t = 0.4$; $p = .69$; 95% CI, −1.12 to 1.68) on impulsivity change after 12 weeks of GPT. Similarly, the interaction term between the ADHD PGS and SD in the right precuneus was not significantly associated with impulsivity change ($\Delta R^2 < 0.001$, $F_{HC3\ 1,87} = 0.03$, $p = .86$).

Moreover, the ADHD PGS did not exert a significant main effect on self-concept change (B = −0.1; SE = 0.42; $t = -0.25$; $p = .81$; 95% CI, −0.94 to 0.74). Similarly, the cross-disorder PGS was also not significantly associated with changes in self-concept (B = −0.27; SE = 0.38; $t = -0.72$; $p = .48$; 95% CI, −1.03 to 0.49). Likewise, the interaction between pretreatment SD in the left precentral gyrus and the ADHD PGS did not significantly predict posttreatment changes in self-concept ($\Delta R^2 = 0.024$, $F_{HC3\ 1,87} = 1.56$, $p = .22$). A similar absence of moderation was observed for the interaction with the cross-disorder PGS ($\Delta R^2 = 0.025$, $F_{HC3\ 1,87} = 1.63$, $p = .21$).

Lastly, neither the ADHD PGS (B = −1.02; SE = 0.89; $t = -1.15$; $p = .25$; 95% CI, −2.78 to 0.74) nor the cross-disorder PGS (B = 0.01; SE = 1.00; $t = 0.01$; $p = .99$; 95% CI, −1.98 to 2.01) showed significant main effects on changes in DSM total symptom severity following 12 weeks of GPT. Moreover, neither the interaction between the ADHD PGS and pretreatment SD ($\Delta R^2 = 0.008$, $F_{HC3\ 1,87} = 0.44$, $p = .51$) nor the corresponding interaction with the cross-disorder PGS ($\Delta R^2 = 0.018$, $F_{HC3\ 1,87} = 0.89$, $p = .35$) reached statistical significance.

DISCUSSION

The variability in treatment response among individuals with ADHD presents a significant challenge in the therapeutic

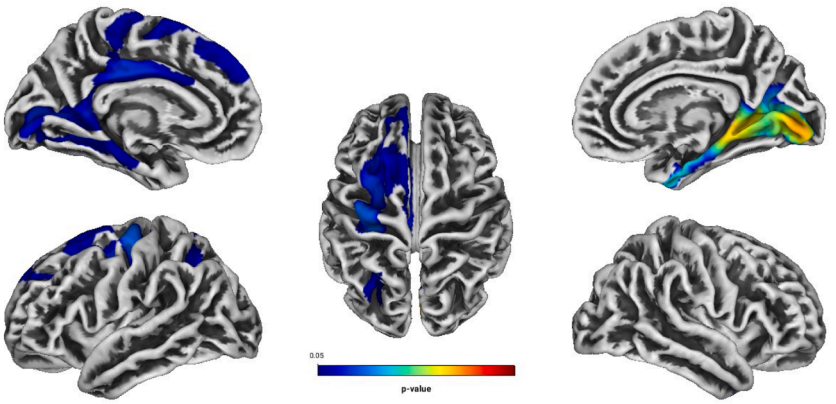

Figure 5. Positive association between sulcal depth and Conners Adult ADHD Rating Scale, self-report inattention change (weeks 0–13) for the psychotherapy subgroup. Cluster of significant positive correlation at $p < .05$ after threshold-free cluster enhancement, familywise error–corrected combined peak-cluster level.

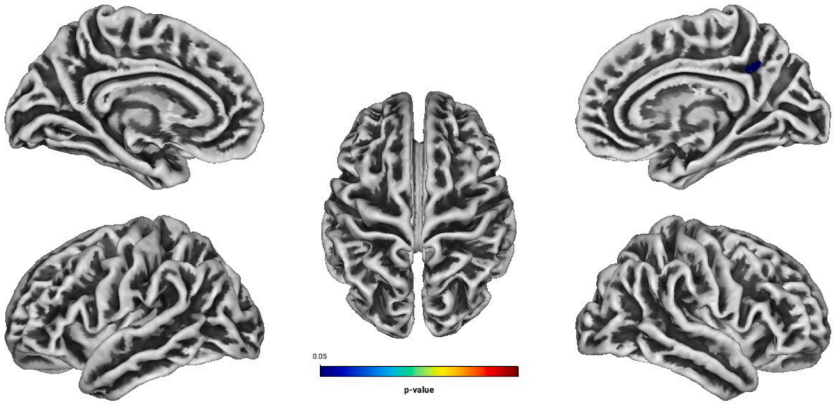

Figure 6. Positive association between sulcal depth and Conners Adult ADHD Rating Scale, self-report impulsivity change (weeks 0–13) for the psychotherapy subgroup. Cluster of significant positive correlation at $p < .05$ after threshold-free cluster enhancement, familywise–corrected combined peak-cluster level.

management of the condition, complicating clinical decision making and effectively limiting therapeutic efficacy. In an effort to explore this variability, we assessed the prognostic value of pretreatment SD on initial treatment response following 12 weeks of treatment with GPT or CM combined with either MPH or PLA in adults with ADHD. Subsequent moderation analyses explored whether cross-disorder genetic susceptibility and ADHD-related genetic risk influenced these relationships, if detected.

Contrary to our expectations, SD in frontal structures did not predict overall ADHD symptom alleviation independent of treatment modality. Instead, we found significant positive associations between SD in the right lingual gyrus and reductions in impulsivity symptoms. This is consistent with the notion that structural variations in the lingual gyrus may be a vulnerability marker for ADHD (61). Further supporting this, previous research has associated greater cortical gyrification in the right lingual gyrus with increased impulsiveness (62) and greater lingual cortex activity with more pronounced symptoms of inattention and impulsivity (63).

Similarly, our findings contradict the initial assumption that shallower pretreatment SD in prefrontal structures would potentiate psychostimulant efficacy in reducing hyperactivity symptoms. Rather, treatment with MPH was more effective in patients exhibiting shallower SD in the left SMG, a key region of the parietal lobe. Additionally, shallower SD in the (left) SMG and postcentral gyrus corresponded to a more pronounced reduction in overall ADHD symptom severity under DSM criteria. As a key region within the somatosensory association cortex, the left SMG is integral to sensorimotor adaptations (64) such as motor attention (65) or spatial processing (66). This functional importance is further underscored by previous research linking lower local efficiency in the left SMG to higher ADHD symptom scores, reinforcing its role in attention and impulse control (67). Subsequent moderation analysis further supports this notion, revealing that genetic susceptibility influences the relationship between SD in the left SMG and changes in hyperactivity symptoms following MPH. Specifically, greater SD in the left SMG may facilitate symptom reduction in individuals with lower genetic risk for ADHD when treated with MPH, whereas the opposite trend is observed in individuals with higher genetic risk. This interplay between genetic predisposition and cortical morphology may reflect differential cortical maturation, with deeper SMG sulci supporting greater neural efficiency and motor regulation. Individuals with lower genetic ADHD susceptibility may develop deeper SMG sulci, providing a more sophisticated neural substrate for MPH to act upon. Consistent with this, Griffith

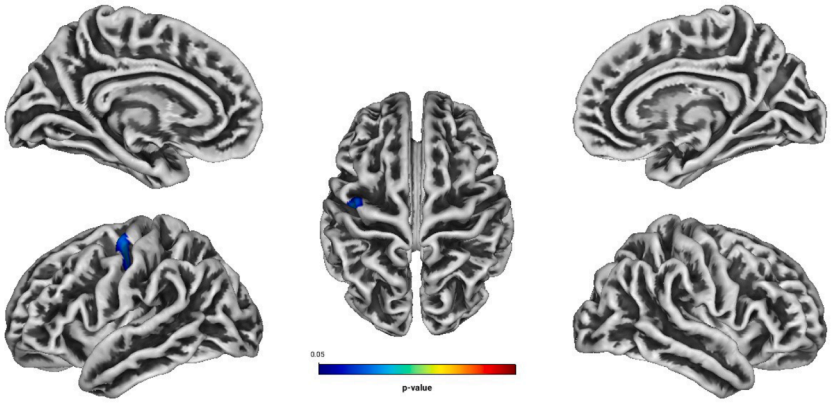

Figure 7. Positive association between sulcal depth and Conners Adult ADHD Rating Scale, self-report self-concept change (weeks 0–13) for the psychotherapy subgroup. Cluster of significant positive correlation at $p < .05$ after threshold-free cluster enhancement, familywise error–corrected combined peak-cluster level.

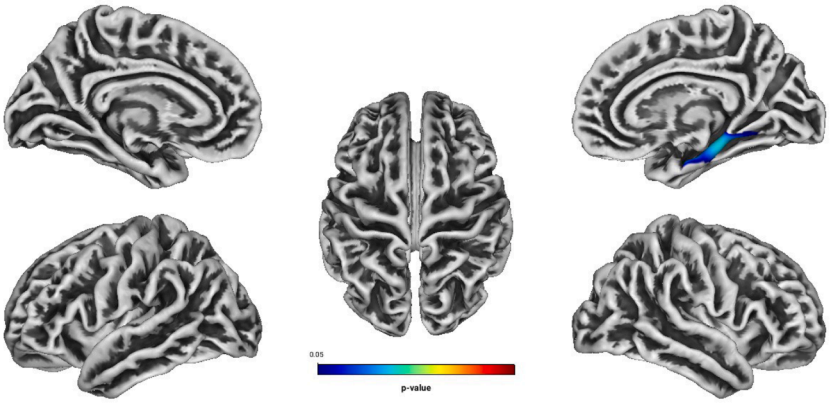

Figure 8. Positive association between sulcal depth and Conners Adult ADHD Rating Scale, self-report DSM total score change (weeks 0–13) for the psychotherapy subgroup. Cluster of significant positive correlation at $p < .05$ after threshold-free cluster enhancement, familywise–corrected combined peak-cluster level.

et al. (68) reported that higher local efficiency in the SMG at baseline predicted greater ADHD symptom reduction following 6 weeks of MPH treatment, although this effect was confined to the right hemisphere.

Contrary to our expectations, we could not confirm our initial hypothesis that reduced SD in parietal regions is linked to a reduction of inattention following GPT. Instead, our findings highlight greater SD in the (right) lingual and parahippocampal gyri as key contributors to GPT efficacy. Furthermore, greater SD in the left superior frontal, superior parietal, and posterior cingulate cortices was associated with attentional improvements, while impulsivity reductions were uniquely linked to greater SD in the (right) precuneus. These findings are also consistent with previous evidence highlighting the role of the superior frontal cortex (69) and the posterior cingulate in attentional (70) and cognitive control (71) and the precuneus in impulsivity modulation (72).

Furthermore, subsequent moderation analysis revealed that genetic cross-disorder susceptibility influences the relationship between SD in the (left) superior- and parietal cortex and attentional improvements after 12 weeks of GPT. Specifically, we showed a bidirectional effect, with greater SD being linked to greater improvement in inattention in individuals with low genetic load who were undergoing GPT but reducing improvement in those with high genetic load. A similar pattern emerged for impulsivity change, where higher cross-disorder PGS was associated with weaker improvements when SD was greater in the (right) precuneus. Impulsivity and inattention are not only hallmark features of ADHD but also of other neurodevelopmental disorders, including autism spectrum disorder and learning disabilities (73). This phenotypic overlap suggests shared neurobiological mechanisms, likely shaped by common genetic variants that influence broad neural network dysregulation. This notion is supported by genetic findings, particularly those from large-scale genome-wide association analyses (32,33), which form the basis of the PGSs used in this study. Demontis *et al.* (33) identified 76 prioritized risk genes that are associated with early embryonic development and involved in cognitive abilities, including *PTPRF*, *SORCS3*, *DCC*, *FOXP1*, and *FOXP2*. While *PTPRF*, *SORCS3*, and *DCC* are linked to integral components of the postsynaptic density membrane that have been linked to ADHD pathology (74), *FOXP1* and *FOXP2* encode transcription factors that regulate transcription in brain tissue and are expressed in major cell types of the brain, including both excitatory and inhibitory neurons and midbrain dopaminergic neurons (75,76). Notably, the most highly pleiotropic locus in the analyses of the Cross-Disorder Group also maps within *DCC*, a key regulator of early white matter development and axon guiding in the brain (77,78). Mutations that compromise *DCC* function lead to severe neurodevelopmental syndromes characterized by the loss of midline commissural tracts and widespread disorganization of white matter pathways (77,79). Its pleiotropic influence on various psychiatric disorders that emerge during childhood and adolescence is consistent with its pivotal role in both the early establishment of neural circuits and the maturation of mesolimbic dopaminergic projections to the prefrontal cortex during adolescence (80,81).

The transition from broad genetic predisposition to distinct psychiatric syndromes, such as ADHD, likely involves a complex interplay of additional genetic and environmental factors, with possible epigenetic modifications mediating their effects on brain structure, function, and behavior, ultimately influencing symptom severity (32). Disruptions in these neurodevelopmental processes, whether of genetic or environmental nature, may then alter cortical folding and increase susceptibility to psychiatric conditions (82). Therefore, cortical folding may not only serve as a marker of neurodevelopmental integrity (83) but may also hold prognostic value in identifying subgroups of patients with low response to treatments (12,84).

Nevertheless, the role of SD as a predictor of treatment success in adults with ADHD requires further validation in independent cohorts. This necessity is further highlighted by the inconsistencies in previous research on SD abnormalities in ADHD. While studies identified structural differences in SD among children with ADHD (28,29), the evidence is not uniform. For example, the largest imaging study to date by Hoogman *et al.* (39) found significant deviations in cortical surface area and thickness in childhood, but differences were no longer evident in adolescence or adulthood. Similarly, our research group did not detect differences in SD between adult patients and control participants (31). Additionally, 3 methodological considerations should be acknowledged while interpreting our

results. First, although FWE correction for multiple comparison was applied within each analysis, no correction was implemented across all analyses. Applying a stringent correction over all analyses would have rendered the observed effects statistically nonsignificant, as the adjusted significance threshold would be prohibitively low for the sample size available in this study. Second, while TFCE has been recognized to improve sensitivity in detecting significant effects, it also induces spatial bias (85). Third, although our sample size (n = 94) for the moderation analyses is comparable with that of previous neuroimaging studies in ADHD, power limitations in detecting small moderation effects need to be recognized. Post hoc power analyses indicated achieved power between 57.66% and 72.21% for significant effects, implying that certain PGS interactions, although not reaching statistical significance, may represent meaningful trends that could solidify with greater statistical power in larger samples.

Further multimodal studies in larger cohorts integrating functional data with structural abnormalities hold promise to lead to a more comprehensive understanding of how cortical and functional irregularities contribute to symptom manifestation and persistence. Extending treatment duration alongside multiple longitudinal anatomical scans may help to identify novel biomarkers linked to treatment response. The specificity and sensitivity of these and our previously identified markers should be validated in independent cohorts, particularly within neurodevelopmental conditions characterized by overlapping traits such as inattention and impulsivity. Lastly, long-term studies spanning treatment outcomes over greater periods of time may offer valuable insight into the durability and sustained efficacy of interventions.

ACKNOWLEDGMENTS AND DISCLOSURES

The COMPAS trial is registered with the Current Controlled Trials registry (ISRCTN54096201) and was carried out within the framework of a multicenter research network focused on psychotherapy for adults with ADHD. This work was supported by the German Federal Ministry of Education and Research (BMBF) (Grant Nos. 01GV0605 and 01GV0606, ADHD-NET). The funding bodies had no influence on the study design, data collection or analysis, interpretation of findings, article preparation, or publication decision.

JL, SMai, SMat, BA, LTvE, AK, and AP contributed to conceptualization. JL, FSD, and CM contributed to data curation. JL and FSD contributed to formal analysis. JL, CM, AJF, and AK contributed to validation. JL, CM, AJF, ES, LTvE, AK, and AP contributed to investigation. JL, FSD, and AK contributed to methodology. JL contributed to writing the original draft of the article and visualization. JL, FSD, FS, AK, and AP contributed to writing, reviewing, and editing the article. FS contributed to software. FS, AJF, SMai, SMat, ES, AK, and AP contributed to supervision. SMai, SMat, and LTvE contributed to MR measurements. AJF, SMai, SMat, LTvE, and AP contributed to project administration. ES contributed to investigation. LTvE and AP contributed to resources.

We extend our sincere appreciation to the dedicated staff at all participating study sites for their commitment and sustained efforts throughout the course of this project. We thank Dr. Franziska Degenhardt, Dr. Per Hoffmann, and Stefan Herms for their essential contributions to the genotyping of the COMPAS sample. Finally, we thank all participants, whose involvement was indispensable to the successful completion of this research.

The data will be made available from the corresponding author (JL) upon reasonable request. The data are not publicly available due to privacy and ethical restrictions.

AP declares that she served on advisory boards, gave lectures, performed phase 3 studies, and received travel grants within the last 5 years from MEDICE Arzneimittel, Pütter GmbH & Co. KG, Takeda, Boehringer, and Janssen-Cilag and receives royalties from books published by Elsevier, Hogrefe, MWV, Kohlhammer, Karger, Oxford Press, Thieme, Springer, and Schattauer. She is a member of the German ADHD Guideline Group and an author of the Updated European Consensus Statement. ES declares that she received a travel grant from Takeda and a grant from BMBF. BA declares that she has held lectures for Takeda. LTvE reported serving on advisory boards, delivering lectures, and receiving travel grants within the last 3 years from Eli Lilly and Co., Janssen-Cilag, Novartis, Shire, UCB, GlaxoSmithKline, Servier Laboratories, Janssen, and Cyberonic. All other authors report no biomedical financial interests or potential conflicts of interest.

During the preparation of this work, the authors used ChatGPT 4.0 in order to enhance linguistic clarity and expression. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

ARTICLE INFORMATION

From the Department of Psychiatry and Psychotherapy, University Hospital Bonn, Bonn, Germany (JL, AK, AP); Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany (FSD, CM, AJF); Department of Psychiatry and Psychotherapy, University of Marburg, Marburg, Germany (FSD, FS); Centre for Human Genetics, University of Marburg, Marburg, Germany (CM); Institute of Neuroscience and Medicine, Research Center Jülich, Jülich, Germany (AJF); Department of Psychiatry and Psychotherapy, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany (SMai, SMat, LTvE); Department of Child and Adolescent Psychiatry Lucerne, Lucerne, Switzerland (ES); and Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty of Mannheim, University of Heidelberg, Mannheim, Germany (ES, BA).

AK and AP contributed equally to this work.

Address correspondence to Jonathan Laatsch, M.Sc., at jonathan.laatsch@ukbonn.de.

Received May 16, 2025; revised Aug 14, 2025; accepted Sep 11, 2025.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2025.09.012.

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