Archival Report

Biological Psychiatry

Generalizable Links Between Borderline Personality Traits and Functional Connectivity

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ABSTRACT

BACKGROUND: Symptoms of borderline personality disorder (BPD) often manifest during adolescence, but the underlying relationship between these debilitating symptoms and the development of functional brain networks is not well understood. Here, we aimed to investigate how multivariate patterns of functional connectivity are associated with borderline personality traits in large samples of young adults and adolescents.

METHODS: We used functional magnetic resonance imaging data from young adults and adolescents from the HCP-YA (Human Connectome Project Young Adult) (n = 870, ages 22–37 years, 457 female) and the HCP-D (Human Connectome Project Development) (n = 223, ages 16–21 years, 121 female). A previously validated BPD proxy score was derived from the NEO Five-Factor Inventory. A ridge regression model with cross-validation and nested hyperparameter tuning was trained and tested in HCP-YA to predict BPD scores in unseen data from regional functional connectivity. The trained model was further tested on data from HCP-D without further tuning. Finally, we tested how the connectivity patterns associated with BPD aligned with age-related changes in connectivity.

RESULTS: Multivariate functional connectivity patterns significantly predicted out-of-sample BPD scores in unseen data in young adults (HCP-YA $p_{permuted}$ = .001) and older adolescents (HCP-D $p_{permuted}$ = .001). Regional predictive capacity was heterogeneous; the most predictive regions were found in functional systems relevant for emotion regulation and executive function, including the ventral attention network. Finally, regional functional connectivity patterns that predicted BPD scores aligned with those associated with development in youth.

CONCLUSIONS: Individual differences in functional connectivity in developmentally sensitive regions are associated with borderline personality traits.

https://doi.org/10.1016/j.biopsych.2024.02.1016

Borderline personality disorder (BPD) is a major mental illness that affects 0.7% to 2.7% of adults in the United States (1). Individuals diagnosed with BPD experience sudden shifts in mood and struggle to maintain stable interpersonal relationships. BPD is also characterized by impulsivity, suicidality, self-harm, feelings of emptiness, intense anxiety and stress, and dissociative symptoms (1,2). BPD is also associated with high rates of death by suicide (4%) compared with other forms of mental illness (1,3–5). BPD and other personality disorders are typically diagnosed in adulthood, but recognizable symptoms often manifest during adolescence (6). Despite their significance, BPD is typically not studied in youth samples, and the relevant underlying developmental neurobiology remains underexplored. Addressing this gap in knowledge is of particular importance given that other major mental illnesses that emerge during adolescence or young adulthood are increasingly understood as disorders of brain development (7).

Previous studies have investigated the link between BPD and brain function and structure using magnetic resonance imaging (MRI) (3,5,8,9) but have yielded inconsistent findings. Studies that have used resting-state functional MRI (fMRI) have reported altered functional connectivity in patients with BPD compared with healthy control participants in networks associated with emotional processing and executive control (8,10,11). Altered functional connectivity has been reported in frontomedial, frontotemporal, and limbic regions (12,13); the frontoparietal network (10,14); the default mode network [e.g., posterior cingulate and precuneus (10,13,15)]; and the salience network [e.g., insula and anterior cingulate cortex (10,12–14)]. More generally, a theoretical perspective on the involvement of frontolimbic circuits in BPD suggests that deficits in the inhibitory function of these regions on circuits associated with social cognition and self-regulation result in emotional dysregulation and behavioral dyscontrol in BPD (16,17). Although functional alterations in these regions may partially explain the disruptions in emotion and regulatory control processes (e.g., impulsivity) common in BPD, some studies have reported no significant differences in neuroimaging data between patients and healthy control participants (18,19). These inconsistencies may be due in part to the heterogeneity in BPD populations. However, interacting methodological factors—in particular,

ISSN: 0006-3223

small sample sizes—may also be the source of such discrepancies (20).

Previous neuroimaging studies of BPD have mainly used case-control designs with small samples of patients with diagnosed BPD. While such designs can be extremely valuable and are ultimately essential for clinical translation, the small size of most case-control studies inevitably reduces the replicability and generalizability of the results. There is growing evidence that large samples, multivariate models, and out-of-sample testing on unseen data are critical to identifying replicable and generalizable brain-behavior associations (20–22). As suggested in part by the Research Domain Criteria (7) and Hierarchical Taxonomy of Psychopathology (23) frameworks, one alternative to small case-control designs in psychiatry is dimensional studies of a clinically relevant construct in larger samples. This perspective is consistent with overwhelming evidence that BPD symptoms vary dimensionally, with functional impairment scaling with symptom severity (23–27). Although dimensional self-report measures of BPD have been developed (28), substantial evidence also supports mapping between personality trait measures and personality disorder constructs (29). Another related caveat in neuroimaging studies of BPD is that dimensional and categorical measures of BPD have usually been assessed only in studies of BPD conducted in small samples of adults; they have not been included in large-scale neuroimaging studies. Few *et al.* (30) recently developed and validated a measure of BPD derived from self-reported personality traits on the NEO Five-Factor Inventory (NEO-FFI), which has been collected widely in larger population surveys and clinical samples. The use of such a proxy measure allows the field to leverage existing large-scale data resources with high-quality neuroimaging data to study BPD, given that the NEO-FFI is available in most large-scale datasets (19).

Here, we aimed to investigate how multivariate functional connectivity patterns are related to borderline personality traits in young adults and adolescents using large-scale publicly available datasets. Specifically, we used fMRI data from 2 large public datasets to characterize functional connectivity in large samples of adolescents and young adults. Then, we used machine learning with rigorous cross-validation to predict borderline personality traits in unseen data from regional patterns of functional connectivity. Finally, to contextualize these results in a developmental framework, we evaluated whether the connectivity patterns that best predicted borderline personality traits aligned with age-related changes of functional connectivity in youth.

METHODS AND MATERIALS

We used functional connectivity from 2 large-scale, publicly available datasets—HCP-YA [Human Connectome Project Young Adult (31)] and HCP-D [Human Connectome Project Development (32)]—to predict individual differences in borderline personality traits estimated by a trait-based BPD proxy score. We note that here the term "predict" refers to a contemporaneous association between BPD and functional connectivity in unseen data rather than prospective prediction of BPD. To investigate the link between functional connectivity and BPD scores in the HCP-YA, a multivariate linear ridge regression model was first trained for each brain region that predicted participants' BPD scores (i.e., dependent variable) from multivariate functional connectivity patterns (i.e., independent predictor) and then was tested on unseen data using cross-validation. As a strong test of the generalizability of our model, we applied a fully trained model from HCP-YA to HCP-D without further training, testing the model on unseen data (i.e., HCP-D was not part of the training). Finally, we assessed the degree to which connectivity patterns that best predicted BPD corresponded to connectivity patterns that displayed the greatest developmental effects in HCP-D.

Participants

Resting-state and task fMRI data from healthy young adults were obtained from HCP-YA (31) (n = 870, ages 22–37 years, 457 female) and from adolescents from HCP-D 2.0 Release (32) (n = 610, ages 5.6–21.9 years, 331 female). Details regarding the scanners, image acquisition protocols, and image processing are included in the Supplement. Preprocessed fMRI time series were parcellated into 400 cortical regions using the Schaefer-400 atlas for the main analysis (33). We also performed sensitivity analyses using another parcellation (Schaefer-200) and subcortex-to-cortex functional connectivity (see the Supplement for details).

Assessment of Borderline Personality Traits

Targeted measures of BPD are usually administered only in focal studies of BPD in adults and are not available in large-scale neuroimaging studies of youths. To obtain a proxy measure of borderline personality traits in HCP-YA and HCP-D, we used a previously validated proxy measure of BPD (30) that has been used to investigate borderline personality traits in large imaging datasets such as HCP-YA (19). This proxy measure estimates BPD scores using 24 items from a widely used personality assessment instrument, the NEO-FFI. Few *et al.* (30) developed and validated this trait-based BPD proxy score across multiple datasets, comparing the BPD score with explicit measures of BPD in both clinical BPD samples and the broader population. Given that the NEO-FFI is available in most large-scale datasets, it provides a useful and scalable route to study BPD-relevant symptoms in large-scale datasets. We used the NEO-FFI instrument to estimate a BPD score for each participant in HCP-YA and HCP-D, as previously described (30) (see Table S1 and the Supplement for more details). Note that the NEO-FFI was available for all participants in HCP-YA, whereas it was only available for participants over age 16 in HCP-D (n = 223, 121 female).

Multivariate Analyses

Previous work has shown that identifying reliable and generalizable brain-behavior associations requires out-of-sample testing and that reliability is enhanced by multivariate analysis approaches (20,21). Accordingly, here we used a machine learning approach to predict BPD proxy scores from multivariate regional functional connectivity patterns. Detailed description of the analysis is included in the Supplement. Briefly, we used linear ridge regression modeling as implemented in Scikit-Learn (34). We trained a separate model for each brain region, predicting each participant's BPD score

from the region's functional connectivity profile in HCP-YA (i.e., all connections between a given region and all other regions). Therefore, the dependent variable was the participant's BPD score, and the independent predictor was a row of their functional connectivity matrix (Figure 1). The models were tested on unseen data from the same cohort using cross-validation. This analysis estimated the association between the BPD score and the functional connectivity profile of each brain region. As described in the Supplement, all models included covariates of age, sex, and in-scanner motion (mean framewise displacement).

Given that multivariate analysis together with large samples and out-of-sample testing are essential for generalizable studies of brain-behavior associations, we next aimed to directly evaluate the generalizability of our approach. We selected HCP-D data because it is a large dataset with a younger age range and was acquired using different sequences and at different scanning sites, which makes it a good candidate to test the generalizability of our model. We used all data from HCP-YA to train regional ridge regression models and applied the trained models to the completely unseen HCP-D data without any additional tuning.

Code and Data Availability

Data used in the current study were obtained from publicly available HCP-YA and HCP-D datasets (31,32). Code used to conduct the analyses is available on GitHub (https://github.com/PennLINC/borderline).

RESULTS

BPD Score Distribution

Following the approach proposed by Few *et al.* (30), the BPD proxy score was estimated from 24 NEO-FFI items in young adults (HCP-YA: mean [SD] = 0.90 [0.39]) and adolescents (HCP-D: mean [SD] = 1.17 [0.43]). We also estimated the internal consistency of the included items using Cronbach's α reliability measure (35). Cronbach's α ranges between 0 and 1, and a value above 0.7 is considered acceptable (acceptable: $0.8 > \alpha > 0.7$; good: $0.9 > \alpha > 0.8$; excellent: $\alpha > 0.9$). Both datasets had acceptable to good α values (HCP-YA: $\alpha = 0.79$; HCP-D: $\alpha = 0.80$). Summary measures from BPD score distributions and sample descriptions are included in Table 1. The BPD score distribution and α values in both samples were comparable to the values reported by Few *et al.* (30) in college students (sample 1: $\alpha = 0.78$, BPD score mean [SD] = 1.76 [0.44]; sample 2: $\alpha = 0.73$, BPD score mean [SD] = 1.83 [0.43]) and a general population of young adults ($\alpha = 0.81$, BPD score mean [SD] = 1.52 [0.43]).

Functional Connectivity Predicts Borderline Personality Traits

We used a multivariate linear ridge regression model to predict BPD proxy scores from regional functional connectivity profiles (i.e., functional connections between a given brain region and all other regions) (Figure 1). Regional models were initially trained on the data from young adults (HCP-YA) and tested on unseen data from the same cohort using cross-validation. We found that multivariate functional connectivity patterns significantly predicted BPD scores (r = 0.14, $p_{permuted}$ = .001) (Figure 2A). For comparison, the group-level model performance was assessed using a global linear ridge regression model where the model was trained and tested using the full upper triangle of functional connectivity data and identified consistent results (r = 0.10, $p_{permuted}$ = .002) (Figure S1A). To ensure that the findings were independent from total brain connectivity, we directly correlated whole-brain mean connectivity with the BPD score and found no relationship between the two (r = 0.07). These findings demonstrate that multivariate functional connectivity patterns are linked to borderline personality traits in young adults. We found that there was substantial heterogeneity in how regional functional connectivity profiles predicted BPD scores (Figure 2B; see regional maps thresholded based on permutation tests in Figure S2). To

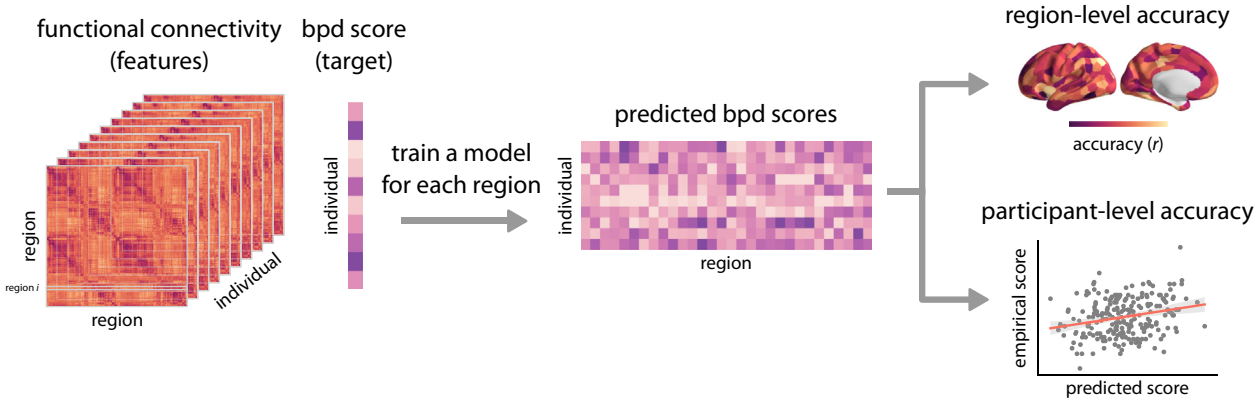

Figure 1. Predicting borderline personality disorder (BPD) proxy scores from multivariate functional connectivity patterns. Functional connectivity data (i.e., features) were used to predict BPD proxy scores (i.e., target) in young adults and adolescents. A separate linear ridge regression model was trained using a given region's functional connectivity profile (e.g., the *i*th row of the connectivity matrix corresponding to the connections between region *i* and all other regions). The regional trained models were applied to the held-out test data to obtain predicted BPD scores for each individual and each region. Region-level accuracy was estimated as the Pearson correlation coefficient *r* between the empirical and predicted BPD scores for each model. Participant-level accuracy was estimated as the Pearson correlation coefficient *r* between the empirical and average predicted BPD scores across regional models.

Table 1. BPD Score Distribution

	HCP-YA, n = 870	HCP-D With NEO-FFI, n = 223	HCP-D, Full Sample, n = 610
Age, Years, Mean (SD) [Range]	28.6 (3.7) [22.0 to 27.0]	19.0 (1.8) [16.0 to 21.9]	14.6 (4.0) [5.6 to 21.9]
Sex, Female/Male, n	457/413	121/102	331/279
BPD Score, Mean (SD) [Range]	0.90 (0.39) [−0.17 to 2.30]	1.17 (0.43) [0 to 2.75]	NA
Reliability Coefficient, Cronbach's α (95% CI)	0.79 (0.77 to 0.81)	0.80 (0.78 to 0.82)	NA

Sample descriptions and BPD score distributions are provided. Note that the BPD proxy score was only estimated for a subset of individuals in HCP-D because the NEO Five-Factor Inventory questionnaire was only available for individuals over age 16. Internal consistency was estimated using Cronbach's α.

BPD, borderline personality disorder; HCP-D, Human Connectome Project Development; HCP-YA, Human Connectome Project Young Adult; NA, not applicable.

investigate whether the regional prediction accuracy was more pronounced in specific functional systems, we estimated the average prediction accuracy for the 7 intrinsic networks defined by Yeo *et al.* (36) (Figure 2C). We found that prediction accuracy was highest for frontoparietal (false discovery rate–corrected p_{spin} = .021) and ventral attention (false discovery rate–corrected p_{spin} = .007) networks, which suggests a link between borderline personality traits and systems involved in emotion regulation and executive function.

Borderline Personality Traits Are Linked to Functional Connectivity in Adolescents

To examine whether the link between functional connectivity and the BPD score identified in early adulthood generalized to late adolescence, we used the previously trained regional models from HCP-YA to predict BPD scores in HCP-D without further tuning. Note that the regional models were trained on HCP-YA data only, and the trained models were applied to HCP-D; as such, the HCP-D data were completely unseen by

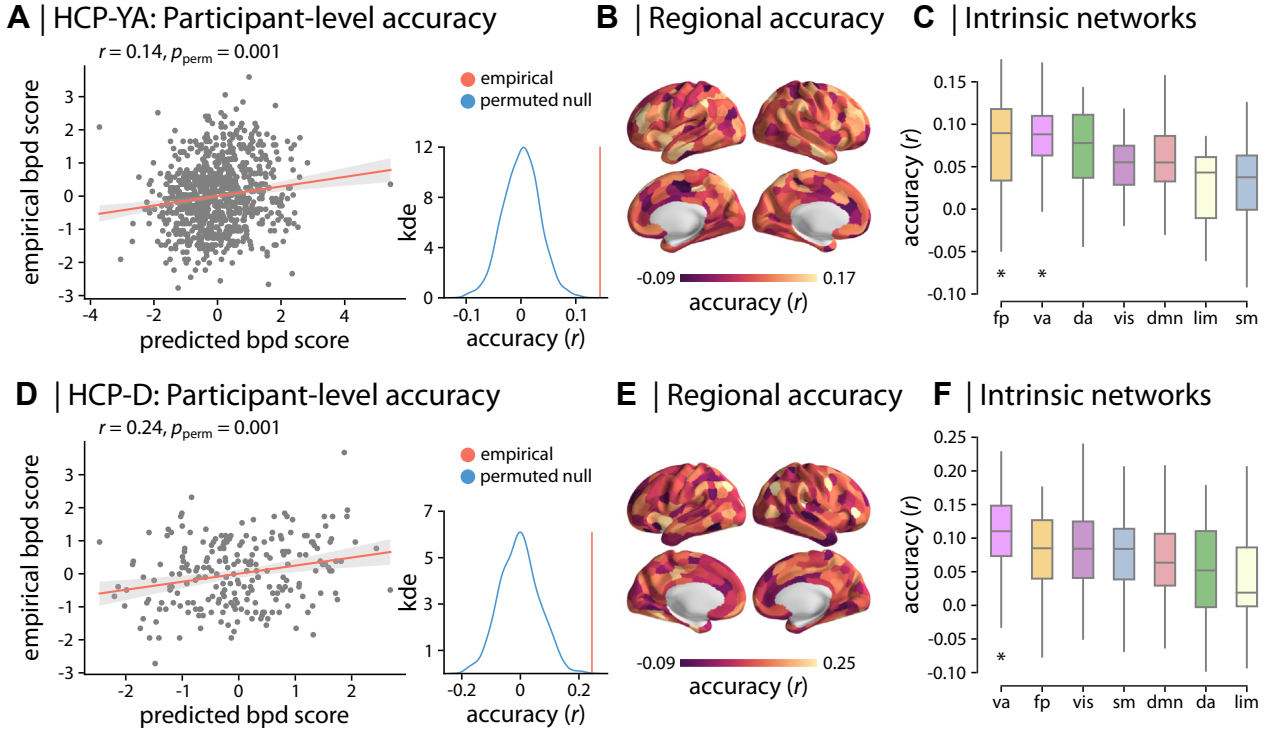

Figure 2. Functional connectivity predicts borderline personality disorder (BPD) scores in young adults and adolescents. Regional linear ridge regression models were used to predict BPD proxy scores from multivariate functional connectivity patterns in **(A–C)** healthy young adults from the HCP-YA (Human Connectome Project Young Adult) data and **(D–F)** adolescents from the HCP-D (Human Connectome Project Development) data. The model performance was assessed as the Pearson correlation coefficient r between the empirical and predicted scores. Participant-level model performance is depicted as scatterplots demonstrating the relationship between the empirical and average BPD scores across regional models (HCP-YA: r = 0.14; 95% CI, 0.08–0.21; HCP-D: r = 0.24; 95% CI, 0.12–0.37). Each point in the scatterplot represents a participant. The participant-level accuracy r (red vertical line) is then compared with a null distribution of accuracies (blue distribution) obtained from 1000 permutation tests, randomly shuffling the samples. Regional out-of-sample model performance is depicted across the cortex for both cohorts (Schaefer-400 atlas; 99% CIs) (see regional maps thresholded based on permutation tests in Figure S2). Finally, the average functional system-level prediction accuracy was estimated for the 7 intrinsic functional networks defined by Yeo *et al.* (32). Asterisk denotes significant system-level prediction accuracy based on 10,000 spatial autocorrelation-preserving null models (false discovery rate [FDR]–corrected $p_{spin} < .05$). Significant system-level accuracy was observed in frontoparietal (FDR-corrected p_{spin} = .021) and ventral attention (FDR-corrected p_{spin} = .007) networks for HCP-YA and in the ventral attention network (FDR-corrected p_{spin} = .0001) for HCP-D. da, dorsal attention network; dmn, default mode network; fp, frontoparietal network; lim, limbic network; sm, somatomotor network; va, ventral attention network; vis, visual network.

the models and therefore assessed the true out-of-sample generalizability of the model. Consistent with the findings in young adults, we found that regional functional connectivity significantly predicted BPD scores in adolescents (r = 0.24, $p_{permuted}$ = .001) (Figure 2D). The fact that the model constructed in young adults significantly predicted the BPD score in an unseen sample of older adolescents suggests that connectivity patterns are generalizably linked to borderline personality traits across ages and multiple datasets. Regional patterns showed similar heterogeneity to that in the adult data (Figure 2E; see correspondence between regional accuracies across samples in Figure S3), with the highest prediction accuracy being observed in the ventral attention network (false discovery rate–corrected p_{spin} = .0001) (Figure 2F). For comparison, the group-level model performance with the global linear ridge regression model is shown in Figure S1B (r = 0.15, $p_{permuted}$ = .026). Consistent with the young adult analysis, whole-brain mean connectivity was not associated with the BPD score in the developmental sample (r = 0.013). Taken together, these results suggest that individual differences in systems important for emotion regulation and executive function are linked to borderline personality traits in both young adults and adolescents.

Regions That Predict Borderline Personality Traits Display Developmental Effects

We sought to situate our findings in the context of brain development. Specifically, we evaluated whether the regions most strongly linked to the BPD score were also those that displayed age-related changes in connectivity during development. To quantify the developmental effects in functional networks, we used regional functional connectivity to predict the age of unseen HCP-D participants (see the Supplement for details). We found that functional connectivity was associated with age but that prediction accuracy varied significantly across the cortex (Figure 3A). To directly examine whether these age-related changes in connectivity aligned with regions associated with the BPD score, we compared the cortical distributions of age prediction accuracy and BPD score prediction accuracy in the developmental sample (Figure 3B). Permutation testing with spatial autocorrelation-preserving nulls (i.e., spin tests) revealed a significant association between cortical distribution of age and BPD score prediction accuracy (r = 0.20, p_{spin} = .001) (Figure 3B). To ensure that the findings were not driven by the relationship between BPD score and age, we directly correlated the BPD score with participant age and found no associations between the two (HCP-D: r = −0.06). This finding suggests that regions associated with borderline personality traits are also those that undergo greater age-related changes in functional connectivity in youth.

Sensitivity Analysis Provides Convergent Results

To evaluate whether our findings were affected by specific analytical choices, we performed multiple sensitivity analyses. First, we repeated the analyses using functional connectivity from resting-state fMRI data only (rather than the original concatenated task- and rest-fMRI scans) to predict BPD scores in HCP-YA and HCP-D and found consistent results in both samples (Figure S4). Second, to ensure that the findings were robust to parcellation resolution, we repeated the analyses with a different parcellation resolution (200 rather than 400 regions). Results were consistent for both HCP-YA and HCP-D (Figure S5). Third, we examined the predictive capacity of functional connectivity from subcortical to cortical regions. We trained a linear regression model for each subcortical region and tested the models on unseen data as previously described. Consistent with cortico-cortical connectivity analysis, connectivity between subcortical and cortical regions significantly predicted the BPD score in HCP-YA and HCP-D (Figure S6). Hippocampal structures were among the regions that contributed substantially to the prediction accuracy in both samples. Fourth, to assess the specificity of the model to borderline personality traits, we included a measure of general psychopathology (i.e., the Achenbach Adult Self-Report total problems score) as a covariate in the model and repeated the analyses (see the Supplement for details). The results were consistent in both samples (Figure S7), confirming that the model went beyond predicting general psychopathology. Fifth, we assessed whether the findings were influenced by total brain volume. We found that results were consistent with the original findings in both samples when total brain volume was included as a covariate in the models (Figure S8). Finally, to verify that the findings were not influenced by scanning site differences in HCP-D, we used CovBat-GAM (37–40) to harmonize functional connectivity data across sites and repeated the analyses with harmonized data. The results were consistent with the original findings (Figure S9). These

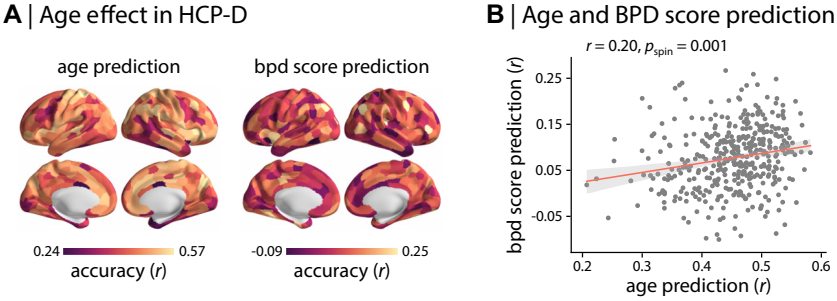

Figure 3. Regional predictive capacity aligns with developmental changes in functional connectivity. **(A)** Regional functional connectivity profiles were used to predict participants' ages in the developmental sample (HCP-D [Human Connectome Project Development]). The age prediction accuracy r is depicted across the cortex along with the previously obtained borderline personality disorder (BPD) proxy score prediction accuracy (Schaefer-400 atlas; 99% CIs). **(B)** Topographic patterns of BPD score prediction and age prediction were compared using the Pearson correlation coefficient r and 10,000 spatial autocorrelation-preserving null models (i.e., spin tests). Each point in the scatterplot corresponds to a brain region.

sensitivity analyses—combined with the generalizability of results across samples—bolster confidence in the reported findings.

DISCUSSION

To our knowledge, this is the largest functional neuroimaging study of borderline personality traits in adolescence and young adulthood reported to date. We found 3 main results. First, functional connectivity significantly predicted BPD scores in large samples of young adults (HCP-YA) and adolescents (HCP-D). Second, the predictive capacity was heterogeneous across the cortex, where the most predictive regions were found in functional systems relevant for emotion regulation and executive function. Finally, we found that regions associated with borderline personality traits colocalized with regions with prominent age-related changes in connectivity in youth.

Previous studies have sought to associate BPD with diverse functional and structural neuroimaging markers (3,8). Findings from previous studies have varied considerably, and to date, there is no consensus regarding how differences in brain function are linked to BPD. However, one relatively consistent finding across studies is the presence of altered structural and functional patterns in frontolimbic networks implicated in emotion regulation and cognitive control (8,10–14,41). One likely cause of the heterogeneity in the existing literature is the relatively small samples studied, hampering efforts to identify reliable and replicable neurobiological signatures of BPD (3).

Such challenges are hardly unique to BPD research; identifying reliable, replicable, and generalizable neuroimaging indices of psychopathology remains a major ongoing challenge (20,22). Recent evidence suggests that large samples, out-of-sample testing, and multivariate methods are essential to investigating brain-behavior associations (20–22). Out-of-sample testing using rigorous cross-validation along with analyses that assess the generalization of results to new, unseen datasets collected under different conditions are required to properly assess brain-behavior relationships. Fortunately, collaborative efforts in collecting and sharing human neuroimaging data with large sample sizes have provided an unprecedented opportunity to examine the brain-behavior association in a systematic and comprehensive manner. Although there has been a growing number of large-scale publicly available datasets in healthy populations and clinical cohorts [e.g., ADNI (Alzheimer's Disease Neuroimaging Initiative) for Alzheimer's disease (42), PPMI (Parkinson Progression Marker Initiative) for Parkinson's disease (43), and the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) consortium for various disorders (44)], most neuroimaging studies that are focused on neuropsychiatric disorders have small sample sizes. An alternative approach suggested in part by the Research Domain Criteria initiative and the Hierarchical Taxonomy of Psychopathology system is to investigate dimensional variations of clinically relevant measures in larger nonclinical samples such as the HCP (7,23).

We used a personality trait–based measure to estimate BPD proxy scores in large samples of healthy young adults and adolescents, leveraging publicly available datasets to study the link between brain function and borderline personality traits. One recent study used a similar approach to investigate the link between structural neuroimaging markers from T1-weighted MRI data and BPD (19). However, the study identified no associations between BPD and the structural markers, including cortical thickness, surface area, and subcortical volumes (19). Considered together with our findings, this is consistent with the recent evidence indicating that functional brain organization may provide a more sensitive tool than anatomical markers for capturing brain-behavior relationships in some settings (20). Here, we investigated the link between multivariate functional connectivity patterns and borderline personality traits in adolescence and young adulthood. Our findings demonstrated that functional connectivity was associated with BPD scores in both samples. Consistent with some previous reports, the link between functional connectivity and borderline personality traits was more prominent in certain functional systems, such as the ventral attention (overlapping with the insular cortex and the salience network) and the frontoparietal networks (11,41). These functional networks are associated with emotion regulation, executive function, and top-down control. In particular, the ventral attention network was robustly associated with borderline personality traits in both adults and adolescents and across the sensitivity analyses. This network is associated with emotional response and emotion dysregulation, and its functional activity gets modulated by emotionally relevant stimuli (45,46). Moreover, structural volumetric changes have been previously reported in salience regions across multiple psychiatric diagnosis (47), which may also affect the functional integrity of those regions. An important contribution of the ventral attention and frontoparietal networks to the link between brain function and borderline personality traits may be linked to impairments in emotion regulation and impulse control that have been reported in patients with BPD (1).

Notably, we found that the link between functional connectivity and the BPD score was generalizable across datasets of young adults and adolescents collected at different sites. This finding indicates that although BPD is usually not diagnosed before the age of 18 years (2), individual differences in functional networks linked to BPD may be present earlier in development. This possibility is particularly relevant given the finding that brain regions that undergo the most functional maturation during development are the ones that contribute the most to the link between functional connectivity and borderline personality traits. Taken together, these findings suggest that, like many other major neuropsychiatric conditions (7,48), BPD may be understood in part as a disorder of neurodevelopment. Examining BPD from a neurodevelopmental perspective may accelerate efforts to identify markers of risk for BPD earlier in life and develop personalized interventions before negative outcomes of this disabling disorder accrue. More generally, studying BPD from a neurodevelopmental perspective may provide insight into neurobiological and environmental correlates of BPD. For example, exposure to adverse experiences in childhood has been associated with BPD in adulthood (49–51). However, there is little to no evidence of a causal association between childhood trauma and BPD, with genetic factors having a stronger influence on BPD-related symptoms in adulthood (52–54). Prevailing theories of BPD emphasize the importance of interactions between a child's emotionally reactive and

impulsive temperament and invalidating or coercive transactions with caregivers (55), which may be related to shared genetic factors.

Findings presented in this work should be considered along with several methodological caveats. First, the analyses were not performed in patients diagnosed with BPD. The 2 datasets used in this study include healthy young adults and typically developing adolescents. The main objective of this study was to conduct a large-scale functional imaging study of borderline personality traits that leverages the large sample sizes of publicly available datasets. Although we used a trait-based BPD score that has been previously validated in multiple datasets including healthy and BPD populations, future work that applies this approach to individuals diagnosed with BPD (or individuals with greater levels of BPD symptomatology) using targeted BPD measures is required to confirm our findings. Second, the NEO-FFI questionnaire, and hence the BPD score used here, was only available in older adolescents and young adults (16 years or older). Using this trait-based BPD measure made it possible to expand our analysis to older adolescents, who have generally not been included in previous studies of BPD. The link between functional brain organization and borderline personality traits in younger adolescents remains an important area for study given that recognizable symptoms of BPD often manifest much earlier in life, even as early as 12 years (1,2). Third, previous reports have suggested that sex differences influence the expression and diagnosis of BPD (56,57). Although biological sex was included as a covariate in all the analyses presented in this study, we did not directly assess how sex differences influenced the findings. Future research is required to directly investigate the neural correlates of sex differences in BPD. Fourth, BPD is a heterogeneous disorder, and patients with BPD often have comorbid mental health problems and other psychiatric conditions (1,5). More work is required to discover the impact of comorbidity with other mental disorders. Finally, in this study, we aimed to reliably identify a link between multivariate functional connectivity patterns and BPD using large samples and rigorous out-of-sample analysis. Future investigations focusing on specific functional connections and regions of interest are essential to identify detailed neural substrates of BPD.

Conclusions

In sum, we demonstrated that multivariate functional connectivity patterns can successfully predict borderline personality traits in unseen data from young adults and adolescents. The findings suggested that regions whose functional connectivity develops the most in youth align with those associated with BPD, providing new evidence for understanding BPD as a neurodevelopmental disorder. Linking within-individual neurodevelopmental trajectories of functional connectivity to the emergence of BPD is an important direction for future longitudinal studies. More generally, the current findings suggest a new perspective on potential neurodevelopmental origins of BPD.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the AE Foundation. Additional support was provided by National Institutes of Health (Grant Nos. R01MH113550 [to TDS and DSB], R01MH120482 [to TDS], R01EB022573 [to TDS], R37MH125829 [to TDS and DAF], R01MH123550 [to RTS], R01MH112847 [to RTS and TDS], RF1MH121867 [to TDS], R01MH123563 [to RTS], DP5OD036142 [to SS], and T32NS091008 [to SS]). GS was supported by a postdoctoral fellowship from the Canadian Institutes of Health Research. Additional support was provided by a 2022 Young Investigator Grant from the Brain & Behavior Research Foundation (to SS), a 2023 Career Award for Medical Scientists from the Burroughs Wellcome Fund (to SS), and the Penn Medicine and Children's Hospital of Philadelphia Lifespan Brain Institute (to TDS).

A previous version of this article was published as a preprint on bioRxiv: https://doi.org/10.1101/2023.08.03.551534.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received Aug 21, 2023; revised Feb 2, 2024; accepted Feb 29, 2024.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2024.02.1016.

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