Common and Distinct Neural Patterns of Attention-Deficit/Hyperactivity Disorder and Borderline Personality Disorder: A Multimodal Functional and Structural Meta-analysis

Nanfang Pan, Song Wang, Kun Qin, Lei Li, Ying Chen, Xun Zhang, Han Lai, Xueling Suo, Yajing Long, Yifan Yu, Shiyu Ji, Joaquim Radua, John A. Sweeney, Qiyong Gong

PII: S2451-9022(22)00147-1
DOI: https://doi.org/10.1016/j.bpsc.2022.06.003

Reference: BPSC 958

To appear in: Biological Psychiatry: Cognitive Neuroscience and Neuroimaging

Received Date: 25 February 2022
Revised Date: 2 June 2022
Accepted Date: 3 June 2022


This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier Inc on behalf of Society of Biological Psychiatry.
Common and Distinct Neural Patterns of Attention-Deficit/Hyperactivity Disorder and Borderline Personality Disorder: A Multimodal Functional and Structural Meta-analysis

Running title: Multimodal Neural Patterns underlying ADHD and BPD

Nanfang Pan ¹ #, Song Wang ¹ #*, Kun Qin ¹, Lei Li ¹, Ying Chen ¹, Xun Zhang ¹, Han Lai ¹, Xueling Suo ¹, Yajing Long ¹, Yifan Yu ¹, Shiyu Ji ¹, Joaquim Radua ², John A. Sweeney ¹. ³, Qiyong Gong ¹*

1. Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, China; Research Unit of Psychoradiology, Chinese Academy of Medical Sciences, Chengdu, China; Functional & Molecular Imaging Key Laboratory of Sichuan Province, West China Hospital of Sichuan University, Chengdu, China

2. Imaging of Mood- and Anxiety-Related Disorders (IMARD) Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERSAM, Barcelona, Spain; Department of Psychosis Studies, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK

3. Department of Psychiatry, University of Cincinnati, Cincinnati, Ohio, USA

# Nanfang Pan and Song Wang contributed equally to this work.

*Corresponding Author:
Qiyong Gong, M.D., Ph.D., or Song Wang, Ph.D., Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, No. 37 Guo Xue Xiang, Chengdu 610041, PR China. Tel.: +86 28 81812593; Fax: +86 28 85423503.
E-mail: qiyonggong@hmrrc.org.cn or wangs_psych@163.com

Keywords: Attention-deficit/hyperactivity disorder, Borderline personality disorder, Neuroimaging, fMRI, Voxel-based morphometry, Meta-analysis

Words: Abstract: 245; Main text: 4134
Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) have partially overlapping symptom profiles and are highly comorbid in adults. However, whether the behavioral similarities correspond to shared neurobiological substrates is not known.

Methods: An overlapping meta-analysis of 58 ADHD and 66 BPD whole-brain articles incorporating observations from 3401 adult patients and 3238 healthy participants was performed by Seed-based d Mapping. Brain maps were subjected to meta-analytic connectivity modeling and data-driven functional decoding analyses to identify associated neural circuit alterations and relations to behavioral dimensions.

Results: Both groups exhibited hypo-activated abnormalities in the left inferior parietal lobule, and altered clusters of the bilateral superior temporal gyrus were disjunctive in ADHD and BPD. No overlapping structural abnormalities were found. Multimodal alterations of ADHD were located in the right putamen and of BPD in the left orbitofrontal cortex.

Conclusions: The transdiagnostic neural bases of ADHD and BPD in temporo-parietal circuitry may underlie overlapping problems of behavioral control, while disorder-specific substrates in fronto-striatal circuitry may account for their distinguishing features in motor and emotion domains respectively.

Protocol pre-registration: Open Science Framework: registration URL

https://osf.io/kfzqn.
1. Introduction

Attention-deficit/hyperactivity disorder (ADHD), manifested in clinical features of inattention, hyperactivity and impulsivity (1), is a common neurodevelopmental disorder persisting into adulthood and impacting 2.5% of adults worldwide (2,3). Borderline personality disorder (BPD) is also characterized by behavioral impulsivity and affective dysregulation that contributes to interpersonal instability and severe stigma (4), with a prevalence of 1.3% in the general population (5). ADHD and BPD frequently co-occur within the adult clinical population and in relatives due to shared familial and heritable risk factors (6,7). Approximately 38% of BPD cases have comorbid ADHD (8), and the lifetime comorbidity of BPD is 33% among ADHD patients (9). Individuals diagnosed with childhood ADHD are at increased risk for BPD in adulthood (7), and the presence of BPD in individuals with ADHD may lead to unfavorable treatment outcome (10).

Overlapping clinical characteristics of ADHD and BPD consist of impulsive behaviors and emotional instability (11,12). Behavioral disinhibition has been recognized as a shared functional impairment in ADHD and BPD, where impulsivity is a prominent psychopathological dimension characterized by premature and ill-considered actions in both conditions (8,13). Accordingly, anomalies of prefrontal-striatal activity reflected the neuropathological mechanism of impulsivity domain in ADHD (14,15), and disturbances in prefrontal-parietal circuitry might be responsible for response disinhibition when
considering BPD samples (16). The other core area of symptomatic overlap is emotional instability—hasty and inflated alterations in affective states (17), centering on dysfunctional frontal-parietal-limbic systems (18,19). Though sharing these similarities, individuals with BPD tend to have trouble controlling emotions related to their inner experience (20), while the affective and motoric hyper-reactivity of ADHD patients is often a response to external events (21,22).

The neuroimaging meta-analysis of ADHD has suggested that volumetric reduction of orbitofrontal and temporal cortices, and blunted activation of inferior frontal gyrus, temporal and striatal substrates have relevance to impairments in executive functions in adulthood (23,24). In BPD, the gray matter reduction and hyper-activation of amygdala contributed to disturbed emotion processing as a hallmark of BPD (25), coupled with brain abnormalities in orbitofrontal, dorsal prefrontal and striatal regions linked to behavioral disinhibition (13). Thus, ADHD and BPD may have shared neural substrates apart from those behavioral similarities, indicating a transdiagnostic phenotype following a common psychopathological pathway (7,26). Individuals with common neural markers may confer high risks for the comorbid condition, and additional attention is warranted to achieve a more effective treatment response in clinical management (11,27). Identifying their disjunctive neural mechanisms may potentially facilitate differential diagnosis. Regarding insufficient studies investigating their comorbidities and making comparisons directly (8,28,29), a systematic understanding of the conjunctive and disjunctive neural alterations
with these disorders remains to be established. Overlapping and comparative meta-analytic approaches offer a promising approach for addressing this issue. Herein, we performed a multimodal meta-analysis of functional and structural neuroimaging studies to map the common and disorder-specific brain abnormalities in adults with ADHD and BPD (25,30,31). Obtained neural markers were then subjected to meta-analytic connectivity modeling (MACM) and data-driven functional decoding analyses to identify the associated neural circuit alterations and their relation to behavioral dimensions (32,33).

2. Methods and Materials

2.1. Literature Selection and Database Construction

Prior to obtaining any dataset, we pre-registered our meta-analytic plan on the Open Science Framework (https://osf.io/kfzqn, registration DOI: 10.17605/OSF.IO/KFZQN). We performed a comprehensive literature search in PubMed, Web of Science and Embase for whole-brain functional magnetic resonance imaging (fMRI) or voxel-based morphometry (VBM) studies based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria before March 2, 2021 (34). Studies were included in the meta-analyses if they compared adult patients with ADHD or BPD (aged 18-65 years) to healthy individuals on blood-oxygen-level-dependent signals (BOLD) or gray matter volume (GMV) (details of the search and article eligibility criteria in Supplementary methods).
A total of 124 whole-brain articles were included in the current meta-analysis [ADHD-fMRI, 45 articles (proportion of cognitive/emotion experiments $= 31/16$); BPD-fMRI, 52 articles (proportion of cognitive/emotion experiments $= 19/33$); ADHD-VBM, 14 articles; BPD-VBM, 14 articles; one article reported parallel anatomic and functional findings, and three articles enrolling duplicated samples were excluded in further analysis]. These articles incorporated eligible observations from 3401 adult patients (ADHD, 1816; BPD, 1585) and 3238 healthy participants (procedures of literature search and included articles in Figure 1 and Supplementary Table S1). All included studies were evaluated for quality and limitation to infer the importance of these findings with a 12-point Imaging Methodology Quality Assessment Checklist (35), and for details see Supplementary methods.

We extracted peak coordinates for brain functional or structural abnormalities and corresponding $t$ values from those articles. Then we coded each study with sample size, mean age, and sex ratio, as well as for parameters of scanner (i.e., Tesla and slice thickness), statistical approach (i.e., kernel smoothing and multiple corrections), and reported clusters. For patient groups, the proportion receiving psychiatric medication and comorbid conditions were recorded. The task and corresponding Research Domain Criteria (RDoC) construct and domain were labeled for included fMRI studies (36) (details of database construction in Supplementary methods and Table S2). We pooled effect-size brain maps from all categories of fMRI experiments for
the following rationales (36–38). A task paradigm has the presumed association with particular psychological processing that attributes to specific neural substrates (36), while a brain region may underlie tasks of different categories (39,40), indicating that not only one-to-many but also many-to-one theory reflects the nature of the relationship between task paradigms and neural circuits. Pooling findings across experiments might be an objective approach that facilitates the comprehensive investigation of brain functional abnormalities of clinical populations (36,41).

2.2. Overlapping Meta-analysis

To investigate brain functional and structural abnormalities of individuals with ADHD and BPD, we conducted a multimodal meta-analysis with Seed-based d Mapping with Permutation of Subject Images toolbox (SDM-PSI, version 6.21, https://www.sdmproject.com/). Voxel-wise effect-size brain maps were reconstructed accommodating the peak coordinates and corresponding statistical values in the pre-processing (30,42). We created mean effect-size maps across studies and experiments with covarying age and sex in random-effect general linear models separately for modalities and disorders to estimate the meta-analytical case-control difference (43).

To evaluate the converging neural substrates within and across disorders and imaging modalities, we performed the overlapping analysis following separate disorder- and modality-specific analyses to obtain conjunctive and comparative findings (37,44). Comparative coordinate-based meta-analytic
approach could identify both common and distinct patterns of two disorders, and it has the potential to inform the emergence of diagnostic biomarkers for comorbid conditions (30,45). To avoid the likelihood that the false positive rate is higher than a preferred degree in the worst-case scenario, the SDM adjusts the raw union of probabilities to the desired threshold (44). To threshold the statistical maps of neural abnormalities of ADHD and BPD, we applied the family-wise error rate correction (FWE) with threshold-free cluster enhancement statistics at $p < .05$ and cluster size $> 10$ voxels to control for multiple comparisons and obtain robust findings (31) (detailed introduction of SDM-PSI and procedures of overlapping analysis in Supplementary methods).

2.3. Meta-analytic Connectivity Modeling

Meta-analytic co-activation analysis examines regions that typically are co-active in prior imaging research with those found to be abnormal in a clinical or psychophysiological study (46,47), allowing for a practical interpretation of the interaction across the whole brain and adding complementary information to task-related and resting-state functional connectivity studies (32,48,49). We delineated the co-activated neural circuits of identified peaks by extracting the peak coordinates and integrated findings of articles that reported activation in the seed regions to yield a convergent co-activation brain map in the Neurosynth package (http://www.neurosynth.org) (50). A 5mm sphere was created for peaks of the identified clusters to search the candidate co-activated brain regions with the false discovery rate correction ($p < .01$) to reduce the
false positive connectomes (32). To characterize neural connectivity at the large-scale network level, we overlaid the co-activation patterns into default mode network (DMN), central executive network (CEN), dorsal attention network (DAN), ventral attention network (VAN), somatomotor network, visual network, cortical affective network (51,52), and calculated the similarity of co-activation patterns to these networks (32) (introduction of Neurosynth and details of MACM and related analysis in Supplementary methods).

2.4. Functional Decoding

Functional decoding analysis allows for a data-driven understanding to bridge the gap between psychophysiological functioning and MRI-derived brain alterations (33,53). We used the Neurosynth to decode the pooled neural anomalies as it currently contains a large-scale neuroimaging database and encodes articles with interactive psychological terms (33). The Pearson correlation coefficients of psychological terms were calculated between the term-based activation maps and our modeled brain maps (53), and we recorded the terms with the top 10 highest correlation coefficients (54). Furthermore, we gathered the correlation coefficients of five behavioral domains (i.e., action, cognition, emotion, interoception, and perception) derived from a paradigm taxonomy and presented with their relative proportions (55,56), to determine the most prominent behavioral domain related to suprathreshold brain regions (details of functional decoding and behavioral domains in Supplementary methods and Table S3).
2.5. Ancillary Analyses

We conducted separate disorder- and modality-specific analyses to supplement with overlapping analysis. Meta-regression analysis was employed to examine the potential role of demographic factors and medication status at the whole-brain level (23). Following the main meta-analyses, we extracted the Hedges' $g$ imputations for peak coordinates of clusters and performed Spearman correlation, Mann-Whitney $U$ and Kruskal-Wallis $H$ tests to explore the modulatory effects of confounding variables (36). For fMRI studies, we calculated the contribution of included experiments attributed to each RDoC domain for identified clusters based on Hedges' $g$ imputations. Additionally, we conducted cognition- and emotion-subgroup analyses to investigate specific brain functional profiles. Publication bias and between-study heterogeneity were assessed via funnel plots, Egger's test, and $I^2$ statistics (43) (details of ancillary analyses in Supplementary methods).

3. Results

3.1. Sample Characteristics

Among 122 eligible studies in the meta-analysis, no statistical difference between patient groups was noted in the sample size-weighted $t$ tests in age (fMRI, $t_{91} = .510, p = .611$; VBM, $t_{25} = .052, p = .959$), but BPD studies consisted of a larger proportion of females than ADHD studies in both modalities (fMRI,
The proportion of medicated patients did not differ by diagnosis ($\chi^2 = .020, p = .889$) (Table 1).

### 3.2. Overlapping Analysis across Disorders

The overlapping analysis indicated that functional abnormalities of the left inferior parietal lobule (IPL) were conjunctive in ADHD and BPD cases (peak coordinates: -40, -50, 52; $Z = 4.454$; $k = 23$; shared hypo-activation pattern), and those of the left anterior superior temporal gyrus (STG)/temporal pole (peak coordinates: -48, -2, -14; $Z = 3.688$; $k = 82$) and right posterior STG (peak coordinates: 52, -38, 18; $Z = 4.255$; $k = 44$; Table 2 and Figure 2) were disjunctive (reduced response in ADHD but hyper-activation in BPD). The meta-analytic connectivity of left IPL mainly overlaid on CEN (%relative distribution, %RD: 12.13%) and left STG on DMN (%RD: 15.49%) and right STG on VAN (%RD: 10.60%, Figure 2 and Supplementary Table S5). The convergent findings of the left IPL and right STG were predominantly correlated with the action domain (%correlation coefficient, %CC: 47.33% and 27.61% respectively), while the left STG/temporal pole was linked to the cognition domain (%CC: 39.82%, Figure 2 and Supplementary Table S6). No conjunctive or disjunctive brain structural abnormalities were found between ADHD and BPD, though both structural patterns involved a part of the left orbitofrontal cortex (OFC) which had different specific anatomic locations (Table 3).

### 3.3. Overlapping Analysis across Modalities
In ADHD, multimodal conjunction analysis revealed that the cluster in right putamen (peak coordinates: 30, 10, 4; $Z = 4.585; k = 145$) exhibited both blunted functional activation and decreased GMV in contrast with controls, while those of left OFC/ anterior cingulate cortex (ACC) converged in multimodality in individuals with BPD (peak coordinates: -4, 34, -10; $Z = 4.044; k = 56$, Table 2 and Figure 3). When overlaying the findings of MACM analysis, the co-activation pattern of right putamen largely located in VAN and that of left OFC in DMN (%RD: 11.79% and 23.15% respectively, Figure 3 and Supplementary Table S5). The multimodal abnormality of ADHD was predominantly associated with the action domain, while that of BPD was associated with the perception domain (%CC: 48.75% and 36.53% respectively, Figure 3 and Supplementary Table S6). No disjunctive findings in multimodality were found in either ADHD or BPD.

3.4. Ancillary Analyses

Separate analyses of ADHD cases alone compared with healthy individuals demonstrated hypo-activation in regions including bilateral inferior frontal gyrus (IFG)/insula/STG, bilateral IPL, left supplementary motor area (SMA), right cerebellum and left OFC, and GMV reduction in the right putamen, left OFC and right supramarginal gyrus (SMG). Patients with BPD exhibited hyper-activation in bilateral STG, right precuneus, left superior frontal gyrus (SFG), right parahippocampal gyrus (PHG)/amygdala, reduced activation in left superior parietal lobule (SPL)/IPL and ventral ACC, and GMV reduction in left OFC and
left middle occipital gyrus relative to controls (Table 3). Co-activation patterns in MACM analysis are shown in Supplementary Table S5 and Figure S1, as anomalies of ADHD mainly co-activated with CEN while those of BPD linked with DMN. Functional decoding analysis revealed that most of the identified clusters of ADHD were primarily associated with the action domain, while those of BPD were diverse (Supplementary Table S6 and Figure S2). The top 10 psychophysical terms correlated with those brain abnormalities to infer its main functioning were shown in Supplementary Table S7, as the left IPL of overlapping analysis predominately correlated with “retention” and “execution”, left STG correlated with “music” and “speak”, right STG correlated with “pain” and “listening”, and the right putamen of distinct multimodal analysis with “sensation” and “motor” and left OFC with “decision” and “value”.

Meta-regression analysis revealed that gender modulated the neuropathological processing in the right putamen in ADHD and those in the left cerebellum and right ACC in BPD. Besides, the medication status modulated structural alterations of the right putamen, SMG and left OFC in ADHD, but no significant clusters were identified in the fMRI modality. In BPD, medication status was associated with structural patterns in the right insula and functional patterns in the left amygdala (details and findings of age in Supplementary Table S8). The modulatory effects of medication status on brain structural patterns of ADHD and BPD overlapped in the right putamen/insula. Among confounding variables of interests, sex and age played critical roles in
identified clusters (20 out of 25 clusters and 7 out of 25 clusters respectively, Supplementary Table S9). The RDoC domain of cognitive systems was prevalent in functional profiles of ADHD (all contributions > 62%) and that of negative valence systems in profiles of BPD (all contributions > 38%), and the differences of contributions did not reach statistical significance within disorders for any clusters (Supplementary Table S10). In subgroup analysis for fMRI studies, ADHD samples exhibited hypo-activations in the right cerebellum, bilateral insula, left SMA, left SFG, right IPL, and right striatum relative to healthy controls in the cognition category, while BPD cases showed functional abnormalities in the right PHG, right STG, right inferior temporal gyrus, left ACC in emotion category (Supplementary Table S11). Inter-study heterogeneity was not significant among all identified clusters according to $I^2$ statistics (all $I^2 < 10$%, details and publication bias results in Supplementary Table S12).

4. Discussion

The current multimodal meta-analysis provides a comprehensive delineation of the similarities and differences in the neural bases of ADHD and BPD in adulthood underlying their shared and distinct clinical features. Following up on overlapping functional patterns centered on the left IPL and bilateral STG, the identified clusters co-activated with CEN, DMN and VAN in the large-scale MACM analysis and data-driven functional decoding indicated that these patterns mainly corresponded to the action and cognition domains. Structural
abnormalities of both disorders emerged in the left OFC yet without shared profiles. The multimodal meta-analysis demonstrated that converging brain functional and structural alterations located in the right putamen in ADHD and the left OFC in BPD, with linkage to VAN and DMN and predominant involvement of the action and perception domains respectively. These findings shed light on the similarities and divergences of brain alterations associated with ADHD and BPD in multimodal dimensions, which may facilitate mechanistic understanding of the two disorders, provide potential information about the basis for their shared behavioral features, and in the longer term potentially facilitate differential diagnosis and provide interventional targets for treatment discovery programs.

4.1. Common neural abnormalities in ADHD and BPD

The overlapping functional abnormality in left IPL may be responsible for the psychopathological model of the comorbid condition of ADHD and BPD in clinical settings. The prior model was constructed based on the view that behavioral disinhibition derived from alterations in the frontostriatal circuitry and attention deficits were triggered by those in frontoparietal systems (57). However, considering symptomatic overlaps of ADHD and BPD, we rephased the model given that the reduced activation of left IPL is linked with deficits in attention (58), which serve as the bases of disinhibitory control and impulsivity in healthy populations and individuals with ADHD and BPD (15,25,59,60). As a key node in the CEN (61), the IPL serves as a multidimensional integrator.
binding cognitive and affective information processing (62,63). Abnormalities of IPL may indicate the executive network disruption in the neuropathological processing underlying cognitive control and decision-making (64). Findings of left IPL in a transdiagnostic approach may contribute to problems of reduced attentional control and behavioral disinhibition that are associated with both ADHD and BPD (2,15,65).

The overlapping but disjunctive functional patterns in bilateral STG have relevance to the cognition and action domains, and their co-activated brain regions are largely instantiated in VAN and DMN. Hypo-activated STG/temporal pole in ADHD adults impinged on cognition as a result of dysfunctional temporal processing (24), and hyper-responsive bilateral STG has been linked to impaired cognitive processing (25,66). Specially, regions of STG engage in action observation that contributes to regulating motor actions and impulsivity (67–69), and it has connections with limbic systems underlying the integration of emotion processing (70). As above, although functional abnormalities of ADHD and BPD overlapped in STG and were anchored to the cognition and action realm, the inverse activation direction suggests diverse psychopathological mechanisms in the two disorders (71,72). Clarifying the differential behavioral effects of these two patterns of abnormality may represent a promising direction for future studies.

Both ADHD and BPD cases exhibited the GMV decrease in the medial OFC that co-activated with the DMN, yielding different locations (gyrus rectus and
part of ACC respectively) and functional decoding (interoception and emotion domain). One role of the OFC is to flexibly adjust adaptive behaviors through reward processing to optimize goal-directed action (73,74), confined to neural correlates of trait impulsivity (67). For correlated psychophysical terms in Neurosynth, the OFC cluster of ADHD was mainly associated with “craving” and that of BPD with “value” and “decision”. Thus, while OFC is impacted in both disorders, somewhat different regions are involved with potential differences in behavioral aspect (1,28). The lack of converging structural alterations seems in conflict with the common phenomenon that ADHD co-occurs with BPD (8), regarding the fact that neuroimaging researchers selectively and exclusively enroll ADHD and BPD cases to emphasize case-control difference at the expense of the representativeness (23).

4.2. Distinct multimodal abnormalities in ADHD versus BPD

The divergent brain functional and structural alterations of ADHD and BPD were located in the right putamen and left OFC/ACC respectively. The connectivity between OFC and striatum accounts for reinforcement learning and behavioral flexibility (15,75). Notably, high trait impulsivity, as a transdiagnostic symptom shared by ADHD and BPD, has been associated with decreased functional activation and integrity of myelination in circuitry including medial OFC/ACC and striatum (76,77). In the MACM analysis, the co-activated spatial pattern of right putamen for ADHD cases is closely aligned with VAN, which partially explains their maladaptive cognitive and emotional processing.
of external stimuli and dysfunctions of inhibitory control in ADHD (64). The co-
activated network of left OFC for BPD individuals was most similar to DMN,
which may account for the associated loss of dynamic control for attention
reorienting between internal and external events (78). Functional decoding
indicated that the cluster of putamen was anchored on the action domain and
OFC on the perception domain. Striatal alterations of ADHD may contribute to
their dysfunctions in the bottom-up processing of behavioral control regarding
its role in the action realm (30,79), while the abnormal OFC pattern of BPD
underlies their processing emotional events, alexithymia and integrating
emotional experience with adaptive action planning—potentially contributing to
their increased risk for impulsive self-injury (80,81). Notably, our disjunctive
findings should be interpreted with caution regarding the possibility that
differences in task paradigms restrict us from a comprehensive understanding
towards neural substrates of ADHD and BPD, and those distinct abnormalities
would be identified in both disorders as more unbiased evidence emerged.

4.3. Disorder-specific abnormalities in ADHD and BPD

In functional alteration patterns, individuals with ADHD showed hypo-
activation in the bilateral IFG/insula/STG. Psychological functions of IFG have
been generally recognized as a brake on affective processing and behavioral
actions (82,83), which is of clinical relevance for the dysfunction of inhibition
and executive control in ADHD (84). Among individuals with ADHD and
comorbid BPD, microstructural abnormalities of IFG co-occurring with limbic
alterations were linked to dysfunctional emotion regulation and other behavioral features (29). In BPD cases, abnormalities were found in the left SFG, SPL and right PHG/amygdala. Psychological functions of frontal components corresponds to top-down cognitive control and emotion regulation, the parietal ones to behavioral integration and social mentalizing, and the limbic substrates to salience detection and emotion processing (15,20). These regions together comprise a fronto-parieto-limbic circuitry that accounts for emotion regulation (19). In addition, patterns of GMV reduction were also found in brain regions of the right putamen and SMG in ADHD and the left MOG in BPD. Given the predominant linkage with the action domain, the SMG contributes to action reprogramming for rapid adaptation to external alterations and to maintaining the memory flow of serial orders (85,86). Apart from relating to visuospatial functioning, the MOG processes the category-selective attention via facial recognition (87). Notably, large-scale mega-analyses revealed that reduced volume of subcortical regions was not found in adults but only children with ADHD compared to typically developing controls, suggesting a neuropathological model of altered subcortical trajectories (88,89).

4.4. Potential role of medication status

The meta-regression analysis revealed that modulated brain structural alterations of ADHD and BPD overlapped in the right putamen/insula pertaining to current medication treatment. The putamen is a potential therapeutic target for ADHD given its role in behavioral inhibition and control (90), and
psychotropic treatment was linked to neural responses in the insula in individuals with BPD (91). While individual relation of imaging to particular medications is not possible for a meta-analysis such as ours, these findings highlight the potential value of studying how treatments typically provided to ADHD and BPD patients may modulate these particular brain regions to reduce behavioral disturbances.

4.5. Limitations

The current study has several limitations. First, our findings may not generalize to pediatric or geriatric populations. Because pediatric BPD is not well studied compared with pediatric ADHD, only articles recruiting adult participants were included in the meta-analysis. Second, the representativeness of our transdiagnostic findings might be weakened due to study issues such as differences in sex ratios or differences in the use of emotional and cognitive fMRI task paradigms between the two disorders of interest. Differences in sex ratios of included samples result from different susceptibility of gender populations in community samples (4,92), and various predominant clinical manifestations contribute to biased research interest and differences in task paradigms (8). Adding sex to covariates in the meta-analysis may reconcile the concern, but further studies accounting for the general clinical presentation of those disorders might be of great interest. Finally, data to permit direct association of brain alterations and behavior at the individual participant level is not available, so we used data-driven approaches to provide suggestive
behavioral linkages with our regional brain findings.

5. Conclusions

The current meta-analysis, to our knowledge, is the first to investigate the multimodal transdiagnostic neural patterns of ADHD and BPD, and it includes data-driven functional decoding and meta-analytic connectivity approaches. Our study depicts a comprehensive presentation of common and distinct neural bases of ADHD and BPD, which indicates shared abnormal patterns in the temporo-parietal profile and distinct patterns in fronto-striatal circuitry. These findings provide novel transdiagnostic information regarding two psychiatric conditions that share clinical features of behavioral disinhibition and affective reactivity (8). Understanding of the distinct disrupted neurocircuits with each disorder could help establish better pathophysiological models and facilitate differential diagnosis. Further, the transdiagnostic and disorder-specific neural bases of illness have the potential to serve as therapeutic targets in the development of novel treatments for ADHD and BPD, and to better understand mechanisms for their high comorbidity rates and overlapping symptom profiles (90,91).
Acknowledgments

We deeply appreciate all the authors of the included studies who responded to our requests for further information.

Funding Statement

This work was supported by the National Natural Science Foundation of China (Q.Y.G., grants 81621003 and 82027808)(S.W., grant 31800963); the National Natural Science Foundation (J.S. and Q.Y.G., grant 81820108018); the Key research and development project of science and technology at department of Sichuan Province (L.L., grant 2021YFS0242).

Declaration of Interest

J.S. consults to VeraSci. Other authors report no biomedical financial interests or potential conflicts of interest.
Reference


27. Ditrich I, Philipsen A, Matthies S (2021): Borderline personality disorder (BPD) and attention deficit hyperactivity disorder (ADHD) revisited – a review-update on common grounds and subtle distinctions. *Borderline Personal Disord Emot Dysregulation* 8: 1–12.


**Figure legends**

**Figure 1.** Flowcharts of the literature search and selection criteria for articles on attention deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) in the meta-analysis. Abbreviations: fMRI, functional magnetic resonance imaging; rs-fMRI, resting-state fMRI; VBM, voxel-based morphometry; DTI, diffusion tensor imaging; ROI, region of interest; SBM, surface-based morphometry.

**Figure 2.** Overlapping functional patterns across attention-deficit/hyperactivity disorder and borderline personality disorder. (A) Transdiagnostic clusters in the left inferior parietal lobule (L. IPL, conjunctive findings) and bilateral superior temporal gyrus (L./R. STG, disjunctive findings). Statistical brain maps available online at https://osf.io/jsdgq/files/. (B) Similarity of co-activation pattern to large-scale network (DMN, default mode network; CEN, central executive network; DAN, dorsal attention network; VAN, ventral attention network; SMN, somatomotor network; VN, visual network; AFN, cortical affective network). Additional details in Supplementary Table S5. (C) Contribution of each behavioral domain to each cluster in functional decoding. Additional details in Supplementary Table S6.

**Figure 3.** Divergent multimodal abnormalities of attention-deficit/hyperactivity disorder and borderline personality disorder. (A) Attention-deficit/hyperactivity disorder in multimodal clusters of the right putamen (R. putamen) and borderline personality disorder in the left orbitofrontal cortex (L. OFC). Statistical brain maps available online at https://osf.io/jsdgq/files/. (B) Similarity of co-activated pattern to large-scale network (DMN, default mode network; CEN, central executive network; DAN, dorsal attention network; VAN, ventral attention network; SMN, somatomotor network; VN, visual network; AFN, cortical affective network). Additional details in Supplementary Table S5. (C) Contribution of each behavioral domain to each cluster in functional decoding.
Additional details in Supplementary Table S6.
Table 1. Characteristics of included sample

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>HC&lt;sub&gt;ADHD&lt;/sub&gt;</th>
<th>BPD</th>
<th>HC&lt;sub&gt;BPD&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>fMRI modality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of articles</td>
<td>45</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample size</td>
<td>981</td>
<td>953</td>
<td>1110</td>
<td>1081</td>
</tr>
<tr>
<td>Mean age</td>
<td>27.9</td>
<td>28.0</td>
<td>29.0</td>
<td>28.3</td>
</tr>
<tr>
<td>% Females</td>
<td>32.7</td>
<td>37.4</td>
<td>86.3</td>
<td>86.3</td>
</tr>
<tr>
<td>% Medication</td>
<td>27.9</td>
<td>-</td>
<td>34.7</td>
<td>-</td>
</tr>
<tr>
<td><strong>sMRI modality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of articles</td>
<td>14</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample size</td>
<td>835</td>
<td>724</td>
<td>475</td>
<td>480</td>
</tr>
<tr>
<td>Mean age</td>
<td>30.4</td>
<td>31.6</td>
<td>29.9</td>
<td>29.5</td>
</tr>
<tr>
<td>% Females</td>
<td>41.9</td>
<td>50.0</td>
<td>85.5</td>
<td>83.3</td>
</tr>
<tr>
<td>% Medication</td>
<td>38.2</td>
<td>-</td>
<td>27.8</td>
<td>-</td>
</tr>
</tbody>
</table>

*Characteristics were reported based on eligible studies excluding three articles with duplicated samples, and one article of ADHD reported parallel anatomic and functional findings.*

*Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BPD, borderline personality disorder; HC, healthy control; fMRI, functional magnetic resonance imaging; sMRI, structural magnetic resonance imaging; % Females, for the proportion of females in whole sample; % Medication, for the proportion of medicated patients two weeks before scanning.*
Table 2. Common and distinct brain abnormalities of attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Contrast /Brain region</th>
<th>BA</th>
<th>MNI coordinates (x, y, z)</th>
<th>SDM-Z</th>
<th>p value</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ADHD vs. HC) vs. (BPD vs. HC) in fMRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L inferior parietal lobule</td>
<td>40</td>
<td>-40, -50, 52</td>
<td>4.454</td>
<td>.026</td>
<td>23</td>
</tr>
<tr>
<td>Disjunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L anterior superior temporal gyrus /temporal pole</td>
<td>21</td>
<td>-48, -2, -14</td>
<td>3.688</td>
<td>.001</td>
<td>82</td>
</tr>
<tr>
<td>R posterior superior temporal gyrus</td>
<td>42</td>
<td>52, -38, 18</td>
<td>4.255</td>
<td>.002</td>
<td>44</td>
</tr>
<tr>
<td>(ADHD vs. HC) vs. (BPD vs. HC) in sMRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disjunction or Conjunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fMRI vs. sMRI in ADHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R putamen</td>
<td>48</td>
<td>30, 10, 4</td>
<td>-4.585</td>
<td>.003</td>
<td>145</td>
</tr>
<tr>
<td>fMRI vs. sMRI in BPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L orbitofrontal /anterior cingulate cortex</td>
<td>11</td>
<td>-4, 34, -10</td>
<td>-4.044</td>
<td>.016</td>
<td>56</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Suprathreshold clusters were identified at family-wise error rate (FWE) correction with $p_{\text{FWE}} < .05$ and cluster size > 10 voxels. Breakdown clusters were shown in Supplementary Table S4.

Abbreviations: L, left; R, right; MNI, Montreal neurological institute; BA, Brodmann area; fMRI, functional magnetic resonance imaging; sMRI, structural magnetic resonance imaging.
Table 3. Disorder-specific brain abnormalities of attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Contrast / Brain region</th>
<th>BA</th>
<th>MNI coordinates (x, y, z)</th>
<th>SDM-Z</th>
<th>p value</th>
<th>Cluster size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADHD vs. HC in fMRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HC &gt; ADHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L inferior frontal gyrus /insula /superior temporal gyrus</td>
<td>47/48</td>
<td>-52, 12, 10</td>
<td>6.163</td>
<td>.001</td>
<td>3626</td>
</tr>
<tr>
<td>R inferior frontal gyrus /insula /superior temporal gyrus</td>
<td>38/47/48</td>
<td>32, 18, -2</td>
<td>6.178</td>
<td>.001</td>
<td>2165</td>
</tr>
<tr>
<td>R inferior parietal lobe</td>
<td>39/40</td>
<td>44, -58, 50</td>
<td>5.628</td>
<td>.002</td>
<td>654</td>
</tr>
<tr>
<td>L supplementary motor area</td>
<td>6</td>
<td>-2, 4, 58</td>
<td>5.382</td>
<td>.001</td>
<td>632</td>
</tr>
<tr>
<td>R cerebellum</td>
<td>37</td>
<td>36, -50, -38</td>
<td>4.541</td>
<td>.002</td>
<td>380</td>
</tr>
<tr>
<td>L orbitofrontal cortex</td>
<td>10</td>
<td>-38, 58, -2</td>
<td>4.373</td>
<td>.018</td>
<td>80</td>
</tr>
<tr>
<td>L inferior parietal lobe</td>
<td>40</td>
<td>-40, -48, 48</td>
<td>5.110</td>
<td>.012</td>
<td>52</td>
</tr>
<tr>
<td><strong>BPD vs. HC in fMRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BPD &gt; HC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R superior temporal gyrus</td>
<td>22/42/48</td>
<td>58, -30, 18</td>
<td>5.475</td>
<td>.001</td>
<td>1386</td>
</tr>
<tr>
<td>L superior /middle temporal gyrus /temporal pole</td>
<td>20/21/38</td>
<td>-46, 2, -22</td>
<td>5.927</td>
<td>.001</td>
<td>1297</td>
</tr>
<tr>
<td>R parahippocampal gyrus /amygdaladala</td>
<td>28/34/36</td>
<td>28, -4, -28</td>
<td>6.293</td>
<td>.001</td>
<td>590</td>
</tr>
<tr>
<td>R precuneus</td>
<td>23</td>
<td>16, -68, 26</td>
<td>5.886</td>
<td>.001</td>
<td>164</td>
</tr>
<tr>
<td>L superior frontal gyrus</td>
<td>10</td>
<td>-8, 58, 12</td>
<td>5.039</td>
<td>.018</td>
<td>65</td>
</tr>
<tr>
<td><strong>HC &gt; BPD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L superior /inferior parietal lobe</td>
<td>7/40</td>
<td>-26, -54, 58</td>
<td>5.469</td>
<td>.001</td>
<td>350</td>
</tr>
<tr>
<td>L ventral anterior cingulate cortex</td>
<td>11/25</td>
<td>-6, 32, -6</td>
<td>4.937</td>
<td>.009</td>
<td>160</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>-</td>
<td>2, -60, -38</td>
<td>4.592</td>
<td>.042</td>
<td>12</td>
</tr>
<tr>
<td><strong>ADHD vs. HC in sMRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HC &gt; ADHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R putamen</td>
<td>48</td>
<td>28, 4, 8</td>
<td>5.722</td>
<td>.001</td>
<td>420</td>
</tr>
<tr>
<td>L orbitofrontal cortex</td>
<td>11</td>
<td>0, 46, -26</td>
<td>5.060</td>
<td>.027</td>
<td>57</td>
</tr>
<tr>
<td>R supramarginal gyrus</td>
<td>40</td>
<td>62, -44, 34</td>
<td>4.329</td>
<td>.045</td>
<td>22</td>
</tr>
<tr>
<td><strong>BPD vs. HC in sMRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HC &gt; BPD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L orbitofrontal cortex</td>
<td>11</td>
<td>-6, 40, -14</td>
<td>5.134</td>
<td>.002</td>
<td>540</td>
</tr>
<tr>
<td>L middle occipital gyrus</td>
<td>17/18</td>
<td>-20, -98, 4</td>
<td>5.118</td>
<td>.007</td>
<td>190</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Suprathreshold clusters were identified at family-wise error rate (FWE) correction with \( p_{\text{FWE}} < .05 \) and cluster size > 10 voxels. Breakdown clusters were shown in Supplementary Table S4.

Abbreviations: L, left; R, right; MNI, Montreal neurological institute; BA, Brodmann area; fMRI, functional magnetic resonance imaging; sMRI, structural magnetic resonance imaging.
A Flowchart for articles on fMRI

Identification
- Records from PubMed (n = 725)
- Records from Web of Science (n = 1208)
- Records from Embase (n = 1841)
- Records from the reference lists of related articles (n = 44)

Records excluded due to duplicate (n = 1670)

Screening
- Total records after exclusion of duplicates (n = 2192)
- Records excluded through abstracts screening: non-human, reviews, abstracts, other methods (e.g., rs-fMRI, VBM, DTI), non-neuroimaging researches, no ADHD subjects (n = 1900)

Eligibility
- Full-text original articles assessed for eligibility (n = 292)
- Records excluded:
  - ROI analyses (n = 56)
  - No controlled comparison or contrast (n = 38)
  - Insufficient data to calculate the effect size (n = 6)
  - Sample characteristics (n = 95)

Included
- Studies included in the meta-analysis of ADHD (n = 45)
- Studies included in the meta-analysis of BPD (n = 52)

B Flowchart for articles on VBM

Identification
- Records from PubMed (n = 335)
- Records from Web of Science (n = 945)
- Records from Embase (n = 730)
- Records from the reference lists of related articles (n = 22)

Records excluded due to duplicate (n = 888)

Screening
- Total records after exclusion of duplicates (n = 1044)
- Records excluded through abstracts screening: non-human, reviews, abstracts, other methods (e.g., fMRI, DTI), non-neuroimaging researches, no ADHD subjects (n = 893)

Eligibility
- Full-text original articles assessed for eligibility (n = 151)
- Records excluded:
  - ROI analyses (n = 49)
  - No controlled comparison (n = 6)
  - Insufficient data to calculate the effect size (n = 2)
  - Sample characteristics (n = 46)
  - SBM (n = 20)

Included
- Studies included in the meta-analysis of ADHD (n = 54)
- Studies included in the meta-analysis of BPD (n = 14)