

ARTICLE



Common alterations of whole and subregion-specific amygdala intrinsic functional connectivity across psychiatric disorders: a meta-analysis

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The amygdala-centered functional networks are pivotal to the neuropathology of many psychiatric disorders, yet transdiagnostic abnormalities across disorders remain unclear. This neuroimaging meta-analysis examined convergence in whole and subregion-specific amygdala functional connectivity alterations across major psychiatric disorders. We included 96 amygdala functional connectivity studies comprising 8730 individuals across seven diverse diagnostic groups (depression, bipolar disorder, anxiety, post-traumatic stress disorder, obsessive-compulsive disorder, schizophrenia, and addiction). Our findings revealed that amygdala functional connectivity alterations converged in the regions associated with sensorimotor, emotional, and cognitive processes identified by behavioral decoding analyses, including the medial prefrontal cortex, hippocampus, insula, inferior and middle temporal gyrus, cuneus, postcentral gyrus, and thalamus. More refined disorder-specific analyses suggested that these overall patterns were shared to varying degrees, with notable differences between psychotic disorders versus nonpsychotic disorders, as well as between anxiety-related disorders versus mood disorders. Follow-up meta-analyses of 27 studies on amygdala subregional functional connectivity further indicated lower connectivity of the subregions with their typical target brain regions across disorders. These findings suggest that amygdala connectivity disruptions may represent a transdiagnostic vulnerability factor in psychopathology and a potential target for therapeutic interventions.

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INTRODUCTION

Contemporary psychiatry relies on symptom-based diagnostic categories. Accordingly, most studies investigating psychopathology adopted a categorical case-control approach, typically comparing the specific disorder group to healthy control participants. However, it is increasingly recognized that the existing diagnostic categories could hinder the search for biomarkers in psychiatry, as they do not reflect unique underlying neural basis [1]. Psychiatric multimorbidity, which is far more common than unimorbidity, exacerbates this issue [2]. Furthermore, accumulated studies have suggested common structural [3], functional [4], and genetic [5] abnormalities across psychiatric disorders. This body of evidence highlights the disconnection between current psychiatry nosology and rapidly emerging biological findings that cut across disorder boundaries, which emphasizes the need to look for transdiagnostic neurobiological substrates across psychiatric disorders.

Although multiple brain regions are implicated in psychiatric disorders, the amygdala, an almond-shaped collection of nuclei buried in the temporal lobe, has received the most intense

scientific attention [6–8]. As the core of brain's affective processing systems, the amygdala plays a multifaceted role including emotion regulation, reward processing, and cognitive functions [9–11], all of which are implicated in the pathophysiology of numerous psychiatric disorders. Multiple lines of research [12–14] have consistently demonstrated altered resting-state functional connectivity (RSFC) of the amygdala in a variety of psychiatric disorders such as depression, anxiety, addiction, and schizophrenia. These findings establish the amygdala as a strong candidate for investigating transdiagnostic biomarkers of psychiatric disorders.

However, when focusing on the amygdala as a whole, the subregional heterogeneity of this region is disregarded. The amygdala should be seen as a complex of several distinct subregions since it is composed of structurally and functionally distinct subnuclei [10, 15]. Specifically, the majority of studies informing neuropsychiatric research delineate the amygdala into three primary subregions. First, the basolateral amygdala (BLA), which is the largest subregion, consists of the accessory-basal, basal, lateral, and paralaminar nuclei [16]. It has extensive

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connections with widely distributed cortical regions and plays a significant role in the perception, evaluation, and regulation of emotionally salient stimuli [17, 18]. Second, the centromedial amygdala (CMA) includes two smallest nuclei: central and medial [16]. It is essential for generation of behavioral responses to emotional stimuli through its connections with subcortical structures including the striatum, thalamus, brainstem, cerebellum, and hypothalamus [19, 20]. Third, the superficial amygdala comprises cortical-like nuclei: the anterior-amygdaloid-area, cortical, and cortico-amygdaloid transition [16], and plays a critical role in social, affective, and olfactory processing [21]. With evidence showing differential neural connections of the discrete amygdala subregions, accumulated research emerged to imply the specific role of amygdala subregional networks in the underlying pathophysiology of psychiatric disorders [12, 22, 23].

Although it is established that the amygdala is important in the psychopathology of psychiatric disorders, most individual studies measuring functional connectivity alterations of the amygdala are limited in their ability to identify transdiagnostic mechanisms due to study and sample specificity. Neuroimaging meta-analysis is a powerful technique to synthesize the large amounts of data across studies to identify common alterations that manifest across psychiatric disorders [4, 24]. We therefore pooled the evidence from multiple appropriate studies with the aim to reach conclusions regarding characteristic connectivity alterations of the amygdala across a transdiagnostic sample of psychiatric patients and control subjects. However, looking at the amygdala as a whole may obfuscate this potential brain marker. Our previous investigation of amygdala functional connectivity in depression did not reveal significant between-group RSFC differences with several regions when the whole amygdala was used as the seed region, despite significant differences at the subregional level [12]. Given that different amygdala subregions exhibit distinct connectivity profiles, their respective RSFC changes might not be detected when using the whole amygdala, especially if different subregions are altered in opposite directions. Accordingly, a deeper investigation into subregions is essential for a comprehensive assessment of amygdala functional connectivity alterations.

Thus, in the current study, we first looked at pooled analyses of “psychiatric patients compared with controls” to examine the amygdala connectivity alterations across psychiatric disorders and then conducted analyses that were disorder specific. This procedure allows for direct comparisons of different diagnostic groupings that were never compared with each other in one original dataset. Then, subgroup analyses and meta-regressions were conducted to evaluate whether the observed neuroimaging alterations were associated with the specific clinical characteristics. Finally, we performed three follow-up meta-analyses for each amygdala subregion to explore potential subregional specialization.

MATERIALS AND METHODS

Literature search and study selection

The meta-analysis was registered on PROSPERO (registration number: CRD42023458074). A systematic approach in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines [25] was adopted.

We searched PubMed, Web of Science and EMBASE databases on June 2nd, 2024, using the keywords “magnetic resonance imaging” or “MRI” plus “rest*” or “intrinsic” plus “connect*” plus “amygdala*” (* for truncation). Detailed search terms and syntax for each electronic database are presented in the Supplement. In addition, manual searches were conducted among the references of retrieved studies and relevant review articles.

Two researchers independently selected pertinent studies, and any discrepancies were resolved through discussion to reach a consensus. Original resting state functional MRI studies that employed whole-brain,

voxel-wise, seed-based functional connectivity analysis using the amygdala or its subregions to compare patients with a psychiatric diagnosis to matched healthy control participants were eligible for inclusion. Among these studies, we focused on disorders more commonly related to mental health issues and excluded those typically associated with altered developmental trajectories of the brain inherent to the expression of disorder phenotypes (e.g., attention deficit hyperactivity disorder and autism spectrum disorder) to enhance the interpretability of our results. No restrictions were made regarding age, illness duration, symptom severity, or medication status to ensure maximal coverage of studies. For the amygdala subregional RSFC meta-analysis, we included only those studies that defined seed using the cytoarchitecture-based template to enhance homogeneity and interpretability. Details of the study selection criteria are provided in the Supplement, and the procedure for literature search and study selection is summarized in Fig. 1.

Data recording and quality assessment

The primary demographic and clinical characteristics of participants (i.e., sample size, age, percentage of females, symptom severity, medication status, comorbidity, age of onset, and illness duration), as well as main methodological information (i.e., imaging acquisition parameters, pre-processing procedures, and seed type) for all included studies are exhibited in Supplementary Table 1–8 and Supplementary Tables 9, 10, respectively. We also extracted the coordinates of significant findings and statistical values related to effect size (e.g. *t* statistics, *Z* score, or *p* value) for SDM calculations.

We used the 13-point checklist (Supplementary Table 11) referring to demographic and clinical characteristics, as well as imaging-specific methodologies, to objectively reveal the quality of each study included in the meta-analysis. This checklist was based on the previous neuroimaging meta-analysis [26] and was modified to reflect the critical variables important in resting-state functional connectivity studies. In the 13-point checklist, each criterion was scored as follows: 1 for fully met, 0.5 for partially met, and 0 for unfulfilled. It is important to note that the checklist was not designed to critique the work itself but rather to provide an objective indication of the rigor of each study.

Meta-analysis

Meta-analyses were conducted using seed-based *d* mapping software (SDM, version 5.15, <https://www.sdmproject.com/software/>), a robust statistical approach that utilizes the peak coordinates to meta-analyze differences in brain activity and has been widely used in recent neuroimaging meta-analyses [27, 28]. The details of the SDM method have been described elsewhere [29, 30], but we summarize the approach here. The SDM first generates the effect-size signed map for each study by employing an anisotropic Gaussian kernel based on the coordinates of cluster peaks and the effect sizes of significant case-control differences. Coordinates of both positive and negative effect are reconstructed in the same map to prevent a particular voxel from incorrectly indicating opposing directions. Eligible studies that reported no significant group difference were also included and estimated conservatively to have a null effect size. Subsequently, the individual maps of each study were combined using random-effect meta-analytic calculations, which are weighted by intra-study variance and inter-study heterogeneity. Statistical significance was determined using standard permutation tests, with an uncorrected $p < 0.005$ and $|Z| > 1$ as the primary threshold, which has been suggested to ensure an optimal balance between sensitivity and specificity and to approximate a corrected $p < 0.05$ based on empirical comparisons. This threshold has been recommended and widely applied in SDM meta-analyses [31]. To further reduce the risk of false-positive errors, we applied a conservative cluster extent threshold of 100 voxels, which is more stringent than the recommended 10-voxel criterion and consistent with most recent meta-analyses [27, 32].

We first performed a pooled meta-analysis in psychiatric patients relative to control participants to identify transdiagnostic patterns (i.e., patterns observed when diagnostic category is not considered) of aberrant amygdala functional connectivity. To test the robustness of the results, a jackknife sensitivity analysis was conducted by repeating the main analysis *N* times (*N* = the number of datasets in the meta-analysis), discarding one dataset each time to determine whether the results remained significant. Inter-study heterogeneity was estimated using I^2 statistic. Publication bias was quantitatively examined and visualized for each cluster using Egger's test and Funnel plot, in which any result showing $p < 0.05$ was judged to have significant publication bias.

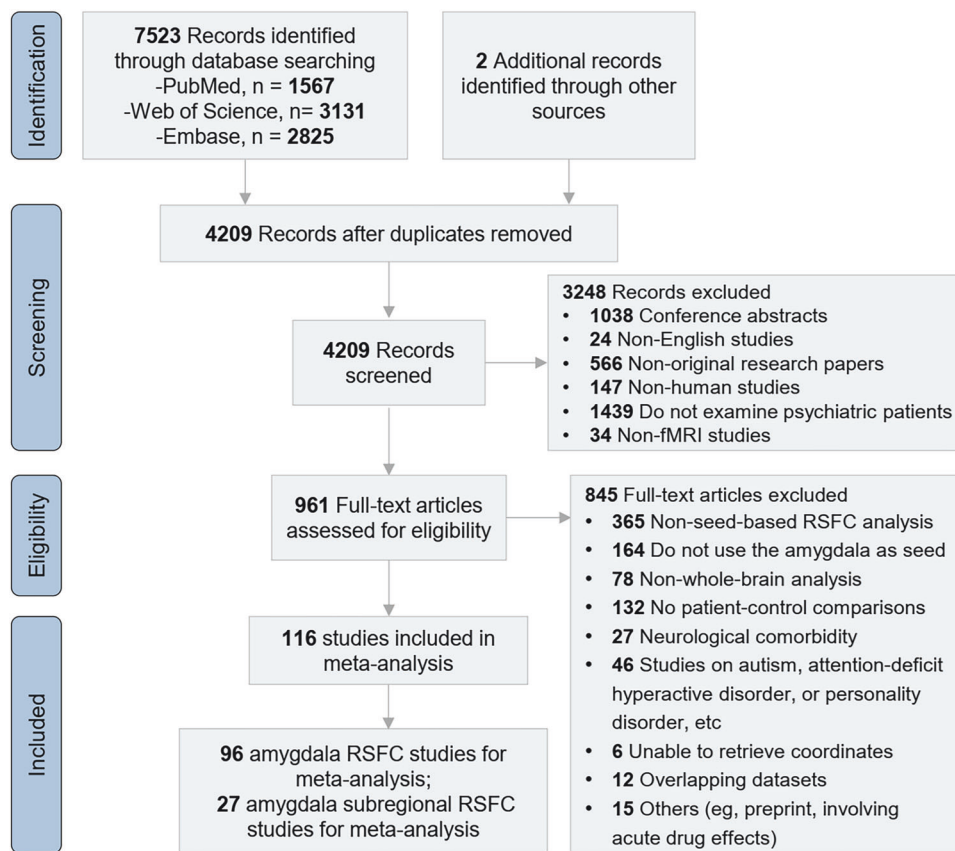


Fig. 1 PRISMA flowchart of literature search and study selection. fMRI functional magnetic resonance imaging, RSFC resting-state functional connectivity.

We then applied behavioral decoding using the BrainMap database [33, 34] to identify behavioral domains significantly associated with the activations of the regions [35] identified in the main meta-analysis. Specifically, we used binomial tests to assess whether the probability of activation for each cluster given a particular behavioral domain, $P[\text{Activation}|\text{Domain}]$ was significantly higher than its overall activation probability across all domains $P[\text{Activation}]$. The resulting p -values were adjusted for multiple comparisons using false discovery rate (FDR) of 5%.

Meta-regression analyses across all datasets were performed to test for potential effects of demographic and clinical variables. The effect size values of each cluster were extracted from the SDM software and used for regression analyses with mean age, percentage of females, illness duration, age of onset, and percentage of medicated patients. The threshold was set at FDR adjusted p -value (or q -value) of 0.05 to control for multiple tests.

Our primary meta-analysis was conducted on combined left and right amygdala to maximize statistical power. We then performed separate subgroup analyses for the left and right amygdala to explore potential laterality effects. Subgroup meta-analyses regarding age range (adult subgroup with a mean age over 18 years old and adolescent subgroup with a mean age below 18 years old) and medication status (medicated and medication-free/naïve psychiatric patients) were also carried out across all datasets. The threshold for subgroup results was set the same as in the main meta-analysis.

Furthermore, we conducted meta-analyses on the following parcellation of the included studies: (1) Separated by psychotic versus nonpsychotic disorders. The psychotic disorders category exclusively included schizophrenia, while the nonpsychotic disorders category comprised depression, bipolar disorder, anxiety, post-traumatic stress disorder, obsessive-compulsive disorder and addiction. (2) Separated by broad diagnostic groupings (i.e., mood disorders, and anxiety-related disorders). Mood disorders included depression and bipolar disorder. Anxiety-related disorders included anxiety, post-traumatic stress disorder and obsessive-compulsive disorder. (3) Separated by individual disorders except OCD due to insufficient number of the included studies. For OCD studies, we performed a narrative review instead.

For studies using basolateral, centromedial, and superficial amygdala as seeds (approximate voxels for size = $2 \times 2 \times 2$ mm: BLA, 470; CMA, 50; SFA, 214.) to investigate case-control differences in amygdala functional connectivity, we performed three parallel meta-analyses for each subregion using SDM software. These analyses aimed to determine subregion-specific alterations in amygdala functional connectivity across psychiatric disorders. The significance threshold was set the same as in the main meta-analysis. Due to the limited number of amygdala subregional functional connectivity studies in each diagnostic group, we did not conduct disorder-specific analysis at subregional level.

To evaluate the robustness of the results, we conducted supplementary analyses using a stricter threshold (uncorrected $p < 0.001$) with a minimum cluster extent of 10 voxels. This validation analysis aimed to examine whether the main clusters identified in the primary analysis remained consistent under a more stringent statistical threshold.

RESULTS

Included studies and sample characteristics

Our final sample for amygdala RSFC meta-analysis included 113 datasets from 96 studies covering a total of 8730 participants (4125 psychiatric patients and 4605 healthy control individuals). Mean ages ranged from 13.7–71.19 years. The vast majority of datasets were from adults ($N = 92$; 18–50 years), followed by adolescents ($N = 18$; <18 years), with very few datasets with older adults ($N = 3$; >50 years). Most datasets were from medication-free/naïve patients ($N = 56$) as opposed to medicated patients ($N = 33$); information on medication status was lacking for 24 datasets. Included diagnostic groups were depression, bipolar disorder, anxiety, post-traumatic stress disorder, obsessive-compulsive disorder, schizophrenia, and addiction (distribution of datasets within each diagnostic group see Fig. 2A). Thus, the meta-analysis included a highly diverse sample of diagnoses

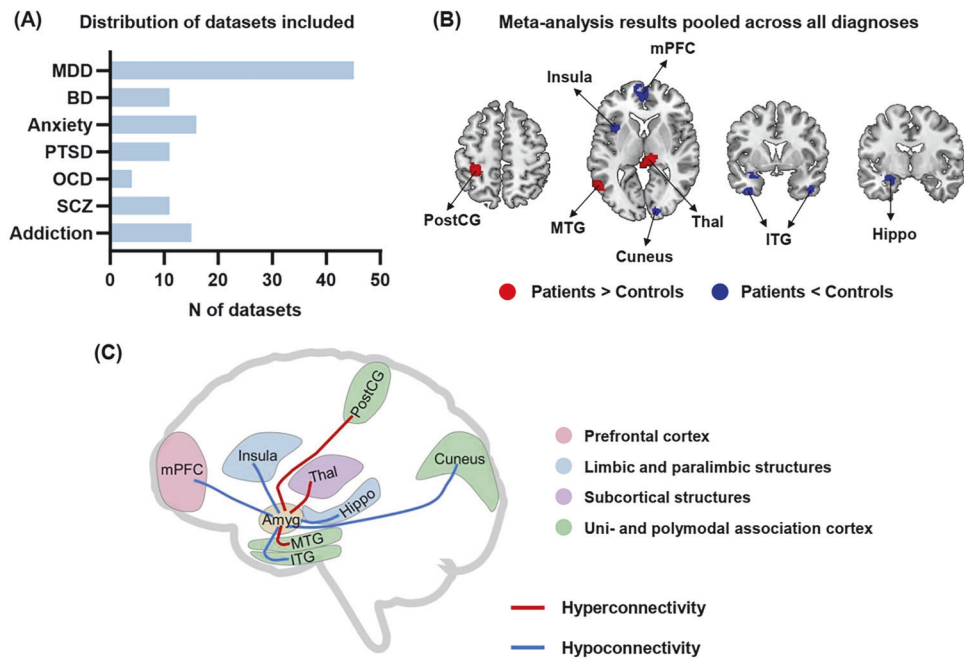


Fig. 2 Meta-analysis results of amygdala connectivity alterations in psychiatric patients pooled across all diagnoses. **A** Distribution of datasets included in the amygdala resting-state functional connectivity meta-analysis within each diagnostic group. **B** Pooled meta-analysis results of amygdala resting-state functional connectivity alterations across all diagnostic groups. **C** Summary of the altered amygdala functional connectivity patterns across psychiatric disorders. Amyg amygdala, BD bipolar disorder, HC healthy controls, Hippo hippocampus, ITG inferior temporal gyrus, MDD major depressive disorder, mPFC medial prefrontal cortex, MTG middle temporal gyrus, OCD obsessive-compulsive disorder, PostCG postcentral gyrus, PTSD posttraumatic stress disorder, SCZ schizophrenia, Thal thalamus.

Table 1. Demographic data of the diagnostic groups included in the amygdala RSFC meta-analysis.

Demographics	Diagnosis						
	MDD	BD	Anxiety	PTSD	OCD	SCZ	Addiction
No. of Studies	39	9	16	10	4	8	11
No. of Datasets	45	11	16	11	4	11	15
No. of Subjects	3734	744	938	749	430	1405	730
Patients (Female)	1894 (~1105)	363 (176)	461 (279)	406(158)	232(106)	401 (151)	368 (29)
Healthy controls (Female)	1840 (~999)	381 (189)	477 (289)	343(167)	198(92)	1004 (444)	362 (39)
Age, Mean, Years	30.6	27.5	~28.9	~39.0	30.3	31.1	30.9
Patients	30.2	27.4	~29.6	~38.3	30.9	31.5	~31.1
Healthy controls	30.9	27.6	~28.3	~39.9	29.7	31.0	~30.7

The number of female subjects and the mean age are approximations because these values were not provided in some studies. One study examined both MDD and BD subjects. *BD* bipolar disorder, *MDD* major depressive disorder, *OCD* obsessive-compulsive disorder, *PTSD* post-traumatic stress disorder, *SCZ* schizophrenia.

across the major categories of psychiatry. Demographic data of the diagnostic groups are presented in Table 1.

The final set of datasets for amygdala subregional RSFC meta-analysis consisted of 31 datasets from 27 studies, of which 26 studies for the BLA (30 datasets, 1072 psychiatric patients and 1194 healthy controls), 24 studies for the CMA (28 datasets, 1013 psychiatric patients and 1133 healthy controls), and 16 studies for the SFA (18 datasets, 740 psychiatric patients and 796 healthy controls). These studies were respectively included in the three parallel meta-analyses for each amygdala subregion.

Each study included in the meta-analysis achieved a total score of 8.5 or above according to the 13-point quality assessment checklist, indicating that the included studies were of high quality. Detailed quality assessment for each item per study can be found in Supplementary Tables 12, 13.

Pooled meta-analysis, meta-regression and subgroup analysis

The meta-analysis pooling across all diagnostic groups revealed consistent hyperconnectivity of amygdala with right thalamus extending to brainstem ($Z = 1.318$, $p < .001$), left middle temporal gyrus ($Z = 1.400$, $p < .001$) and left postcentral gyrus ($Z = 1.159$, $p < .001$), as well as hypoconnectivity of amygdala with bilateral medial prefrontal cortex (mPFC) ($Z = -3.702$, $p < .001$), right cuneus ($Z = -3.329$, $p < .001$), left hippocampus ($Z = -3.334$, $p < .001$), bilateral inferior temporal gyrus (ITG) (left: $Z = -3.225$, $p < .001$; right: $Z = -3.381$, $p < .001$) and left insula ($Z = -3.775$, $p < .001$) in psychiatric patients relative to healthy control subjects (Fig. 2B and Supplementary Table 14). Figure 2C shows a summary of the disrupted amygdala network patterns across psychiatric disorders. Heterogeneity analysis indicated that all main findings had low heterogeneity among studies (Supplementary Table 14). Jackknife sensitivity analysis confirmed replicability and reliability

of these findings (Supplementary Table 15). The Egger's tests of funnel plot asymmetry showed no significant publication bias for most clusters, except for the bilateral mPFC, right cuneus, left hippocampus, bilateral ITG, and left insula (Supplementary Fig. 1).

Decoding analysis revealed associations between each identified region and specific behavioral domains, detailed in Supplementary Fig. 2. Overall, these domains particularly pertained to emotional (e.g., positive/negative emotions, anxiety, fear, pain perception), sensorimotor (e.g., somatosensory perception, motor execution, action observation), and cognitive (e.g., social cognition, language processing, memory) processes.

Meta-regression analysis observed that the mean age in the study cohort was negatively correlated to amygdala functional connectivity with right cuneus ($R^2 = 0.68$, $p_{\text{uncorrected}} = .0018$), and bilateral ITG (left: $R^2 = 0.73$, $p_{\text{uncorrected}} = .0011$; right: $R^2 = 0.89$, $p_{\text{uncorrected}} = .0028$) (Supplementary Fig. 3). The findings of other correlations between amygdala RSFC changes and demographic or clinical features were not statistically significant after FDR correction.

Based on 90 datasets of left amygdala seed and 86 datasets of right amygdala seed, we found that both left and right amygdala exhibited increased connectivity with the right thalamus and decreased connectivity with the left insula in psychiatric patients compared with healthy controls. Other key regions identified in the main meta-analysis, such as the medial prefrontal cortex and middle temporal gyrus, were not detected in the separate left or right amygdala analyses. However, when applying a more lenient statistical threshold (i.e., uncorrected $p < 0.005$ and $|Z| > 1$ with a cluster extent threshold of 10 voxels), these connectivity alterations were observed in the right amygdala subgroup but not in the left. Detailed results of left and right amygdala subgroup analyses can be found in Supplementary Fig. 4 and Supplementary Table 16.

Detailed results of subgroup analyses regarding age and medication status are presented in Supplementary Fig. 5 and Supplementary Table 17. The results pertaining to the adult and medication-free/naïve subgroup were highly consistent with those of the main meta-analysis. Adolescent sample showed hyperconnectivity of amygdala with right insula extending to superior temporal gyrus and hypoconnectivity of amygdala with bilateral lingula gyrus. Medicated patients exhibited hypoconnectivity between amygdala and left supplementary motor area.

Meta-analysis separated by disorder groupings

Separating studies by psychotic versus nonpsychotic disorders revealed that psychotic disorders were characterized by hyperconnectivity of amygdala with right thalamus and hypoconnectivity of amygdala with left insula, and right supplementary motor cortex (Fig. 3A and Supplementary Table 18). Nonpsychotic disorders showed hyperconnectivity of amygdala with left postcentral gyrus, left middle temporal gyrus, and hypoconnectivity with bilateral medial prefrontal cortex, right cuneus, bilateral inferior temporal gyrus and left hippocampus. The reliability of these apparent differences between psychotic/control and nonpsychotic/control patterns was confirmed in direct between-group contrasts. As this comparison we conducted is particularly unbalanced to essentially compare schizophrenia with all other disorders, it may introduce confounding effects due to imbalance in sample size and clinical characteristics between groups. To address this issue, we then conducted a resampling analysis by randomly selecting 11 datasets (matching the psychotic group size) from the non-psychotic group across 50 iterations. Despite the reduced data size, the key regions remained significant in a substantial proportion of resampling runs (left insula: 31/50; right supplementary motor area: 29/50; right thalamus: 24/50), supporting the relative robustness of the results.

Grouping studies into broad diagnostic spectra (i.e., mood disorders, and anxiety-related disorders) highlighted convergent

hypoconnectivity of amygdala with bilateral medial prefrontal cortex across these two spectra (Fig. 3B). Comparative meta-analysis showed stronger amygdala functional connectivity with right putamen in anxiety-related disorders relative to mood disorders. Detailed results of separate meta-analysis for mood disorders, and anxiety-related disorders are shown in Fig. 3B and Supplementary Table 19.

All diagnostic groups except BD showed changes in amygdala functional connectivity with prefrontal cortex, with PTSD exhibiting hyperconnectivity and the other diagnostic groups displaying hypoconnectivity. Detailed results of meta-analysis refined to individual disorder categories can be found in Supplementary Fig. 6 and Supplementary Table 20. A narrative review of OCD studies is provided in the Supplementary Results.

Meta-analysis for each subregion

Among studies using amygdala subregions as seeds, almost all utilized the Julich Brain Atlas [16] to define cytoarchitecture-based subregions of the amygdala, with only one exception [36] using the coactivation-based parcellation of the amygdala, which has been shown to align well with cytoarchitectonic definitions [37]. The schematic diagram of each amygdala subregion is shown in Fig. 4A. Figure 4B displays the distribution of datasets in each amygdala subregion within each diagnostic group.

To investigate the specific role of amygdala subregions, we conducted three parallel meta-analyses for each subregion. This analysis revealed hypoconnectivity of BLA with right orbitofrontal cortex ($Z = -1.923$, $p < .001$) and bilateral dorsal anterior cingulate cortex ($Z = -1.342$, $p = .001$), as well as hypoconnectivity of CMA with bilateral striatum (left: $Z = -1.548$, $p < .001$; right: $Z = -1.752$, $p < .001$) and bilateral cerebellum ($Z = -1.342$, $p < .001$) in psychiatric patients compared to healthy control subjects. The SFA demonstrated hyperconnectivity with left precentral gyrus ($Z = 1.037$, $p < .001$) and hypoconnectivity with left cerebellum ($Z = -1.385$, $p < .001$) and left brainstem ($Z = -1.278$, $p < .001$) in psychiatric patients relative to healthy controls. Detailed results can be seen in Fig. 4C and Supplementary Table 21. Figure 4D presents a summary of the altered functional architecture of amygdala subregions across psychiatric disorders.

The validation analysis using a stricter threshold (uncorrected $p < 0.001$) yielded relatively consistent results with the primary analysis (detailed results see Supplementary Fig. 7), supporting the robustness of the findings.

DISCUSSION

In this meta-analysis across a large transdiagnostic sample of psychiatric disorders, we identified that amygdala functional connectivity alterations converged across diagnoses in the regions associated with sensorimotor, emotional, and cognitive processes, including the medial prefrontal cortex, hippocampus, insula, inferior and middle temporal gyrus, cuneus, postcentral gyrus, and thalamus. In contrast to the common alterations, we also characterized disorder-specific patterns of abnormalities in psychotic versus nonpsychotic disorders, as well as mood disorders versus anxiety-related disorders, which may serve as contrasting markers between disorders. In the follow-up meta-analyses of the amygdala subregions, we found that each subregion exhibited lower connectivity with their typical target regions across psychiatric disorders. Specifically, the basolateral subregion had hypoconnectivity with prefrontal cortex, while centromedial and superficial subregion showed hypoconnectivity with subcortical structures.

Common alterations of amygdala functional connectivity across psychiatric disorders

We found weaker amygdala connectivity with the medial prefrontal cortex, hippocampus, and insula, regions implicated in

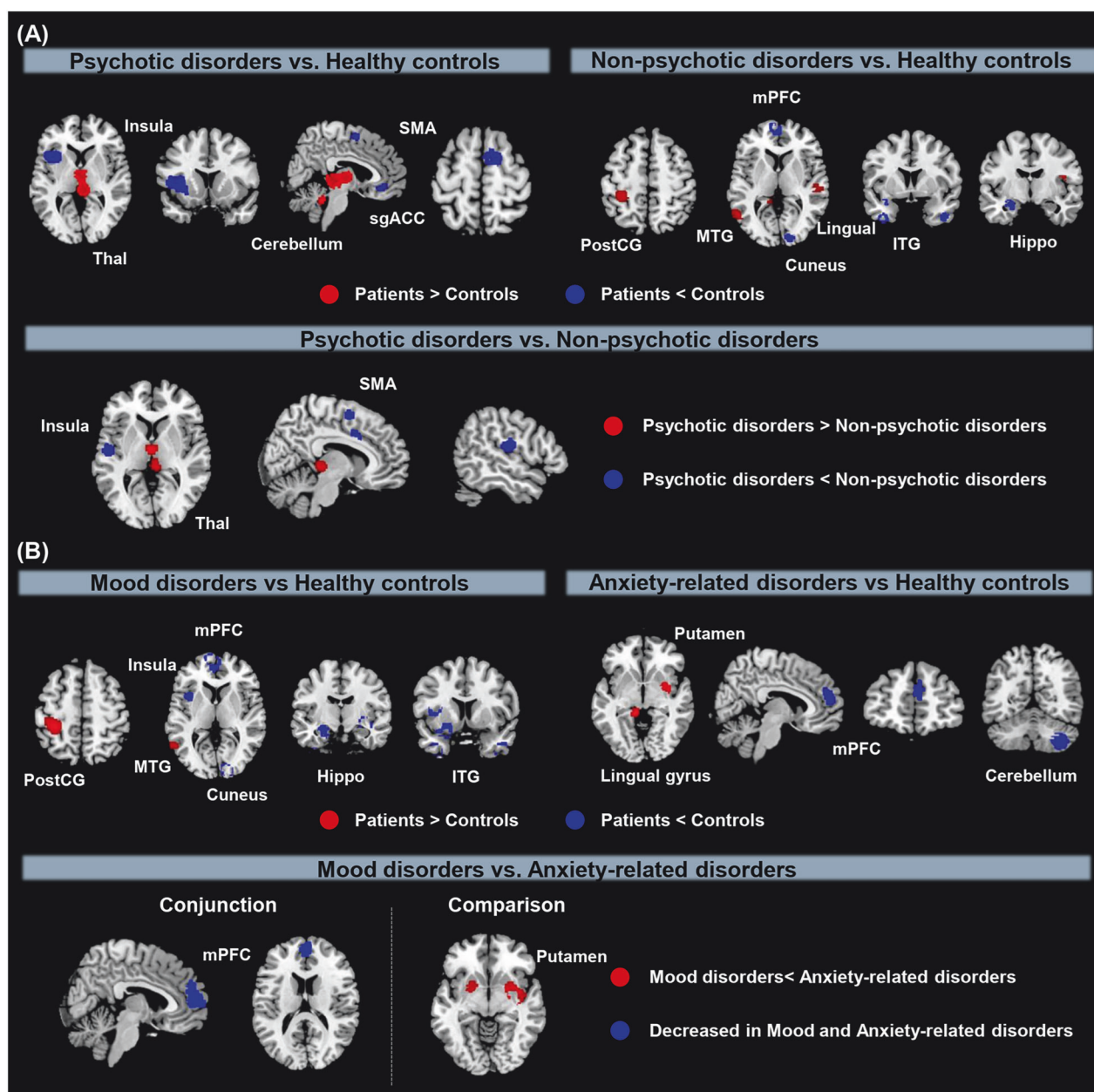


Fig. 3 Meta-analysis results of amygdala connectivity alterations separated by diagnostic groupings. **A** Meta-analysis results of amygdala functional connectivity studies separated by psychotic disorders versus non-psychotic disorders. **B** Meta-analysis results of amygdala functional connectivity studies grouping into mood disorders versus anxiety-related disorders. Mood disorders included depression and bipolar disorder. Anxiety-related disorders included anxiety, post-traumatic stress disorder and obsessive-compulsive disorder. HC healthy controls, Hippo hippocampus, ITG inferior temporal gyrus, mPFC medial prefrontal cortex, MTG middle temporal gyrus, PostCG postcentral gyrus, sgACC subgenual anterior cingulate cortex, SMA supplementary motor area, Thal thalamus.

social cognition, emotion regulation, and interoception. Anatomical studies have demonstrated dense structural connections between the amygdala and these regions, highlighting their critical role in emotion processing [38–41]. Decoding results reinforce their functional roles, suggesting that reduced connectivity to these regions may contribute to affective instability and impaired emotional processing, commonly observed in psychiatric disorders. Conversely, stronger amygdala connectivity was observed in the thalamus, though no specific behavioral association of this cluster was identified in decoding analysis. Prior research suggests that thalamo-amygdala circuit is critical for fear extinction [42]. We thus speculate its hyperconnectivity may reflect heightened fear responses, potentially contributing to fear-

related symptoms in psychiatric conditions. We also observed amygdala connectivity alterations in sensory-perceptual regions, including the postcentral gyrus (somatosensory perception and motor execution) and the cuneus (visual motion processing), suggesting disruptions in sensorimotor integration and visuospatial processing. While sensorimotor systems are often overlooked in psychiatric studies, prior meta-analyses have also highlighted transdiagnostic dysconnectivity in sensory and motor networks, aligning with calls to better integrate these domains in psychiatric neuroscience [43]. Finally, abnormal connectivity with the inferior and middle temporal gyrus, which are linked to language processing and social cognition, may contribute to difficulties in social communication and emotional expression across psychiatric

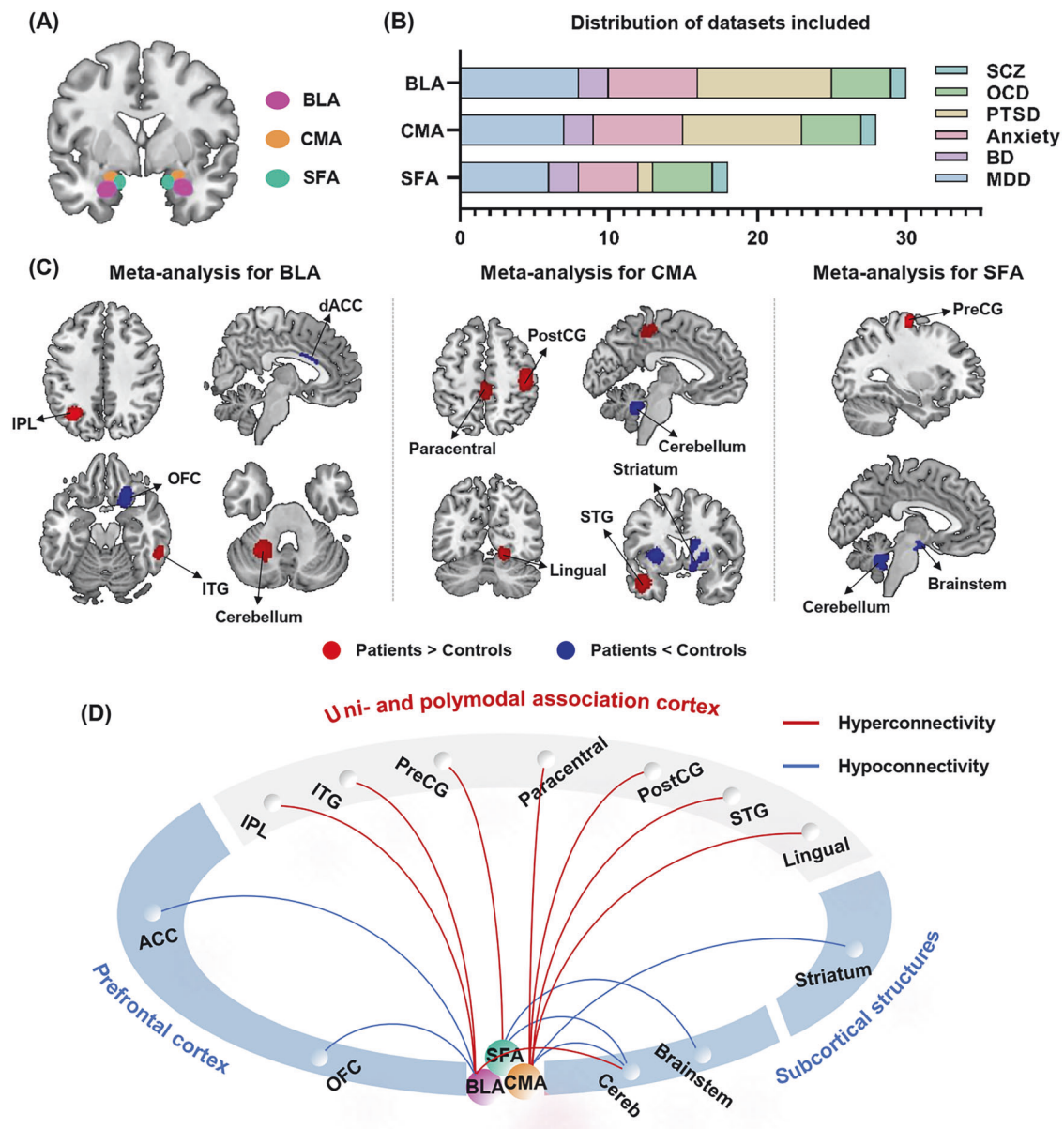


Fig. 4 Meta-analysis results of amygdala subregional connectivity alterations in psychiatric patients pooled across all diagnoses. **A** The schematic diagram of amygdala subregions. **B** Distribution of datasets included in the amygdala subregional resting-state functional connectivity meta-analysis within each diagnostic group. **C** Meta analysis results for each amygdala subregion. **D** Summary of the altered functional architecture of amygdala subregional connectivity across psychiatric disorders. BD bipolar disorder, BLA basolateral amygdala, Cereb cerebellum, CMA centromedial amygdala, dACC dorsal anterior cingulate cortex, HC healthy controls, IPL inferior parietal lobule, ITG inferior temporal gyrus, MDD major depressive disorder, OCD obsessive-compulsive disorder, OFC orbitofrontal cortex, P patients, PostCG postcentral gyrus, PreCG precentral gyrus, PTSD posttraumatic stress disorder, SCZ schizophrenia, SFA superficial amygdala, STG superior temporal gyrus.

disorders. Overall, these findings suggest amygdala dysconnectivity as a common feature of psychiatric disorders, impacting emotional, sensorimotor, and cognitive processes. The robustness of these key findings was confirmed by jackknife analysis, which showed that altered amygdala connectivity patterns remained significant across nearly all leave-one-out iterations.

However, one key issue is whether these findings from pooled analyses can be called transdiagnostic. A robust interpretation of transdiagnostic should suggest that all disorders in question show significant differences from the control group [44]. To evaluate this, we further conducted disorder-specific analyses and observed that amygdala-prefrontal cortex connectivity appeared to show similar deficits across disorders, with alterations evident in

the subgenual anterior cingulate cortex in psychotic disorders and the medial prefrontal cortex in nonpsychotic disorders. Grouping studies into mood disorders, and anxiety-related disorders highlighted shared hypoconnectivity between the amygdala and medial prefrontal cortex. Refined analyses to individual diagnostic groups revealed that all groups exhibited changes in amygdala-prefrontal cortex connectivity, only except bipolar disorder. We thus cautiously conclude that the functional connectivity between the amygdala and prefrontal cortex aligns with a strong definition of transdiagnosis. However, this pattern was not observed in BD. While limited statistical power may have contributed to this null finding, another possibility is that BD is characterized by greater heterogeneity in amygdala-prefrontal connectivity compared to

other disorders, potentially due to the inclusion of patients in different mood states (euthymic, manic, or depressive). Previous research has indicated that the amygdala shows hyperactivation during mania, variable activation during depression, and normal activation during euthymia in BD compared with healthy subjects [45]. Accordingly, amygdala-prefrontal connectivity may also differ across mood states, which could obscure a consistent connectivity pattern across BD patients. In addition, medication effects may have contributed to this null finding, as 10 out of 11 datasets included medicated patients. Lithium, a commonly used mood stabilizer, has been reported to modulate amygdala-prefrontal connectivity associated with global clinical improvement [46], which might have attenuated group differences. Future studies stratifying BD patients by both mood state and medication status are needed to clarify this hypothesis.

While separate diagnosis-specific meta-analyses have previously been conducted in MDD and anxiety disorders [13, 32], our diagnosis-specific sub-analyses not only replicated several findings from these earlier studies (e.g., hypoconnectivity between the amygdala and insula in MDD and hypoconnectivity between the amygdala and mPFC in anxiety, which also align with our transdiagnostic results), but also provided updated evidence reflecting the rapidly growing number of amygdala RSFC studies. More importantly, because our diagnosis-specific sub-analyses were derived from an overall analysis using a uniform study selection process and analytic methods, the results can be more meaningfully compared with each other to identify both shared and distinct amygdala circuits across psychopathology, which is an advancement not achievable in previous disorder-focused work.

Age and medication effects on amygdala functional connectivity

Subgroup analyses demonstrated that findings in adult and medication-free/naive subgroups were highly consistent with the main meta-analysis, likely reflecting the fact that most included studies focused on these populations. In the adolescent subgroup, we observed amygdala hyperconnectivity with the right insula (extending to the superior temporal gyrus) and hypoconnectivity with the bilateral lingula gyrus, suggesting potential developmental differences in amygdala-related neural circuitry. Meta-regression further indicated that amygdala functional connectivity with the right cuneus and bilateral inferior temporal gyrus negatively correlated with mean age of the study cohort, suggesting these alterations were more pronounced in older individuals. These findings highlight the need to consider age-related effects in future research. In the medicated subgroup, we identified amygdala hypoconnectivity with the left supplementary motor area, which may reflect either medication-induced normalization of amygdala-SMA connectivity or a direct pharmacological effect on this circuit. Further research is needed to clarify how medication status influences amygdala functional connectivity in psychiatric populations.

Functional lateralization of amygdala functional connectivity

An additional finding of our study is the functional lateralization of amygdala connectivity in psychiatric disorders. Although both left and right amygdala demonstrated increased connectivity with the right thalamus and decreased connectivity with the left insula, the right amygdala showed more widespread alterations, particularly in the connectivity with the medial prefrontal cortex and temporal regions. This finding aligns with evidence from animal models, which consistently demonstrate greater right than left amygdala activation across various psychopathology models [47]. Our results suggest that the right amygdala may play a more prominent role in amygdala connectivity alterations across psychiatric disorders. This highlights the importance of considering laterality effects in amygdala functional connectivity studies. Using only a unilateral

amygdala seed or simply averaging connectivity across hemispheres may obscure meaningful lateralized differences. Therefore, we recommend that future research systematically examine both left and right amygdala connectivity separately and apply statistical methods to account for potential hemisphere effects before combining results.

Disrupted amygdala functional connectivity separated by disorder groupings

Differences in the alterations of amygdala functional connectivity emerged between psychotic and nonpsychotic disorders. Psychotic disorders, particularly schizophrenia, showed pronounced hyperconnectivity of amygdala with the thalamus and hypoconnectivity with the insula and supplementary motor cortex. Despite the convergences discussed above, these features are more strongly altered in schizophrenia than in other psychiatric disorders, which might have some potential for being a contrasting marker between schizophrenia and other psychiatric disorders [48]. We would speculate that schizophrenia is located at one end of the spectrum of psychiatric disorders based on these disorder-specific biomarkers (e.g. stronger functional connectivity between the amygdala and the thalamus compared with both healthy control subjects and other disorders).

Anxiety-related disorders were marked by stronger functional connectivity between the amygdala and putamen compared to mood disorders. The putamen serves as a crucial node in the fear circuit, and anatomical studies support the involvement of amygdala-striatal circuits [40, 41]. Recent data suggest a prominent role of amygdala-striatal connectivity, particularly involving the putamen, in anxiety-related psychopathology [49]. Notably, shared abnormalities in task-related brain activity have been reported in mood disorders and anxiety-related disorders [50]. Our findings extend this body of literature by suggesting that differential patterns of amygdala-striatal functional connectivity may help differentiate these two conditions.

Our findings suggest that distinct amygdala connectivity alterations across diagnostic groups may correspond to specific symptom dimensions, though further research is needed to validate these associations. In psychotic disorders such as schizophrenia, amygdala hyperconnectivity with the thalamus and sensory-perceptual regions may contribute to disruptions in sensory processing and aberrant salience attribution, potentially underlying hallucinations and delusional thinking [51]. Anxiety-related disorders exhibited stronger amygdala-putamen connectivity, which may correspond to heightened threat sensitivity and exaggerated fear responses—core features of pathological anxiety [52]. Future studies integrating connectivity biomarkers with transdiagnostic symptom dimensions will be crucial for refining these associations.

Potential translational value of amygdala functional connectivity

Our findings highlight both transdiagnostic and disorder-specific patterns of amygdala functional connectivity alterations, providing circuit-based insights that may inform targeted interventions. The consistent disruptions in amygdala-prefrontal connectivity across disorders suggest that therapeutic strategies capable of modulating this circuit could have broad clinical benefits. Consistent with this idea, pharmacological agents such as selective serotonin reuptake inhibitors and intranasal oxytocin have been shown to modulate amygdala-prefrontal connectivity in depression and anxiety [53, 54], offering a promising avenue for targeting shared neural mechanisms across disorders. Beyond pharmacological interventions, noninvasive and behavioral therapies can also modulate amygdala-prefrontal connectivity. Mindfulness-based therapies, which have been shown to enhance amygdala-mPFC connectivity [55], can improve emotion regulation and alleviate symptoms underlying anxiety and depression, making them a

promising transdiagnostic approach. Similarly, neuromodulation techniques, such as transcranial magnetic stimulation may help restore prefrontal-amygdala circuit and serve as a candidate treatment for transdiagnostic psychopathology [56, 57].

On the other hand, disorder-specific connectivity patterns highlight the need for personalized treatment strategies [58]. For instance, in psychotic disorders such as schizophrenia, amygdala-thalamic hyperconnectivity aligns with evidence that antipsychotic medications exert effects on both the thalamus and amygdala [59]. In anxiety-related disorders, where we observed stronger amygdala-putamen connectivity, interventions targeting amygdala-striatal circuits, such as dopamine-modulating medications, may be particularly relevant.

Specialized alterations of amygdala subregional functional connectivity across psychiatric disorders

Investigation into the amygdala subregions revealed that the basolateral amygdala exhibited reduced connectivity with prefrontal cortex, while the centromedial amygdala showed diminished connectivity with subcortical structures across psychiatric disorders. The distinct connectivity profiles of amygdala subregions have been established by animal models of amygdala circuits [10, 15] and previous neuroimaging studies in human subjects [22, 60, 61]. Each subregion showed preferential connectivity with specialized target brain regions: the BLA is primarily associated with cortical networks, including the prefrontal cortex and sensory regions, while the CMA exclusively connects with subcortical structures such as the striatum, brainstem and cerebellum. The observed reduction in connectivity pattern of amygdala subregions with their specialized target brain regions suggests weaker differentiation of amygdala subregional networks. Prior research indicate that such weakened amygdala network segregation is associated with developmental immaturity or atypical neurodevelopment [61], which may contribute to vulnerabilities in psychiatric disorders.

Limitations

Several issues need to be further addressed. First, the number of included studies varied across disorders, which might have influenced the meta-analytic results. To address this potential bias, we performed a leave-one-disorder-out analysis. The main findings remained generally robust across diagnostic groups, although the effect attenuated when anxiety disorder studies were excluded. Moreover, because most included studies examined internalizing disorders, we further performed separate subgroup analyses for internalizing and non-internalizing conditions. Both subgroups partly replicated the primary pattern but were not fully consistent with the overall results, likely due to fewer included studies and reduced statistical power. The detailed results of these analyses are shown in Supplementary Fig. 8. Overall, these findings indicate a broadly transdiagnostic pattern with somewhat stronger contributions from anxiety-related studies, underscoring the need for future meta-analyses with larger and more balanced diagnostic representation. Second, while this is the most comprehensive meta-analysis of amygdala functional connectivity in psychiatric disorders, our findings are most applicable to younger adults because of the paucity of published studies in adolescent and older adults. Third, although the medication-free subgroup analysis yielded results consistent with the main analysis, the possibility of residual or long-term medication effects cannot be fully ruled out. Furthermore, as this meta-analysis was based on cross-sectional studies, it cannot elucidate the causal influence of medication on amygdala functional connectivity. Future longitudinal studies with prospective medication tracking and larger medication-naïve cohorts are warranted to clarify medication-related effects. Finally, publication bias is an inherent concern in all meta-analyses, as studies reporting negative or nonsignificant findings are less likely to be

published. In the present work, we attempted to minimize this bias by including only whole-brain studies and by incorporating datasets reporting null results whenever available. Nevertheless, potential publication bias cannot be fully excluded. Connectivity alterations showing significant asymmetry in funnel plots should therefore be interpreted with caution and warrant further validation in future studies.

CONCLUSIONS

In summary, we identified common alterations in amygdala functional connectivity across psychiatric disorders. We found that amygdala functional connectivity alterations converged across diagnoses in the medial prefrontal cortex, hippocampus, insula, inferior and middle temporal gyrus, cuneus, postcentral gyrus, and thalamus. These cross-disorder brain phenotypes might be relevant to sensorimotor, emotional, and cognitive processes associated with a broad spectrum of psychiatric disorders. In contrast to the common alterations, disorder-specific patterns of abnormalities were characterized that may serve as contrasting marker between disorders. Essentially, investigation into the amygdala subregions revealed lower connectivity of the subregion with their typical targets, presumably leading to immaturity in amygdala subregional circuits. These findings underscore the potential role of amygdala functional connectivity as common vulnerabilities to a broad spectrum of psychopathology.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conception and design: Cao, Huang. Acquisition, analysis, or interpretation of data: Cao, Balajoo, Gao, Li, Bao, Zhou, Zhang, Hu, Huang. Drafting of the manuscript: Cao, Huang. Critical revision of the manuscript for important intellectual content: Cao, Huang, Genon, Gong.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval and consent to participate were not sought or required as this study was based on secondary data from previously published, publicly available data. The data used for analysis includes fully anonymized information.

ADDITIONAL INFORMATION

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