

Archival Report

Borderline Personality Traits Are Not Correlated With Brain Structure in 2 Large Samples

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ABSTRACT

BACKGROUND: Borderline personality disorder is associated with severe psychiatric presentations and has been linked to variability in brain structure. Dimensional models of borderline personality traits (BPTs) have become influential; however, associations between BPTs and brain structure remain poorly understood.

METHODS: We tested whether BPTs are associated with regional cortical thickness, cortical surface area, and subcortical volumes ($n = 152$ brain structure metrics) in data from the Duke Neurogenetics Study ($n = 1299$) and Human Connectome Project ($n = 1099$). Positive control analyses tested whether BPTs are associated with related behaviors (e.g., suicidal thoughts and behaviors, psychiatric diagnoses) and experiences (e.g., adverse childhood experiences).

RESULTS: While BPTs were robustly associated with all positive control measures, they were not significantly associated with any brain structure metrics in the Duke Neurogenetics Study or Human Connectome Project, or in a meta-analysis of both samples. The strongest findings from the meta-analysis showed a positive association between BPTs and volumes of the left ventral diencephalon and thalamus (p values $< .005$ uncorrected, p values $> .1$ false discovery rate-corrected). Contrasting high and low BPT decile groups ($n = 552$) revealed no false discovery rate-significant associations with brain structure.

CONCLUSIONS: We find replicable evidence that BPTs are not associated with brain structure despite being correlated with independent behavioral measures. Prior reports linking brain morphology to borderline personality disorder may be driven by factors other than traits (e.g., severe presentations, comorbid conditions, severe childhood adversity, or medication) or reflect false positives. The etiology or consequences of BPTs may not be attributable to brain structure measured via magnetic resonance imaging. Future studies of BPTs will require much larger sample sizes to detect these very small effects.

Keywords: Alcohol, Borderline personality, Brain structure, Impulsivity, Personality trait, Suicidal thoughts

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Borderline personality disorder (BPD) is a severe form of psychopathology characterized by affective instability, interpersonal dysfunction, identity disturbance, and impulsivity. It has a lifetime prevalence of 5.9% in the United States (1), is overrepresented in clinical outpatients (10%–12%) and inpatients (20%–22%) (2), and is associated with high rates of suicide (nearly 10% completed, 75% attempted) (3,4), comorbid psychopathology, treatment utilization (5), and poor treatment response (3). However, despite the widespread individual and societal consequences of BPD (3) and its centrality to general personality dysfunction (6), remarkably little is known about its etiology and neurobiological correlates.

A nascent literature based predominantly on small patient samples ($n = 7$ –76 patients with BPD) has begun to examine brain structure correlates of BPD with meta-analyses ($n = 104$ –395 patients with BPD) and individual studies providing evidence that BPD is associated with reduced volume of corticolimbic structures (7–15), including the

hippocampus (9–13), amygdala (11,13,15), and medial prefrontal cortex (7,14). These differences are located in regions that are critical for cognitive functions including affective processing and decision making, among others (16–20), leading to speculation that they may contribute to the expression of BPD (21). However, these findings arise from small samples that may be more prone to generate false positive and false negative results, and have been largely constrained to region of interest analyses based on a priori hypotheses about the particular brain regions (i.e., corticolimbic structures, primarily the amygdala and hippocampus) that may play a role in the pathology.

A growing body of work suggests that dimensional trait models of personality disorders, including BPD, are clinically useful, valid, and reliable (22). Recent developments in the dimensional, trait-based assessment of BPD (23) enable investigation of BPD-associated personality traits in large unselected samples that are well powered for analyses

unconstrained by prior knowledge. A recently developed BPD-associated metric (the Five-Factor Inventory–Borderline Personality Disorder [FFI-BPD]) from the NEO Five-Factor Inventory (24) converges with explicit measures of BPD (r values = .35–.72); correlates with a time-invariant component of borderline pathology (r = .81); is heritable (40%) with evidence of substantial genetic correlation with explicit BPD measures (r_G = .84); and demonstrates a highly similar profile of correlations with clinical criterion variables (e.g., childhood sexual abuse, depression) (23–26).

In the current study, we examined whether this borderline personality trait (BPT) metric is associated with variability in cortical thickness, surface area, or subcortical volume in data from the Duke Neurogenetics Study (DNS) (n = 1299) and the Human Connectome Project (HCP) (n = 1099). We hypothesized that BPT would be associated with reduced cortical thickness and surface area, and reduced subcortical volume, particularly of corticolimbic regions. Such evidence would suggest that variability in brain structure may predispose individuals to the expression of borderline pathology. To further validate our BPT measure and its investigation in our samples, we expected to replicate links with BPD-associated phenotypes (i.e., impulsivity, psychopathology, childhood maltreatment, perceived stress) as a positive control analysis. Finally, we expected that associations between BPT and brain structure would be primarily attributable to shared genetic variation in our family-based HCP dataset (27) and that such differences may account for links between BPTs and behavioral correlates or may arise as a consequence of the expression of related traits.

METHODS AND MATERIALS

Data were drawn from 2 independent samples: the discovery DNS (n = 1299) and the HCP (n = 1099), the latter of which served as a replication sample.

Participants

Duke Neurogenetics Study. The DNS (N = 1334) assessed a wide range of behavioral, experiential, and biological phenotypes among young adult college students (18–22 years of age). Our final analytic sample consisted of n = 1299 participants (mean age \pm SD, 19.67 \pm 1.25 years; 555 males; 264 diagnosed with a DSM-IV Axis I disorder) (Table 1,

and Table S1 in Supplement 1). Additional information regarding sample recruitment, consent, and inclusion and exclusion criteria are provided in Supplement 1.

Human Connectome Project. The HCP (N = 1206) examines individual differences in brain circuits and their relation to behavior and genetic background among adult (22–35 years of age) participants recruited from the community in a family-based (3–4 siblings per family, most including a twin pair) design (28). We had a final analytic sample of n = 1099 (mean age \pm SD, 28.79 \pm 3.69 years; 503 males) (Table 1). Additional information regarding sample recruitment, consent, and inclusion and exclusion criteria are provided in Supplement 1.

Measures

FFI-BPD Composite. The FFI-BPD is a composite representing BPTs generated using 24 NEO-FFI items (Table S6 in Supplement 1) (23). These items reflect 14 personality facets, drawn from all 5 major personality factors, that expert consensus and meta-analysis agree are associated with BPD. This composite correlates highly with explicit BPD measures across 7 large independent community and adult outpatient samples, including the Personality Assessment Inventory–Borderline Scale (r values = .6–.72), the Structured Clinical Interview for DSM-IV Axis II Disorders BPD subscale (r values = .63–.66), the Structured Interview for DSM-IV Personality BPD subscale (r values = .35–.42), and the Personality Diagnostic Questionnaire–Revised BPD subscale (r = .51) (23,25). The FFI-BPD was drawn from the 240-item NEO Personality Inventory–Revised in the DNS (α = .78; mean = 1.72; SD = 0.41; skewness = 0.26; range: 0.58–3.29) and the 60-item NEO Five-Factor Inventory (24) in the HCP (α = .79; mean = 1.40; SD = 0.39; skewness = 0.30; range: 0.33–3.33). Figure S1 in Supplement 1 shows FFI-BPD distributions in both samples. The mean and distribution of data in the DNS college and HCP general adult community samples were highly comparable to FFI-BPD scores seen in other college (i.e., Sample 1: mean = 1.76; SD = 0.44; and Sample 2: mean = 1.83; SD = 0.43) and general population adult samples (i.e., Sample 3: mean = 1.52; SD = 0.43; and Sample 4: mean = 1.35; SD = 0.37) (23). To better align our results with prior work in clinical samples, we also computed groups of individuals endorsing relatively high (i.e., top decile,

Table 1. Comparison of Discovery (DNS) and Replication (HCP) Samples

	DNS (n = 1299)	HCP (n = 1099)	t/χ^2	p Value
FFI-BPD (BPT) Score, Mean (SD)	1.71 (0.40)	1.42 (0.39)	18.21	$< 2.2 \times 10^{-16}$
Age, Years, Mean (SD)	19.70 (1.25)	28.79 (3.69)	–77.97	$< 2.2 \times 10^{-16}$
Female, ^a n (%)	744 (57.27%)	596 (54.23%)	2.12	.145
Caucasian, ^a n (%)	579 (44.57%)	758 (68.97%)	142.68	$< 2.2 \times 10^{-16}$
African/African American, ^a n (%)	146 (11.24%)	160 (14.56%)	5.60	.018
Asian/Asian American, ^a n (%)	352 (27.1%)	62 (5.64%)	190.38	$< 2.2 \times 10^{-16}$
Hispanic, ^a n (%)	83 (6.39%)	94 (8.55%)	3.77	.052
Multiracial/Native American/Other, ^a n (%)	139 (10.7%)	25 (2.27%)	65.02	7.42×10^{-16}
Segmented Brain Volume, cm ³ , Mean (SD)	1194.76 (114.07)	1180.60 (123.1)	2.90	.004

BPT, borderline personality trait; DNS, Duke Neurogenetics Study; FFI-BPD, Five-Factor Inventory–Borderline Personality Disorder; HCP, Human Connectome Project.

^aAnalysis was run as a χ^2 test, all others were run as t tests.

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FFI-BPD ≥ 2.13 ; total $n = 276$ [$n = 233$ from DNS]) and low (i.e., bottom decile, FFI-BPD ≤ 1.04 ; total $n = 276$ [$n = 61$ from DNS]) levels of FFI-BPD traits across both samples for secondary post hoc analyses (Figure S1 and Table S3 in Supplement 1). Decile groups were selected so that the high group would have FFI-BPD scores comparable to those observed in outpatient clinical samples (23) (means of 1.91 and 2.29) while still retaining a large enough sample size to sufficiently power neuroimaging analyses.

Magnetic Resonance Imaging: Acquisition and Processing of Structural Data

Acquisition parameters and processing of brain structural data for each study are detailed in Supplement 1.

Behavioral Correlates of BPD

Alcohol Use Disorder and Other Forms of Psychopathology. The presence of a DSM-IV alcohol use disorder (i.e., abuse or dependence: DNS $n = 142$; HCP $n = 230$) was assessed in the DNS (past 12 months: abuse $n = 73$, dependence $n = 69$) and HCP (lifetime: abuse $n = 168$, dependence $n = 62$) using the electronic Mini-International Neuropsychiatric Interview and Semi-Structured Assessment for the Genetics of Alcoholism, respectively (29,30). Other DSM-IV Axis I psychopathology and characteristics were also assessed using these same interviews (Table S2 in Supplement 1).

Suicidal Thoughts and Behaviors. The electronic Mini-International Neuropsychiatric Interview suicidality module (30) was used to quantify the presence of suicidal ideation/behavior in the DNS (i.e., ≥ 1 ; $n = 46$) (see Supplement 1). Lifetime suicidal ideation ($n = 103$) was assessed in the HCP using a single item within the Semi-Structured Assessment for the Genetics of Alcoholism (29). Across studies, these variables were queried outside of the depression module.

Impulsivity. DNS participants completed the 30-item self-report Barratt Impulsiveness Scale (31). HCP participants completed the Achenbach Adult Self-Report for Ages 18–59 (ASR) (32). The attention-deficit/hyperactivity disorder (ADHD) score from the ASR was used as a measure of impulsivity.

Perceived Stress. Participants in both samples completed the 10-item version of the Perceived Stress Scale (33), which instructs participants to appraise how unpredictable, uncontrollable, and stressful their daily life was in the preceding week.

Childhood Trauma. Participants in the DNS completed the 28-item Childhood Trauma Questionnaire (34), which asks participants to retrospectively report on the occurrence and frequency of emotional, physical, and sexual abuse as well as emotional and physical neglect before 17 years of age. The instrument's 5 subscales, each representing 1 type of abuse or neglect, have convergent validity with a clinician-rated interviews of childhood abuse (35). The HCP did not include a measure of early-life stress.

Analyses

Positive Control Analyses: Behavioral and Self-report. Positive control analyses tested whether BPTs are associated with BPD-related behavior, perception, and experience. Analyses were conducted in fashion identical to those described for brain structure measures with the exception that brain volume and scanner were not included as covariates. Self-report questionnaire data were winsorized to maintain variability while limiting the influence of extreme outliers (winsorization counts: DNS: FFI-BPD = 2, Barratt Impulsiveness Scale = 6, Perceived Stress Scale = 4, Childhood Trauma Questionnaire = 23; HCP: FFI-BPD = 3, ASR-ADHD = 8, Perceived Stress Scale = 3). Analyses tested associations with both continuous FFI-BPD scores and the difference between participants with low and high FFI-BPD scores.

Primary Analyses: Brain Structure. Primary analyses tested whether BPTs are associated with regional estimates of cortical thickness and surface area, and subcortical volume. These analyses were conducted in R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria), as linear regressions (DNS) and mixed-effect models (HCP) (36), which nested data by family as a random effect. All variables were standardized (z scored) prior to analyses. Covariates included sex, age, segmented brain volume, and self-reported race/ethnicity (i.e., Caucasian/not, African American/not, Hispanic/not) as covariates. DNS analyses controlled for scanner. Further, HCP analyses included dummy-coded variables for genomically verified twin status (dizygotic/not, monozygotic/not) and sibling status (half-sibling/not), and DNS analyses included Asian American/not, as additional covariates in all analyses because of the composition of these samples.

Analyses first focused on corticolimbic regions that have been associated with BPD—the left and right medial prefrontal cortex (thickness and surface area of the medial orbitofrontal cortex and rostral and caudal anterior cingulate cortex), and left and right hippocampus and amygdala (volume). Discovery analyses were conducted using the DNS ($n = 16$ total tests), with replication analyses in the HCP ($n = 16$ total tests), and were false discovery rate (FDR)-corrected for multiple comparisons within each study. Subsequently, analyses examined associations of BPTs with structure across every regional summary measure in the DNS ($n = 152$ total tests), with replication in the HCP ($n = 152$ total tests), with FDR-correction within each study.

To better align our analyses with prior work in clinical samples, post hoc analyses compared participants with scores in the top and bottom deciles (total $n = 552$; see Participants). Finally, as all prior analyses were null (see Results), additional unplanned post hoc analyses examined whether the presence of one or more borderline personality disorder symptoms (binary, $n = 118$ have at least 1 symptom) was associated with brain structure in the DNS (no measure of BPD symptoms was collected in the HCP). As we found no associations between BPTs and brain structure (see Results), we did not test our hypotheses that shared genetic variation would account for observed associations and links between BPTs and behavioral correlates.

Table 2. Borderline Traits Are Robustly Associated With Positive Control Measures

Outcome	DNS (<i>n</i> = 1299)			HCP (<i>n</i> = 1099)		
	β (SE)	<i>t/z</i>	<i>p</i> Value	β (SE)	<i>t/z</i>	<i>p</i> Value
Alcohol Abuse or Dependence ^a	0.43 (0.09)	4.59	4.35×10^{-6}	0.32 (0.08)	4.12	3.85×10^{-5}
Suicidal ideation or Behavior ^a	0.73 (0.16)	4.70	2.60×10^{-6}	0.6 (0.1)	6.16	7.48×10^{-10}
Impulsivity (BIS or ASR)	0.54 (0.02)	22.90	1.13×10^{-97}	0.61 (0.02)	25.29	2.10×10^{-111}
Perceived Stress	0.60 (0.02)	27.55	7.82×10^{-132}	0.59 (0.02)	23.77	6.8×10^{-101}
Childhood Trauma	0.34 (0.03)	12.43	1.39×10^{-38}	–	–	–
Any Borderline Personality Disorder Symptom ^a	0.86 (0.11)	7.96	1.69×10^{-15}	–	–	–

Associations of borderline personality traits (Five-Factor Inventory–Borderline Personality Disorder scores) (dependent variable) with positive control measures (independent variable).

ASR, Achenbach Adult Self-Report impulsivity subscale, measured in the HCP; BIS, Barratt Impulsivity Scale, measured in the DNS; DNS, Duke Neurogenetics Study; HCP, Human Connectome Project.

^aAnalysis was run as a logistic regression; presented effect sizes and standard errors have not been transformed. All effect sizes are standardized; all associations survive Bonferroni correction for multiple comparisons. Analyses included the same covariates as neuroimaging analyses. No measure of borderline personality disorder symptoms or diagnosis, nor any measure of childhood trauma, was present in the HCP.

Meta-analyses. As no region survived FDR-correction in either sample (see Results), association results from the 2 samples were meta-analyzed in an exploratory analysis. Standardized effect sizes from regression analyses (β slope and corresponding standard error) from both samples were entered into meta-analyses conducted with the metafor package in R (37). As in prior analyses, results were FDR-corrected for multiple comparisons ($n = 152$ total tests).

Sensitivity Analysis. As sample sizes were determined by data sources, sensitivity analyses were conducted to determine the minimum effect size that meta-analyses of the DNS and HCP could be expected to detect. Power was set at 99% and 80%, and $\alpha = .0005$ (i.e., controlling for familywise error), using the pwr package in R (38). Results indicated that analyses of BPT and brain structure were well powered to detect small effect sizes, as low as $r = .12$ with 99% power and $r = .09$ with 80% power. Considering each sample independently, analyses were powered at 80% to detect effects as small as $r = .12$. Importantly, these effect sizes are smaller or comparable with reported associations between personality traits and brain structure (39), and between BPD and brain structure (11,13).

RESULTS

Sample Comparisons and Associations Between BPT and Demographic Factors

Comparisons between samples are reported in Table 1. The average age of participants differed between the DNS and HCP, as the DNS recruited exclusively young adults. Consistent with this age difference, BPT scores and brain volumes were higher in the DNS (40,41). Samples also differed in the distribution of self-reported ethnicity; more participants in the DNS reported being from minority backgrounds. Samples did not differ by self-reported sex. BPT was associated with age and ethnicity in both samples and differed according to sex in the HCP (Table S1 in Supplement 1).

Positive Control Results: BPT and BPD-Related Behavioral Phenotypes

Positive control analyses in both samples revealed consistent evidence that BPTs are associated with increased self-

reported impulsivity (Barratt Impulsiveness Scale/ASR-ADHD), perceived stress, childhood maltreatment, suicidal thoughts and behavior, and psychopathology including alcohol use disorder (DSM-IV abuse or dependence) (Table 2). These results survived FDR-correction for multiple comparisons, associations are in the same direction in both samples, and post hoc analyses found that associations remained largely unchanged when participants with an Axis I diagnosis were excluded (Table S5 in Supplement 1). Notably, consistent with evidence that the FFI-BPD composite aligns with explicit measures of borderline personality pathology (23), BPTs were predictive of one or more borderline personality symptoms ($\beta = 2.3$, $p = 1.69 \times 10^{-15}$) (Table 2) and a variety of psychiatric disorders in both samples ($\beta = 1.1$ – 1.25 , $p = 2 \times 10^{-3}$ to 3×10^{-16}) (Table S1 in Supplement 1).

BPT and Brain Structure

BPTs were not significantly associated with individual differences in the 16 a priori brain metrics in either the DNS or HCP, with no nominally significant associations ($p < .05$ uncorrected) in either sample (Supplement 2). Across the 152 extracted summary measures, no association survived FDR correction for multiple comparisons in either sample (Figure 1A, Figures S2 and S3 in Supplement 1, Supplement 2). There were nominally significant associations in both samples (14 in the DNS and 15 in the HCP) (Supplement 2); however, only 3 measures (left pars orbitalis thickness, left superior frontal gyrus surface area, and left ventral diencephalon volume) were associated with BPTs across both samples, and only 1 of these, volume of the left ventral diencephalon, was directionally consistent (DNS $\beta = .04$, $p = .046$; HCP $\beta = .05$, $p = .023$) (Supplement 2). Meta-analyses of results from the 2 samples (Figure 1B, Figure 2, Figure S2 in Supplement 1) revealed no FDR-corrected significant associations and 5 nominally significant associations: 1) left thalamus ($\beta = .047$, $p = .0007$), 2) left ventral diencephalon ($\beta = .043$, $p = .003$), 3) right ventral diencephalon ($\beta = .035$, $p = .01$), 4) left superior frontal thickness ($\beta = .042$, $p = .037$), and 5) left paracentral surface area ($\beta = -.033$, $p = .048$). None of the 16 a priori imaging-derived phenotypes reached nominal significance in the meta-analysis—the top 2 ($p < 0.1$ uncorrected) were positive associations of BPTs with increased volume of the left and right hippocampus (Supplement 2). Results comparing participants

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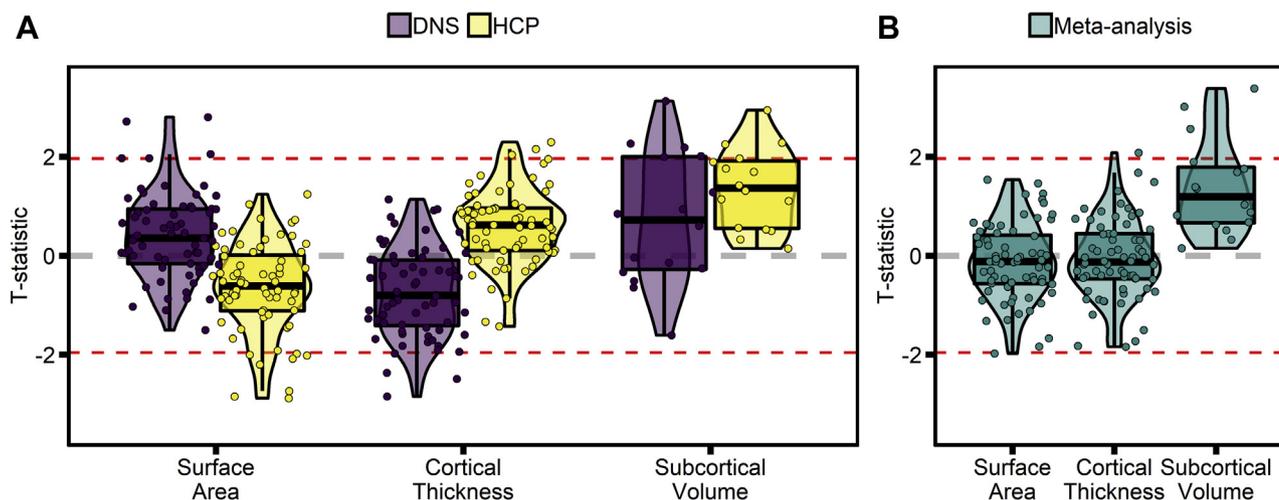


Figure 1. Associations of borderline personality traits with brain structure. T statistics of the association of borderline personality traits (Five-Factor Inventory–Borderline Personality Disorder scores) with summary measures of brain structure (**A**) in the Duke Neurogenetics Study (DNS) and Human Connectome Project (HCP) samples and (**B**) in the meta-analysis of the 2 samples. Associations are displayed by measurement type (cortical surface area, cortical thickness, or subcortical volume), highlighting that findings were most consistent in the subcortex. Dotted red lines are at $T = \pm 1.96$, corresponding to $p = .05$ uncorrected. No association survives correction for multiple comparisons.

with high and low BPT decile groups did not differ substantially, and no association surviving FDR-correction was identified in any analysis (Supplement 2).

Unplanned post hoc analyses found that the presence of at least 1 BPD symptom ($n = 118$) was associated with decreased thickness of the right precentral ($\beta = -.098$, $SE = .028$, $t = -3.535$, $p = .00042$, $p_{FDR} = .04$) and paracental ($\beta = -.095$, $SE = .028$, $t = -3.469$, $p = .00054$, $p_{FDR} = .04$) (Supplement 2) gyri in the DNS even after FDR correction for 152 tests. However, these associations were not robust when correcting for prior analyses of BPTs and brain structure (total tests $n = 304$, both $p_{FDR} = .082$). Associations between BPTs and these regions were similarly negative in the DNS, while associations were positive in the HCP. BPD symptoms were not associated with a priori corticolimbic structures (all uncorrected p values $> .05$); the strongest, nonsignificant correlation was with increased bilateral amygdala volume ($p < .1$) (Supplement 2).

DISCUSSION

Using 2 large independent and unselected neuroimaging samples that were well powered to detect small effects (i.e., r values = .09–.12, 80%–99% power), we examined whether BPTs were associated with individual differences in brain structure and BPD-related behavioral constructs. Two notable findings emerged. First, contrary to our hypotheses, we found no evidence that BPTs are associated with variability in brain structure in unselected samples. Second, we observed consistent associations between BPTs and BPD-related phenotypes (i.e., impulsivity, problematic alcohol use, suicidal thoughts and behaviors, perceived stress, childhood maltreatment) that align with reports of increased rates of alcohol use disorder (1), suicidality (42), impulsivity (43,44), trauma (45), and perceived stress (46) among BPD patients. These later results provide evidence for the validity of the FFI-BPD measure as an assessment of borderline pathology. As such, the null results for structure raise the possibility that prior

positive reports in small clinical patient samples may be attributable to differences in sample composition associated with clinical BPD (e.g., severity, comorbidity, environmental experience, medication) rather than borderline personality traits or may reflect false positive associations.

Brain Structure

Structural imaging studies of BPD patient samples have linked the disorder to reduced gray matter volume in the hippocampus and amygdala, and several cortical regions, with several meta-analyses suggesting that BPD has robust associations with brain structure (7,9–13). Given the prominent role that corticolimbic structures play in emotion and stress regulation (47), the structural differences observed in clinical BPD samples have been conceptualized as reflecting a potential pre-existing vulnerability to emotion and stress dysregulation (11,21,48). In contrast to these positive studies in small patient samples, we observed no evidence that BPTs are associated with structural variation across 2 large unselected neuroimaging samples.

Post hoc analyses found some evidence for associations between the presence of at least 1 BPD symptom and thickness of somatomotor regions, which has been observed in prior reports (14). However, these findings do not survive multiple-comparison correction accounting for prior analyses with BPTs, and associations of BPTs with these structures are directionally opposite in the 2 samples, suggesting that this association may be a false positive or may be developmentally constrained. Indeed, BPD is highly comorbid with ADHD, an association that we replicate (49). Work in large clinical samples has found that structural associations with ADHD are largely constrained to childhood (50,51). If this is also the case with BPD—even though prior reports have exclusively used adult samples—we would not expect to detect such effects in the current study.

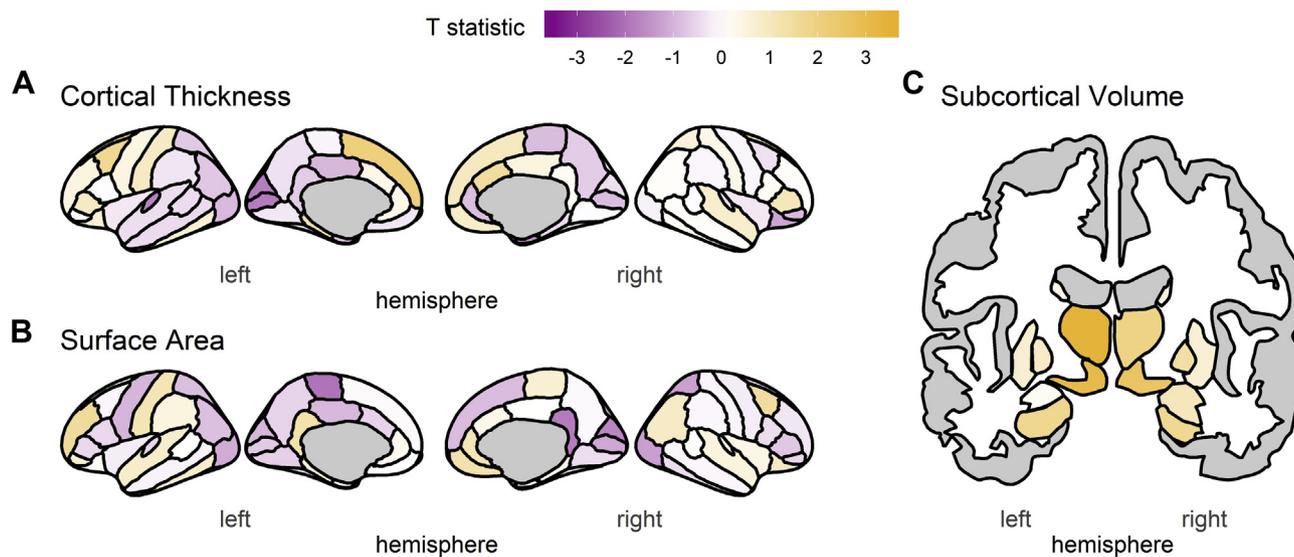


Figure 2. Regional meta-analysis of borderline personality traits and brain structure. Results from the meta-analysis of results from the Duke Neurogenetics Study and Human Connectome Project, including (A) cortical thickness, (B) cortical surface area, and (C) subcortical volume. Colors correspond to the *T* statistic of the association of borderline personality traits (Five-Factor Inventory–Borderline Personality Disorder scores) with regional summary measures—no region survives false discovery rate correction for multiple comparisons.

Many potential explanations may be invoked to account for the discrepancy between our null results and positive reports in clinical patient samples. Unlike BPD patient samples, our studies were unselected for BPD. It is possible that BPD associations with brain structure may be observed only in clinical or extreme presentations of BPD or might be associated with BPD-associated severe comorbidities (e.g., psychopathology, physical health conditions) or experiences (e.g., childhood adversity, medication). Consistent with this speculation, one study reported reduced hippocampal volume only among patients with severe presentations of BPD (i.e., ≥ 7 BPD criteria, $n = 18$) (52). We must also note that differences in subcortical volume, including the hippocampus, are not unique to BPD but have also been reported in depression (53), schizophrenia (54), bipolar disorder (55), ADHD (50), and obsessive-compulsive disorder (56). Thus, some of the previously reported associations with BPD may reflect not borderline pathology but severe general psychopathological distress. If only the most severe cases underlie previously reported associations with BPD, our sample would not have sufficient extreme scores to detect this, and one would not expect to see linear negative correlations between brain structure and BPTs—a central assumption of our statistical models. However, our BPT extreme groups approach, which yielded BPT scores comparable with those observed in outpatient clinical samples with a formal BPD diagnosis (23), revealed null associations.

Further, we observed expected correlations with phenotypes that were not collinear in item composition with our FFI-BPD composite (i.e., suicidal thoughts and behaviors, alcohol use disorder, childhood maltreatment) and with the presence of at least 1 borderline personality disorder symptom (odds ratio: 2.36) (Table 2), and we replicated prior reports of large correlations between BPTs and ADHD symptoms (49). While BPTs were associated with Axis I disorder diagnoses in both samples, a finding that is consistent with well-established

broad comorbidities of BPD (57), correlations between positive control measures and BPTs remained even when participants with a diagnosis were excluded from analyses (Table S5 in Supplement 1). While we cannot rule out that our positive control findings are driven by the presence of general psychopathology, these correlations are consistent with patterns expected of a measure of borderline personality traits.

Thus, these results suggest that our phenotype was sufficiently severe and variable to identify these expected patterns of association, and that previously observed links between BPD and brain structure might not be attributable to BPD-related personality. It remains possible that our samples had other protective factors (e.g., those associated with attending college in the DNS, those associated with participating in a community-based research study in HCP) that in the context of high BPTs prevented clinical levels of expression and related neural correlates.

The present null findings also stand in contrast to a large body of work documenting correlations between brain structure and broad personality traits (i.e., the big five) (58). However, few replicable associations have emerged from these efforts (59). Recently, data from the HCP, which were used as a replication sample in this report, have been repeatedly examined for associations between brain structure and broad personality traits (39,60–64). While there is evidence for associations within this sample that are robust to analytic method (39,61), few findings have so far been independently replicated (59,65–68).

We must also consider more mundane explanations that may also account for our discrepancy with prior literature, including the possibility of false positive results. Small samples and publication bias are more likely to generate false positive results, which may have led meta-analyses to overestimate the association between BPD and brain structure (69,70). Indeed, it is possible that false positive associations may be

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widespread in clinical psychiatric neuroscience where studies of difficult-to-recruit patient samples are often hindered by their limited size and high heterogeneity (71). Consistent with this notion, a large mega-analysis of depression (>17,000 cases) (53) found that the effect size of the association between depression and reduced hippocampal volume is less than half of what was reported in one of the first meta-analyses, which included 351 patients (72). Similarly, while recent studies examining structural correlates of broad personality traits have been well powered by current standards, the scarcity of convergent findings (59,65–68) suggests that associations are smaller than anticipated.

Despite including a replication component, the present report may reflect a false negative finding. While our sensitivity analysis indicated that we were well powered to detect small correlations ($r > .12$, 99% power, $\alpha = .0005$), it is plausible that correlations between borderline personality traits and brain structure exist but that they are smaller than what we could reliably detect. Thus, at minimum, the present report places an upper bound on the effect size that future investigations should plan to detect. For example, if there are correlations at $r = .08$ between BPTs and brain structure, more than double the number of participants ($n = 5300$) would be needed to attain comparable (99%) power. The precision of mapping correlations between BPTs and brain structure may also be improved in future work by using more recently developed algorithms for segmenting subcortical structures (73).

Conclusions

Results of the current study suggest that BPTs are associated with related behavioral constructs but not variability in regional brain structure. A major strength of our work was the consistency of results across 2 large, independent datasets. Notably, these findings should be interpreted in the context of study limitations, including our unselected samples and cross-sectional designs. It remains possible that unique features or correlates of a formal BPD diagnosis, including extreme severity (52), may be associated with structural variability as opposed to BPTs. Nonetheless, our findings suggest that prior reports in small samples linking BPD to brain differences may have detected associations with correlates of its clinical presentation, may have overestimated effects, or may represent false positive associations. Clearly, additional research in large samples enriched for BPD are needed. If extreme severity, not present in our sample, is driving these effects, it will be important to model nonlinear effects in addition to continuous symptom counts. Finally, this work provides strong evidence that future research into the structural neural correlates of BPTs should be powered to detect very small effects.

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