Tracing neurodiverse disruptions underlying emotional episodic memory to diagnosis-specific network of emotional regulation in psychiatric disorders

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Abstract

Objective: Emotional dysfunctions are prevalent across various psychiatric disorders, leading to diverse emotional problems. Disrupted emotional episodic memory is a prominent deficit and may underlie various affective symptoms in clinical phenotypes. However, diagnosis-specific of neurodiverse disruptions remain elusive.

Methods: We used task-based functional magnetic resonance imaging (fMRI) and a normative modelling framework to establish a reference for functional activation during emotional episodic memory, drawing from a large dataset of healthy individuals (n = 409). Individualized deviations from this reference were evaluated using a clinical dataset of 328 participants, which included 168 healthy controls and patients with major depressive disorder (MDD, n = 56), bipolar disorder (BD, n = 31), and schizophrenia (SZ, n = 73). Regional deviations were mapped to four large-scale emotional regulation networks and used to predict affective symptoms across different mental disorders.

Results: We constructed a verifiable normative model of functional activation during emotional episodic memory to parse clinical heterogeneity. Diagnosis-specific regional deviations were enriched in the non-overlapping large-scale emotional regulation networks: MDD showed enrichment in emotion regulation network related to emotion perception and generation, BD in cognitive appraisal and emotional reactivity, and SZ in working memory and response inhibition. Individualized deviations significantly predicted affective symptom in distinct disorder, and specific emotional regulation network showed maximum feature weight.

Conclusions: These findings have potential implications for the understanding of dissociable neuropathological patterns of affective symptoms and improving individualized clinical diagnosis and treatment in psychiatric disorders.

Introduction

Emotional dysfunctions are central to psychopathology, being highly prevalent across multiple psychiatric conditions, including major depressive disorders (MDD) (1), bipolar disorder (BD) (2) and schizophrenia (SZ) (3). Individuals with psychiatric disorders manifest an inability to regulate emotion, the result of which is emotional extremes in perception (4), attention (5), and memory (6, 7), and could further contribute to specific affective syndromes (8). In clinic, patients with MDD show persistent low mood and rumination about negative thoughts, whereas the hallmark feature of BD patients is fluctuating episodes of depression and mania (9). Diminished emotion expression or affective flattening are also a core feature of persistent functional disability in SZ and may heighten impending psychotic relapse (10). Identifying differential neural underpinnings underlying impaired emotional processing might afford important insights into explicit distinction of affective symptoms, and is thus fundamental to support diagnosis-specific intervention optimization of affective symptoms.

Emotional stimuli enhance human memory during the process of episodic memory, a unique neurocognitive mechanism that allows individuals to consciously recall and access past experiences (11). However, disrupted emotional memories have been frequently observed in various mental illness and were thought to be interconnected with clinically affective perturbative patterns (12, 13). Psychiatric patients exhibit altered processing of negative stimuli in emotional memory-related tasks (14), demonstrated by diagnostic differences in neural dysfunctions that can be mapped to

regions and circuits associated with emotional processing (15). Specifically, patients with MDD tend to use a negative memory schema in information processing, leading them to selectively memorize negative materials and interpret happy ones as unhappy (16). Biased mood-congruent memories of MDD are facilitated by functional alterations in the medial orbitofrontal gyrus and the medial temporal lobe (MTL) system (17, 18). Hypoactivation in the occipital gyrus is observed only in individuals with BD and is associated with lower affective control over negative mood states (19, 20). In addition, among negative symptoms in SZ patients, anhedonia and reduced emotional expression may enhance the experience of negative emotion, which could be related to deactivation of the inferior parietal gyrus (IPG) and the prefrontal cortex (PFC) (21, 22). However, previous studies focusing on emotional memory have often yielded inconsistent results even within one specific diagnosis. For example, several studies focusing on emotional memory of SZ reported that there is no significant recall differences during the viewing of emotional faces or pictures but activation of left amygdala and hippocampus was significantly lower in patients (23, 24), although other functional magnetic resonance imaging (fMRI) study revealed lower memory performance and greater activation in hippocampus in those diagnosed with SZ (25). In a picture task, the activation of cingulate cortex and IPG was significantly higher in patients with BD relative to SZ (26), but similar tasks found lower activation of cingulate cortex in BD (27). Additionally, higher coupling of amygdala and ventromedial prefrontal cortex was found in MDD compared with BD patients (28), but another study have shown no difference (29).

One major reason for these mixed findings could be considerable individual heterogeneity. Recent progress in neuroimaging studies characterizing individual-specific brain imaging phenotypes suggested that traditional case-control designs often failed to capture individual heterogeneity, thus contributing to abovementioned inconsistence (30, 31). Normative modeling approach address this issue by charting normative expectations for MRI-derived brain phenotypes based on clinical or cognitive characteristics. This approach quantifies each patient with a mental disorder as an extreme deviation relative to a normative reference range derived from a large healthy population (32). Unlike case-control methods, normative modeling is less vulnerable to intersubject differences and can help avoid confounds arising from inconsistent results (32, 33). Another critical issue is that majority of studies usually focus on the memory encoding, overlooking the fact that emotional memory involves multiple processing stages, not just encoding, thus potentially missing crucial findings related to emotional processing in various mental illnesses (34, 35). Beyond the specific neural mechanisms that enhance memory for emotionally arousing stimuli during memory encoding (36, 37), this memory-enhancing effect is further supported by top-down emotional regulations that control memory accessibility, aiding in the reconstruction and integration of emotional experiences during memory retrieval (38, 39). Neuroimaging studies on emotional memory retrieval have showed that the reactivation of amygdala and orbitofrontal cortex, which are engaged during encoding, occurs again during the retrieval of emotional features, thereby processing the affective significance of items (40, 41). Additionally, more extensive activation, such as PFC and

IPG, modulates MTL activity during retrieval and is associated with processes of retrieving self-relevant emotional experience (42). These limitations highlight the necessity of using more advanced methods to capture the full spectrum of emotional memory processing and to better understand the diagnosis-specificity of neurodiverse disruptions underlying the emotional dysfunction in mental illnesses.

In the present study, we aimed to go beyond traditional group-averaged differences to investigate specific patterns of emotional dysfunctions in patients with MDD, BD and SZ by considering neural activation during emotional memory retrieval. As shown in Figure 1, we employed two task-based fMRI datasets and a normative modeling framework to identify personalized neural deviation during emotional memory retrieval. Additionally, we embedded regional-level deviation patterns into large-scale emotional regulation networks to explore the mechanisms behind biased emotional memory. Finally, we applied machine-learning approaches to uncover the associations between individualized neural disruptions of emotional function and specific effective symptoms dimension in each diagnostic condition. Although the existing literature does not provide a complete basis for predicting the results of our study, building on previous findings related to the emotional neurobiology of psychopathology (43, 44), we hypothesize that the neural substrates of emotional dysfunction may be linked to specific networks related to emotional regulation and further connected to affective symptoms in different mental disorders.

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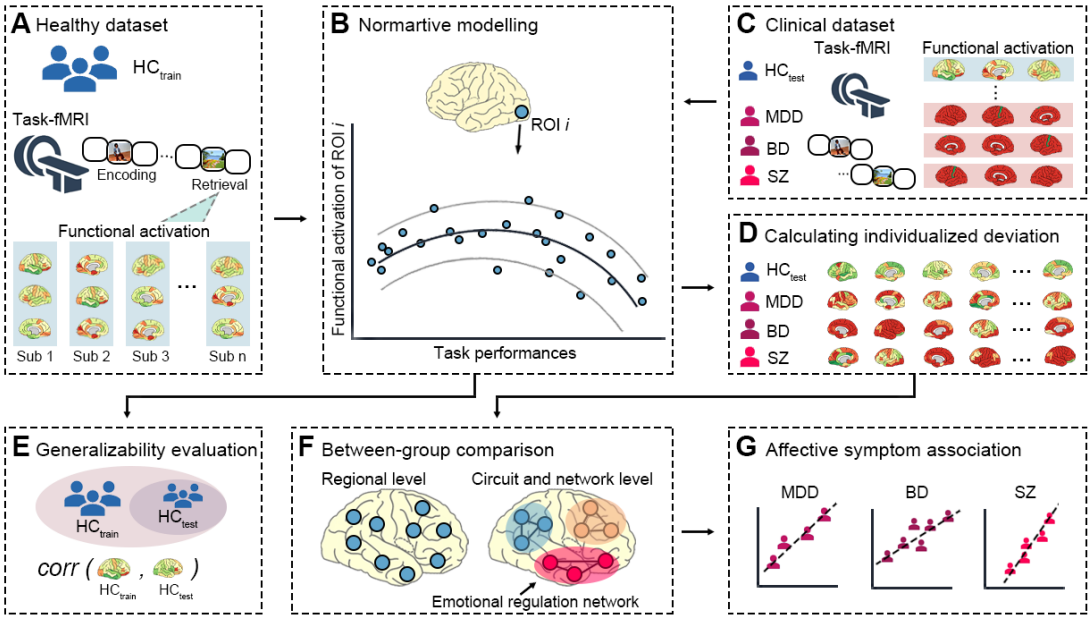

Figure 1. The workflow of the current study design. **(A)** Functional activation maps for each participant under "aversive > neutral" condition in retrieval phase were extracted in HC_{train}. **(B)** The normative model was built based on functional activation of each region as response variables and task performances as predicted covariates. Functional activations of participants in the dataset II were further put into normative model **(C)**, and deviations from model predictions were quantified as a deviation *z* value at each participant at any given brain region **(D)**. The model generalizability was assessed based on the similarity between HC_{train} and HC_{test} in individual and spatial level **(E)**. The percentage maps were obtained via calculating the proportion of individuals showing an extreme deviation in each group of the dataset II. **(F)** The difference between the percentage map of each case and healthy controls was evaluated at regional level, as well as circuit and network level. **(G)** Individual deviations with significant difference were used to predict affective symptom of each psychiatric disorder. MDD, major depressive disorder; BD, bipolar disorders; SZ, schizophrenia; HC, healthy controls; fMRI, functional magnetic resonance imaging; ROI, region of interest

Material and methods

2.1 Participants

The participants of this study were draw from two datasets. To construct the normative models, dataset I included 409 healthy controls (HC_{train}) recruited from the Center for MRI Research, Peking University. The dataset II consisted of 328 individuals:

56 with MDD, 31 with BD, 73 with SZ, and 164 healthy controls (HC_{test}). These participants were recruited from the Center for Neuroimaging, Peking University Sixth Hospital. The study was approved by the medical ethics committee of Peking University Sixth Hospital (see Supplement for details of the Ethics Reviews) and all participants provided informed consent. All patients were assessed and diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria by experienced psychiatric physicians. The severity of depression in MDD patients was accessed using the Hamilton Depression Scale (HAMD), while the clinical symptoms of BD were assessed using both HAMD and the Young Mania Rating Scale (YMRS). The symptoms of patients with SZ were evaluated using the Positive and Negative Syndrome Scale (PANSS). The heathy controls had no current or lifetime history of axis I psychiatric disorders or neurological disorders. See Supplement for additional criteria for participants inclusion and exclusion and quality control details.

2.2 Task paradigm

The fMRI paradigm of emotional episodic memory was adopted in dataset I and II, which has been used in previous studies (45). All participants conducted an emotional pictures-encoding and retrieval task during fMRI scanning. During encoding phase, participants firstly were instructed to determine whether each aversive or neutral picture represented an 'indoor' or 'outdoor' scene. All participants were not informed about the subsequent retrieval phase before scanning and thus were not realized that they were engaged in a memory task. About 2 minutes after the encoding phase,

participants then need to memorize whether the image presented was seen during the encoding session in the case of mixing with half new picture. Finally, both reaction time (RT) and accuracy (ACC) in encoding and retrieval phase were extracted from log files of task performance after scanning. Response accuracy was also estimated by sensitivity (d prime, d′) based on signal detection measures. The schematic diagram of task shown as Figure 2A and detailed description is in Supplement.

2.3 Image acquisition and preprocessing

Images of all participants were acquired on a 3.0 T GE Discovery MR750 scanner in the Center for MRI Research, Peking University (dataset I), and the Center for Neuroimaging, Peking University Sixth Hospital (dataset II). The high-resolution structural T1-weighted MRI was acquired in a sagittal orientation using an axial 3D fast, spoiled gradient recalled (FSPGR) sequence with the following parameters: time repetition (TR) = 6.66 ms, time echo (TE) = 2.93 ms, field of view (FOV) = 256 × 256 mm^2, slice thickness/gap = 1.0/0 mm, acquisition voxel size = 1 × 1 × 1mm^3, flip angle = 12°, 192 contiguous sagittal slices. For the fMRI, each echo-planar image consisted of 33 (4.2 mm thick, 0 mm gap) axial slices covering the entire cerebrum and cerebellum (TR/TE = 2000/30 ms, flip angle = 90°, FOV = 224 × 224 mm^2, 64 × 64 matrix). Scanning parameters were selected to optimize the stability and quality of the blood oxygenation level-dependent (BOLD) signal with the exclusion of the first 4 images as dummy scans.

The preprocessing of functional imaging was preprocessed using the SPM12

(Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm) with a standardized protocol whose details can be found elsewhere (46). Briefly, image processing included 1) performing slice-timing correction in remaining images; 2) realigning remaining images to the first volume for head motion correction using a six-parameter (rigid body) linear transformation; 3) conducting brain tissue segmentation and spatial normalization using the standard stereotaxic space of Montreal Neurological Institute (MNI) template; 4) performing the spatial smoothing with a Gaussian filter set at 8mm full-width at half-maximum. Each task-evoked stimulus was modeled as a separate delta function and convolved with a canonical hemodynamic response function, ratio normalized to the whole-brain global mean to control for systematic differences in global activity, and temporally filtered using a high-pass filter of 128s. Each task-evoked stimulus event was modeled for correctly performed trials. Incorrect responses and residual movement parameters were also modeled as regressors of no interest.

2.4 Task activation analysis

The analysis of functional activations under emotional episodic memory was based on SPM12 and custom code in MATLAB (The MathWorks, Natick, MA, USA). For each participant, general linear modelling (GLM) analysis was used to identify functional activated by task of each brain regions defined by the Desikan-Killiany (DK) atlas(47). The brain parcellation included 68 cortical regions and 14 subcortical regions, which limited computational burden. In GLM, regressors firstly were constructed from the rest, aversive and neutral blocks which were then convolved with a canonical

double-gamma haemodynamic response function and combined with the temporal derivatives of each main regressor. Then, first-order autoregressive model was used to remove serial correlations, and a high-pass filter (128 s) was applied to remove low-frequency signal. Next, the contrasts of interest were brain activation responses under rest, aversive and neutral condition with the six parameters of head motion as nuisance covariates. Finally, condition-specific regional responses were obtained in three task conditions during retrieval phase, and the "aversive > neutral" activation difference maps in retrieval phase were generated to indicate the effect of emotional episodic memory and avoid the interference of cognitive effect.

2.5 Normative modeling and estimating individual deviations

Compared with classical group-average evaluations, the normative modeling approach sought to construct a normative distribution to represent the reference range of interest characteristics by calculating the mean and variance of a response variable from a set of predictive factors, thus allowing to characterize a personalized differences pattern for each clinical patient relative to the normative reference (30, 32). Specifically, in our model, we employed gaussian process regression (GPR) to estimate normative models reflecting relevant neural activation during the emotional episodic memory using Predictive Clinical Neuroscience toolkit (PCNtoolkit) software (https://pcntoolkit.readthedocs.io/en/latest) implemented in python 3.10. Then, individual-specific "aversive > neutral" activation maps during retrieval were used as response variables for the normative models and cognitive functions comprising of task

performances including RT in encoding and retrieval phase and ACC in retrieval phase. The training sample for the normative model is HC_{train} in this study and the testing sample of normative model comprised of dataset II, including HC_{test}, cases with MDD, with BD, and with SZ. For individuals in testing sample of HC_{test} and all case group (dataset II), the activation of each brain regions firstly was positioned on the normative percentile charts from HC_{train} to estimate individualized deviation for the subsequent analyses. We derived a z value that quantified the deviation from the normative model in each brain region based on their observed activation values and the predictive activation values obtained from the model. The model generalizability was further assessed based on internal and external validations (Supplement). We then thresholded the individualized deviation maps using $z = \pm 2.6$ (corresponding to $p < .005$ in standard normal distribution) as was well-done in previous studies and obtained extreme deviations in the emotional memory-related activation of individuals (30, 48). Finally, a group-specific percentage map quantifying the proportion of individuals showing an extreme deviation was calculated, separately for positive and negative extrema.

2.6 Between-group comparison of individual deviations in the regional, network and circuit level

The statistical analyses were conducted for HC_{test} and each diagnostic group of dataset II in the regional, circuit and network level (Supplement; Figure S1). Our analysis mainly aimed to depict between-group differences after removing intersubject

heterogeneity rather than differences of group-averaged patterns. Thus, between-group differences across different spatial scales were assessed as percentage difference of individuals with extreme deviations at any regions based on a nonparametric group-based permutation test. The details of method can be found in Supplement and previous studies (48). The significant differences of positive and negative extrema in current study were respectively defined as supra-normal and infra-normal regions, circuits, or networks. The higher or lower infra-normal deviations in relative to the normative range implied that the hyper- and hypo-deactivation of emotional memory, while higher or lower supra-normal deviation suggested hyper- and hypo-activation, respectively.

Between-group comparison in the regional level. The percentage maps showing extreme regional deviation in HC_{test} were subtracted from each case's percentage map to obtain the percentage difference maps of each disorder at any given brain region. The differences in the regional level were further assessed based on permuted group labels of case group and HC group. The *p* values were obtained as the proportion of null values that exceeded the observed difference and statistical significance was set at 0.05 with multiple comparisons correction based on the false discovery rate ($p < .05$, FDR corrected).

Between-group comparison in the network level. To further explore neural mechanisms behind biased emotional memory across various mental disorders, the functional networks of the region-level individual deviations were considered. We focused on the network-scale functional alterations by mapping the regions with extreme deviations in each patient into a well-recognized framework of four brain

networks of emotional regulation (ERNs), as revealed by a recent meta-analysis study (49), and positioned ERNs on DK atlas (Figure S2). These networks engaged neural correlates associated with emotional regulation, ranging from generation to expression, and included two cognitive emotional regulation and two emotional generation networks. A total of 36 brain areas with distinct spatial distributions and functional profiles were included in these four ERNs (Table S2), each presenting different emotional regulation processes (ERN 1: working memory and response inhibition; ERN 2: appraisal and language processing; ERN 3: emotion perception and generation; ERN 4: emotional reactivity). Network-level deviations were characterized by assigning each region with extreme deviation to one of four emotional regulation networks and extreme network deviation was estimated as the proportion of individuals that showed at least one positive and negative extreme deviation in a region within the network. The case-specific network difference was then evaluated by computing differences between network percentage of HC_{test} and each diagnostic group using 10,000 times group-based permutation test ($p < .05$, FDR corrected), as at regional level.

Between-group comparison in the circuit level. The network-level analysis preliminary explored specific representation of individualized deviations at the level of more extensive emotional regulation networks. We further investigated whether the convergence of regional deviation in networks associated with emotional regulation could be driven by between-regions functional interactions, considering the extensive involvement of regulate processing during memory retrieval for emotional stimuli. We estimated circuit level individual deviations using lesion network mapping

methodology (50, 51). Briefly, each region showing an extreme deviation was mapped into functional circuitry defined by psychophysiological interaction (PPI) analysis in each group (Supplement). We thresholded individualized deviant-related functional circuitry based on a one-way *t*-test within each group, and extreme circuit deviations were obtained by binarizing the value of statistically significant functional circuitry as 1. The union of the extreme functional circuit across all of seeds in each person were determined as final extreme circuit deviation. Following the analysis in the regional and network level, circuit percentage map was yielded by calculating the proportion of individuals in each extreme circuit deviation and significant circuit percentage difference maps between HC_{test} and clinical group was evaluated using 10,000 times group-based permutation test ($p < .05$, FDR corrected). The significant seed-based functional circuit was further located into four ERNs to assess the relationship between individual deviations at regional level and network level.

2.7 Association with clinical affective symptoms

The multiple linear regression analyses were conducted to investigate the underlying relationships between individualized deviations of emotional episodic memory and clinical affective symptoms across different diagnostic groups. The affective symptoms in MDD patients were defined using anxiety/somatization factor derived from six-factor domains of HAMD. Considering the lack of specific item scores, the total scores of HAMD were alternatively used as affective symptoms in BD patients. For SZ patients, since a specific assessment scale for depressive symptoms was not

adopted, the anxiety/depression factor from five-factor scores of PANSS was used. We used individual deviation of brain regions with significant infra-normal and supra-normal deviation to predict clinical scores in distinct diagnostic category. The nested leave-one-out cross-validation (LOOCV) was adopted to avoid selection biases and evaluate the performance of the linear regression models. The Pearson correlation and root mean square error (RMSE) between the observed clinical scores and predicted clinical scores were used to assess the performance of prediction model. The statistical significance of correlation coefficient was estimated by applying a non-parametric permutation test, which calculated by randomly shuffling the clinical scores and re-calculated Pearson correlation coefficient. An empirical distribution of correlation coefficient was then obtained based on 10,000 times permutation and the significance level threshold was set at $p_{\text{perm}} < .05$. Furthermore, we used virtual lesion analysis to determine the important features in the clinical prediction model. We re-calculated the prediction accuracy (correlation coefficient between observed scores and predicted scores) by removing one feature at a time (i.e., virtual lesion). If the prediction accuracy of model decreased after removing a feature, we considered the feature to be important for prediction. We identified the important features at regional and network level, respectively.

2.8 Validation analysis

To demonstrate the robustness of our main findings, we validated our results by considering several potential confounding factors. Firstly, we re-constructed the

normative models by including sex and age into predictor set to evaluate potential age/sex effects on model design. Secondly, we estimated the effect on the results of threshold for defining extreme deviations. We also calculated percentage differences maps of each group based on a threshold-weighted deviation analysis, which integrated results across a range of thresholds. Thirdly, we evaluated the influence of different brain parcellation atlas, including Anatomical Automatic Labelling atlas and Brainnetome atlas. Finally, to validate whether our results could be influenced by the medication effect, the correlation analysis between individualized regional deviations and dose of medicine was performed at each disorder. Details were described in the Supplement.

Results

3.1 Demographic, clinical characteristics and task performances

The demographical and clinical characteristics are presented in Table 1. A total of 409 HC_{train} participants (mean age, 24.6 ± 3.8 years; age range, 18 to 43 years; 206 female) were recruited in the healthy dataset I. The accuracy for aversive scenes during retrieval phase was significantly higher than for neutral accuracy ($t = 12.284$, $p < .001$), indicating an emotional memory-enhancing effect. In clinical dataset II, there were no significant differences in sex ($\chi^2 = 0.333$, $p = .954$) and age ($F = 2.195$, $p = .089$) among the HC_{test}, MDD, BD and SZ groups. The enhanced effect of emotional memory was also observed in each group (HC_{test}: $t = 8.722$; MDD: $t = 5.094$; BD: $t = 4.543$; SZ: $t =$

4.249; all $p < .001$). In addition, d′ values were statistically significantly greater during the retrieval phase compared to the encoding phase across all groups (HC_{train}: $t = 14.168$; HC_{test}: $t = 10.658$; MDD: $t = 6.618$; BD: $t = 4.071$; SZ: $t = 5.184$; all $p < .001$). Detailed results of task performances are provided in the Supplement.

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Table 1. Demographic and clinical characteristics

	Healthy dataset	Clinical dataset				
	HC_{trian} (n = 409)	HC_{test} (n = 164)	MDD (n = 56)	BD (n = 31)	SZ (n = 73)	Statistical test χ^2/ F (p)
Demographic characteristics						
Sex (M/F)	203/206	63/101	20/36	13/18	28/45	0.333 (.954[a])
Age, years	24.6 (3.8)	24.6 (4.0)	25.1 (5.0)	27.0 (5.3)	25.2 (5.6)	2.195 (.086[b])
Clinical characteristics						
HAMD			24.982 (5.472)	12.581 (14.631)		
YMRS				4.581 (8.007)		
PANSS					67.833 (14.049)	

Data are presented as mean (standard deviations). HC, healthy control; MDD, major depressive disorder; BD, bipolar disorder; SZ, schizophrenia; M, male; F, female; HAMD, Hamilton depression scale; YMRS, Young mania rating scale; PANSS, positive and negative syndrome scale

[a] The *p*-value was obtained by a chi-square test.

[b] The *p*-value was obtained by a one-way ANOVA with post hoc analyses.

3.2 Normative model of emotional episodic memory

We constructed a normative model based on functional activation evoked by the emotional episodic memory paradigm, which was fitted in each region respectively. The model represented a normative reference for neural activations given behavioral performances of emotional episodic memory. As shown in Figure 2B, our normative models predicted a standard normal range of emotional episodic memory and fitted well in healthy individuals, showing that 99.51% of individuals in HC_{train} and 100% of individuals in HC_{test} were located within the normative range ($-2.6 < z < 2.6$) in current study for the mean regional deviations. There was no significant difference of the

distribution of mean regional normative z scores between HC_{train} and HC_{test} (Kolmogorov-Smirnov test, $K\text{-}S = 0.087$, $p = .320$). Traditional group-level task evoked functional activation in HC_{train} based on general linear model showed that regions with higher activation located mostly in the occipital cortices, amygdala and other MTL areas, while those with decreased deviations were mainly in precentral and postcentral gyrus, and insula ($p < .05$, FDR corrected; Figure 2C), consistent with previous studies (42, 52). This spatial distribution of emotional memory-related brain activation is highly correlated with individual-level mean distribution patterns of HC_{train} ($r = 0.973$, $p_{spin} < .001$, 10,000 times permutation tests with spatial autocorrelation), indicating that such an effect of group-averaged could be disentangled into individualized components by characterizing neural activation of emotion memory in given task performances. More importantly, our normative model exhibited a higher generalizability indicated by internal cross-validation (Supplement; Figure S3) and independent external sample validation, showing mean regional deviation map in HC_{train} and HC_{test} was highly associated (Figure 2C, $r = 0.956$, $p_{spin} < .001$, 10,000 times permutation tests with spatial autocorrelation). The normative models established based on behavior performances, sex and age showed high correlation with current models, which implied that sex and age had no significant effect on our normative model (Supplement; Figure S4).

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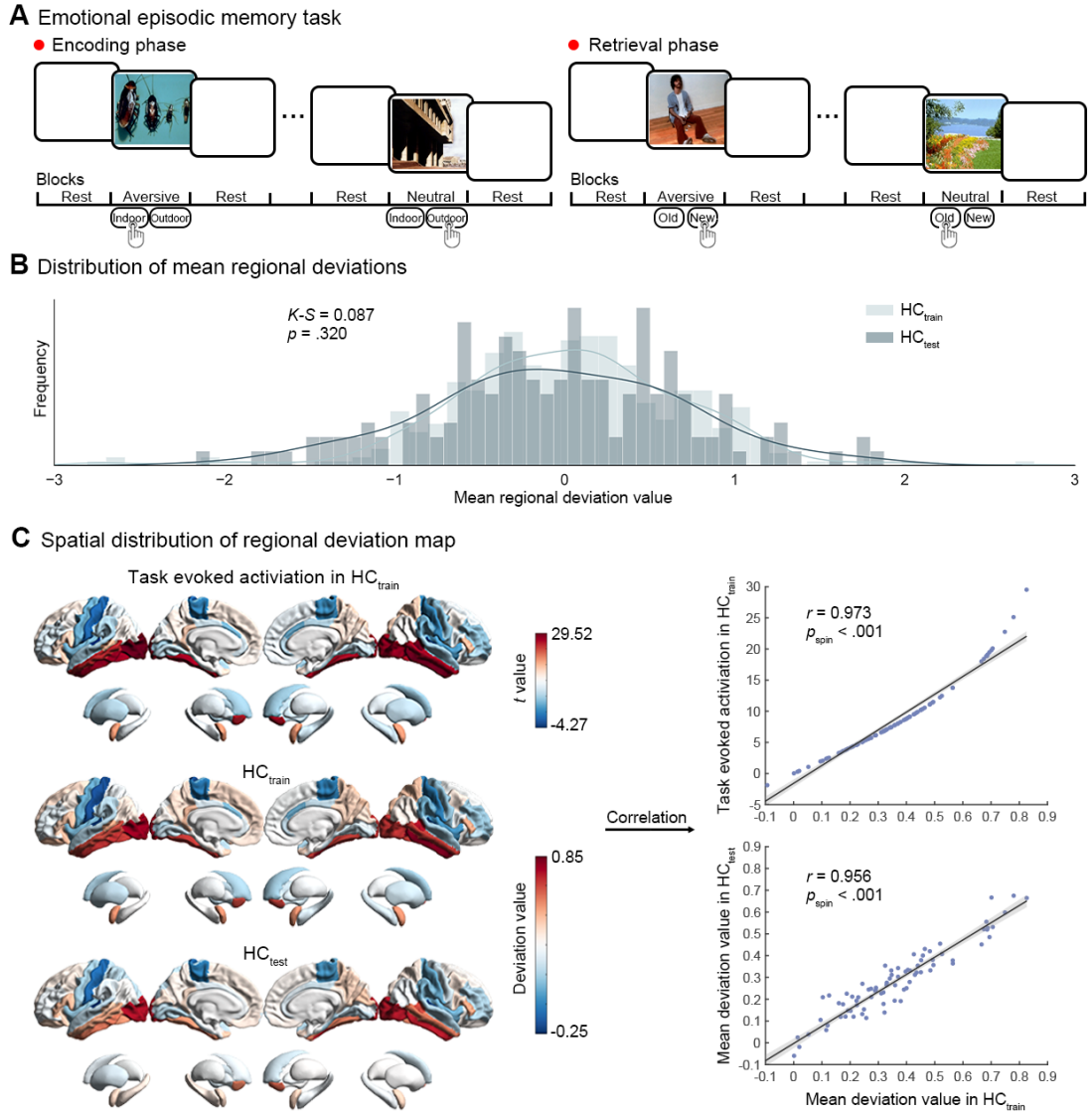

Figure 2. The schematic diagram of emotional episodic memory task and generalizability evaluation of normative model of emotional episodic memory. **(A)** The emotional episodic memory task paradigm consisted of encoding and retrieval phases and each phase included neutral and aversive scenes. The participants were instructed to determine whether each image represented an 'indoor' or 'outdoor' scene in encoding phase (left) and respond 'new' or for 'old' in retrieval phase (right). **(B)** The distribution of mean regional deviations in HC_{train} and HC_{test}. There was no significant difference between these two distributions. **(C)** The spatial distribution of regional deviation map in HC_{train} exhibited significant spatial correlations with group-level activation and regional deviation map in HC_{test}. HC, healthy controls

3.3 Regional level individual deviations in patients with MDD, BD and SZ

Similar to the generalizability evaluation of the normative model of emotional memory in the validation sample of healthy participants in dataset II, each patient with specific psychiatric disorder was positioned on the normative percentile charts to calculate individual deviations in each brain region (Figure 3A). Our results showed that regional extreme deviations exhibited considerable intersubject heterogeneity in patients with same diagnosis. About 50% of patients showed extreme deviations in at least one brain region and distributed diffusely in ~75% of cortical brain regions (Supplement; Figure S5). More specifically, patients with MDD exhibited a higher percentage of supra-normal deviations (90.24%) compared to infra-normal deviations (40.24%). In contrast, BD patients had fewer regions with positive extrema deviations, showing 37.80% supra-normal regions and 65.85% infra-normal regions. For patients with SZ, both positive and negative out-of-range alterations were widely distributed across brain regions, with 93.90% showing supra-normal deviations and 89.02% showing infra-normal deviations (Supplement).

The group-based permutation test was then used to compare the regional differences showing significant extreme deviation between HC_{test} and each diagnostic group in dataset II. This was done by assessing the observed difference for each disorder in any given brain region against an empirical null distribution. The results showed that there are few spatial overlaps, such as amygdala and insula, across all mental disorders ($p < .05$, FDR corrected; Supplement), but the overall spatial distribution of emotional dysfunctions is extraordinary different. The infra-normal regions in the patients with

MDD mainly located in frontal lobe and temporal lobe, while supra-normal regions were mainly located in superior frontal gyrus, superior temporal gyrus and amygdala (all $p < .0167$ (.05/3), FDR corrected; Figure 3B). The regions with statistically significant difference in MDD patients were summarized in Table S3. Relative to controls, the patients with BD showed infra-normal regions in the occipital lobe, precuneus, hippocampus and amygdala but supra-normal regions in the insula, striatum, and amygdala (all $p < .0167$ (.05/3), FDR corrected; Figure 3C; Table S4). The between-group comparison between SZ patients and HC_{test} showed that the infra-normal regions in insula, hippocampus, and caudate ($p < .0167$ (.05/3), FDR corrected) and supra-normal regions in insula, fusiform gyrus, putamen, and amygdala ($p < .0167$ (.05/3), FDR corrected) in SZ group (Figures 3D; Table S5). The results of individual deviations of emotional episodic memory in all disorders observed in main findings remained high similarity using different validation strategies, including different threshold setting in percentage differences map that avoids reliance on a single threshold (Figure S6) and different atlas for brain parcellation (Figure S7). All regional deviations were unrelated to dose of medicine in MDD, BD and SZ patients (Figure S8). As a control analysis, we found that the classical group-level comparison did not reveal any significant regional case-control differences of functional activations (Figure S9). This finding underscores the efficiency of normative modeling in parsing inter-individual differences.

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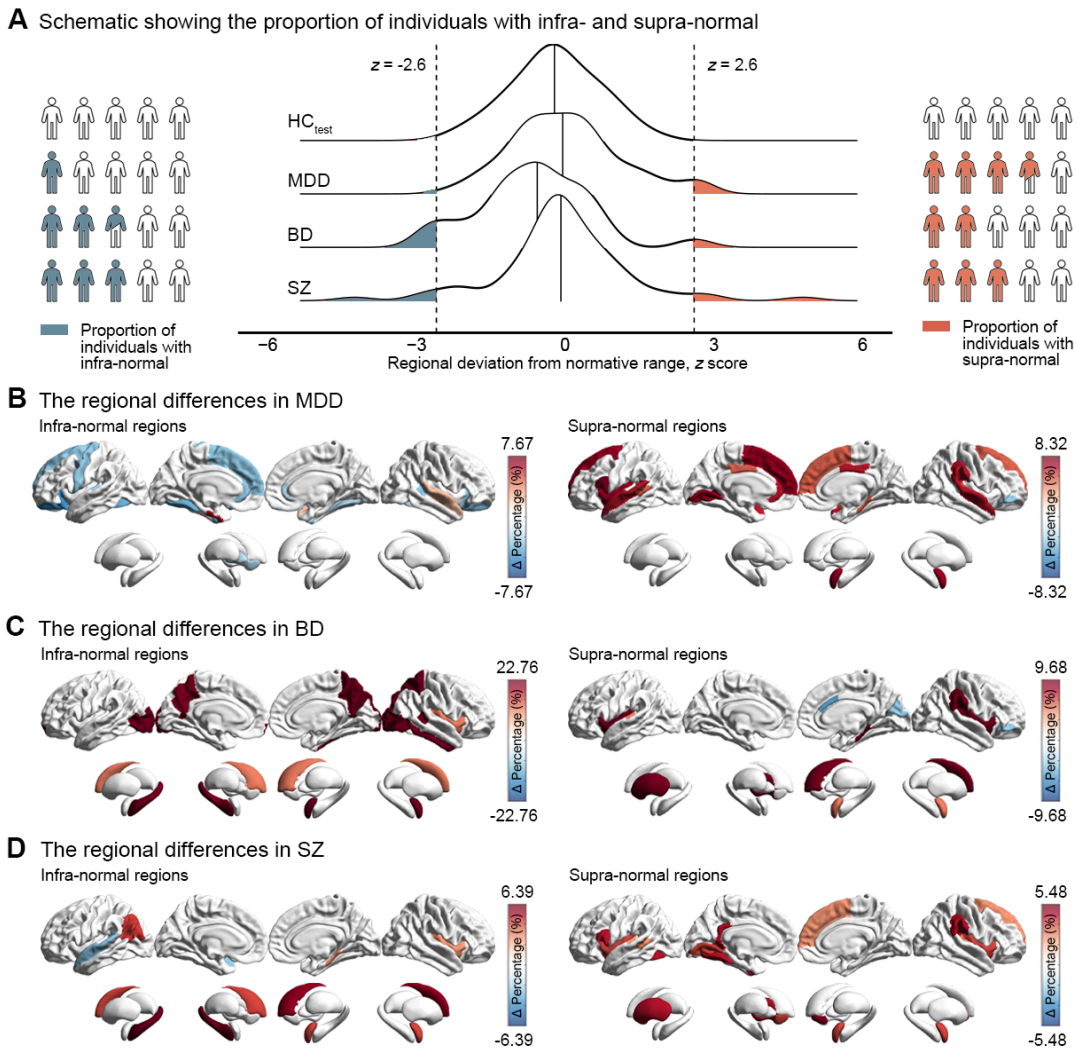

Figure 3. Regional differences between all cases and HC. **(A)** Schematic showing the proportion of individuals with infra-normal or supra-normal at any given regions in HC_{test} and each diagnostic group. The infra-normal and supra-normal regions in MDD **(B)**, BD **(C)** and SZ **(D)** patients were identified using 10,000 times group-base permutation test and statistical significance was adjusted by FDR.

3.4 Network level individual deviations in patients with MDD, BD and SZ

Network level analysis is further conducted to determine whether regional deviation underlying emotional dysfunctions is attributable to total deviation burden driven by functional alterations of emotional regulation networks. To this end, we embedded regions with extreme deviation into four distinct large-scale emotional

regulation networks, and estimated individualized deviations at network level. These networks also covered most of the regions that showed significant functional activation under task conditions (Supplement; Figure S10). Consistent with the statistical analysis at the regional level, network differences between HC_{test} and each diagnostic group were assessed using group-based permutation test. The results indicated that the emotional regulation networks are affected differently across various diagnoses (Figure 4A-C). Compared to HC, patients with MDD exhibited supra-normal deviations in ERN 3 (Δ percentage = 8.84%, p = .013, FDR corrected; Figure 4A), indicating higher functional activation in the brain network associated with emotion perception and generation during the emotional episodic memory task; BD patients exhibited infra-normal deviations in networks for appraisal and language processing (ERN 2, Δ percentage = 16.66%, p = .009, FDR corrected) and emotional reactivity (ERN 4, Δ percentage = 19.71%, p = .001, FDR corrected) (Figure 4B); SZ patients showed infra-normal deviations in network involving working memory and response inhibition (ERN1, Δ percentage = 8.21%, p = .025, FDR corrected; Figure 4C).

3.5 Circuit level individual deviations in patients with MDD, BD and SZ

Our analysis showed that regional deviations underlying emotional dysfunctions of distinct disorders couple into dissociable networks of emotional regulation. However, network analysis only extends our understanding to arbitrarily grouped regions and may not reflect actual connections. To address this, we conducted a circuit-level analysis to estimate whether regional activation deviations and broader deviant patterns at the

network level were mediated by functional couplings with deviant regions. Compared to HC, MDD patients showed infra-normal seed-based functional circuits predominately in the prefrontal cortex and visual regions and supra-normal functional circuit in the fusiform gyrus and medial orbitofrontal gyrus ($p < .0167$ (.05/3), FDR corrected; Figure 4D; Table S7). The most significant circuit were located in ERN 3 ($p < .000203$ (.05/3/82), Bonferroni corrected; Figure 4G). In BD patients, infra-normal circuits were mainly in the occipital cortex and supramarginal gyrus, while supra-normal circuits were in the cingulate gyrus, thalamus, and striatum ($p < .0167$ (.05/3), FDR corrected; Figure 4E; Table S8), with the most infra-normal regions in ERN 4 (Bonferroni corrected; Figure 4H). SZ patients exhibited significant infra-normal circuit in the parietal and frontal gyri, and large-scale supra-normal circuits involving frontal, temporal and occipital regions ($p < .0167$ (.05/3), FDR corrected; Figure 4F; Table S9). The most significant infra-normal regions were in ERN 1 (Figure 4I). Collectively, these findings align with the network-level analysis results.

---------- Insert Figure 4 here ----------

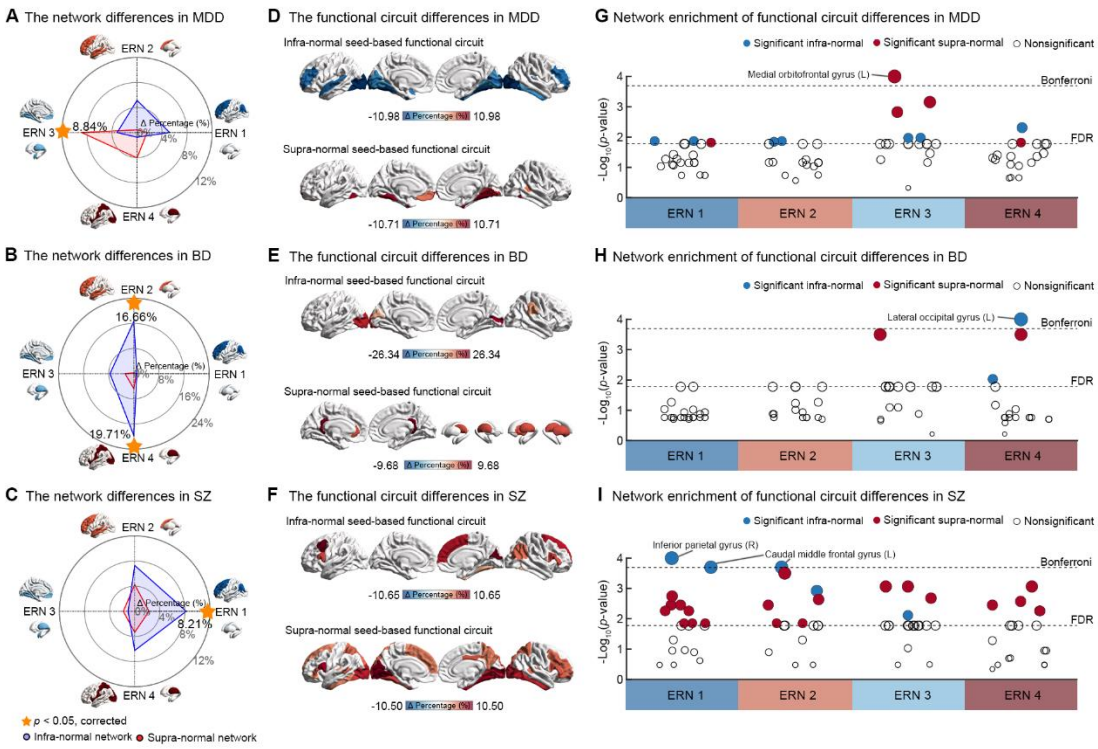

Figure 4. Network and circuit differences between all cases and HC. The infra-normal and supra-normal alterations at network level in the patients with MDD **(A)**, BD **(B)** and SZ **(C)** were identified, and abnormal circuit based on seeds showing significant deviations in the regional level in MDD **(D)**, BD **(E)** and SZ **(F)** patients were shown. The statistically significance was determined by using 10,000 times group-base permutation test and adjusted by FDR. Functional circuit differences were further enriched into four emotional regulation networks. Significant deviations were shown, with blue and red colors respectively indicated the infra-normal and supra-normal deviations and circle size proportional to the significant level. The most significant differences (Bonferroni correction) for MDD **(G)**, BD **(H)** and SZ **(I)** patients were labeled.

3.6 Clinical affective symptom association based on individual deviations

To test the associations between individual neural deviations of emotional dysfunctions and clinical affective symptoms in patients with psychiatric disorders, a machine learning model was performed to predict domain of affective symptoms using regional activation deviations underlying emotional memory in different mental disorder. As shown in Figure 5, there are significant correlations between predicted

scores and observed scores of anxiety/somatization factor of HAMD in MDD patients (r = 0.295, p_{perm} = .032, RMSE = 2.324; Figure 5A), total scores of HAMD in BD patients (r = 0.415, p_{perm} = .020, RMSE = 18.515; Figure 5B), and anxiety/depression factor of PANSS in SZ patients (r = 0.319, p_{perm} = .007, RMSE = 5.297; Figure 5C). The important features were identified by virtual lesion analysis that estimated feature weight of each region based on a re-calculated performance when removed from the predictive model at each iteration. Diagnosis-specific networks of emotional regulation in the deviation analysis exhibited specific maximum predictive weight respectively: ERN 3 for MDD, ERN 4 for BD, and ERN 1 for SZ (Figure 5D-F).

---------- Insert Figure 5 here ----------

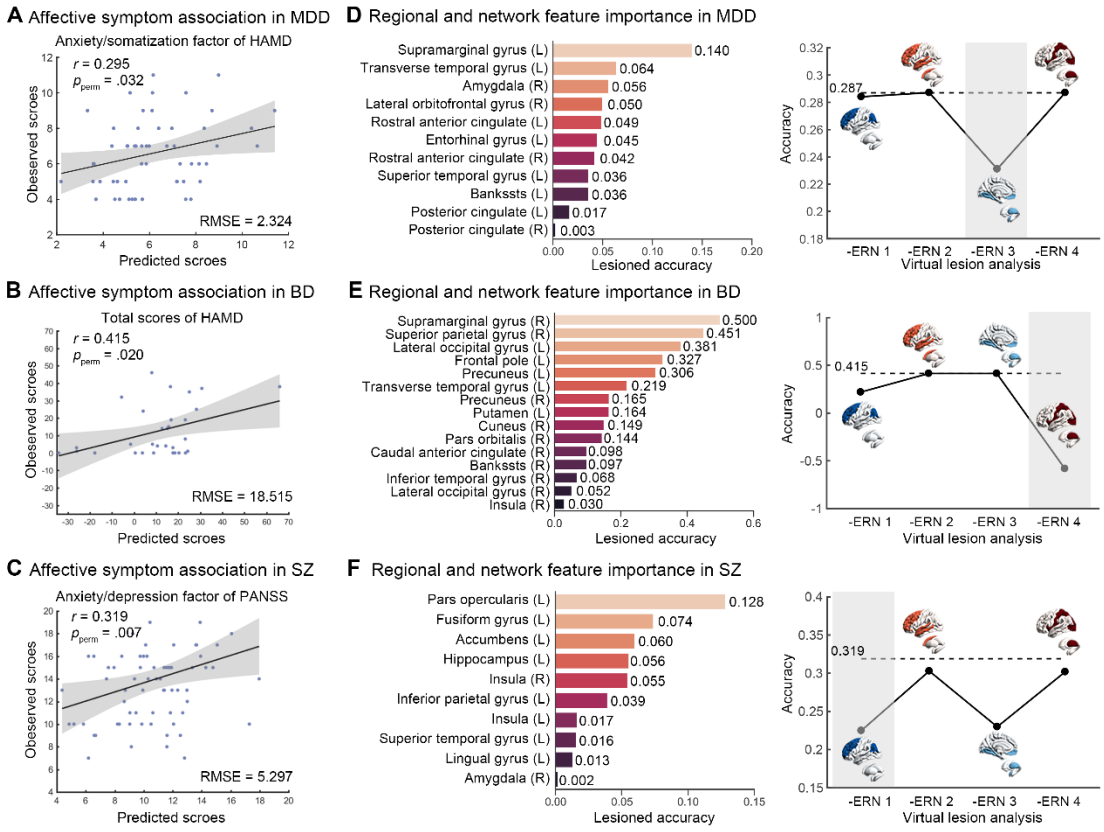

Figure 5. Association with clinical symptom in MDD, BD and SZ patients. The scatter plot showed the prediction accuracy defined by correlation coefficient between observed scores and predictive scores (left). **(A)** Individual deviations significantly predicted the anxiety/somatization factor of HAMD in MDD patients. **(B)** Total scores of HAMD in BD patients were predicted based on individual deviations. **(C)** Individual deviations predicted the anxiety/depression factor of PANSS in SZ patients. The virtual lesion analysis was applied to identify important features in prediction model of MDD **(D)**, BD **(E)** and SZ patients **(F)**. The bar plot exhibited the regional predictive weights (middle) and line chart showed the predictive weights at network level (right). In line chart, the dotted line indicates the original prediction accuracy and the network that exhibits the largest feature weight marked by shadow. MDD, major depressive disorder; BD, bipolar disorder; SZ, schizophrenia; RMSE, root mean square error; HAMD, Hamilton depression scale; PANSS, positive and negative syndrome scale; ERN, emotional regulation network; R, right; L, left

Discussion

The present study aims to identify individualized neurofunctional signature that underpin emotional dysfunction by disentangling neuropsychological heterogeneity in three major psychiatric disorders. By combining emotional memory task-based fMRI with individualized measures of normative modelling framework, our results support the hypothesis that neural dysfunctions underlying emotional memory are embedded within diagnosis-specific emotional regulation network and associated with specific domain of affective symptoms. Using lesion network mapping, our findings further revealed that the neural coupling relationship between deficiencies in emotional memory and emotional dysregulation was mediated by abnormalities in functional couplings between regions with significant functional deviations. Overall, our study provides neuroimaging evidence for better understanding the neural mechanisms underlying psychopathology of affective symptoms in distinct psychiatric disorders.

The emotional dysfunctions are a common feature of psychopathology in various mental disorder. However, until recently, few studies have explored the neural basis of emotional dysfunctions in distinct mental disorders and their relationship with clinical affective symptoms. Disrupted emotional memory is an important component of cognitive and affective deficits in psychiatric symptom dimensions (53). The emotional episodic memory paradigm used at current study has been broadly used to demonstrate the neural correlates of emotional memory for better characterizing emotion-related brain circuitry compared with task-free neuroimaging marker (45, 54). However, high intersubject heterogeneity is a main issue that may limit our ability to detect systematic differences of emotion memory-related functional activity in multiple psychiatric disorders. According to the sample sizes required for traditional case-control designs provided in Table S10, previous studies have often used relatively small samples. Normative modelling technique incorporated neural alterations underlying each psychiatric condition into a continuous spectrum in the population, which enabled us to disentangle the clinical heterogeneity for accurately quantifying patients' personalized deviations underlying emotional memory bias. We found that, although most patients existed functional alterations of emotional memory, only a low proportion of the patients shared the consistent extreme deviation for any single brain region (Figure S5). These results partly explained inconsistency of the results across studies that prevented us from finding objective and reliable neuroimaging representations of emotional dysfunctions. More importantly, these investigations have critical heuristic value for understanding different degrees of neurobiological deviation patterns with distinct

diagnostic categories in disorder-related affective symptom dimension, which are compatible with the objectives of Research Domain Criteria (RDoC, http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml) (55). Additionally, medical use may also be another confound, that resulting in inconsistent results across studies (56). Different psychoactive drugs may impact on neurocognitive systems supporting procedural learning and conditioning and thereby modulate emotional memory processes (52). Individualized measures based on our normative model showed an ability to resist the interference of medical effects (Figure S8), which has critical consequences for understanding long-term effects relevant to impaired emotional memory in different diagnostic conditions.

The percentage of individuals with infra-normal or supra-normal functional activation at network level has increased relative to individual percentage at regional level (MDD: about 4%; BD: about 3%; SZ: about 6%; Figure S12), showing regionally heterogeneous deficits aggregate within lesioned large-scale emotional regulation network. Retrieving concepts related to emotional connotations may heavily rely on emotional regulation. For instance, focusing on concepts with negative contexts may create a negative frame of mind. Previous studies indicated that emotional memory retrieval relies on coordinated responses of multiple neural systems involved in emotional regulation (57). On one hand, cognitive emotional regulations during retrieval might temporarily increase access to positive memories (58). On the other hand, avoiding negative memory retrieval might be facilitated by reduced access to memory and decreased intrusions from unpleasant memories (59). The convergence of

functional deviations at the network level suggests that functional interactions between different regions under emotional episodic memory drive these patterns, as shown in our circuit-level analysis. This raises the possibility that impaired patterns of functional connectivity may affect regulation processes and competencies in emotional memory within psychiatric disorders.

Distinct patterns of deviated functional activations underlying impaired emotional memory were reflected by diagnosis-specific emotional regulation network among MDD, BD and SZ patients. Specifically, we found that patients with MDD exhibited hyper-activations in a network related to emotion perception and generation, which comprised of amygdala, fusiform, and medial orbitofrontal gyrus. Cognitive theories of MDD hold that biased emotional memory derived from a negative schema for representing negative knowledge and experiences (60). Activated schema could alter perceptions and evaluations of external stimulus (61), and its weakening have been hypothesized to underlie of recovery (62, 63). A recent study implicated that emotional regulation during emotion perception could be used to reduce negative emotional memory and therefore improve depressive symptoms (34). The patients were reported lower negative affect ratings for external stimuli after emotional regulation strategy to impact emotional generation (34). Together, we speculated that specific regulation strategies might improve memory bias through impacting brain network of emotion perception, ultimately resulted in reduction of negative emotion. SZ patients showed infra-normal deviation in a cognitive emotion regulation network strongly associated with working memory and response inhibition, which is a frontoparietal network

consist of dorsolateral PFC and IPG. The emotional dysregulation of SZ was thought to be associated with negative symptoms, manifesting emotional flattening and anhedonia (10, 64). The emotional impairment in SZ patients may reflect overuse of suppression strategy and thereby disrupt emotional appraisal and recognition (10, 65), which align with our findings of dysfunctions of the network with dorsolateral PFC and IPG. In contrast, individuals with BD were associated with two networks of emotion regulation, jointly responsible for integrating emotional reactivity and cognition. These findings provided consistent evidence for support that the effective segregation of neural mechanism between over-sensitive reactivity cognitive dysregulation in different emotional states of BD (66). Echoing our research results, previous studies showed abilities to regulate emotions were significantly influenced by depressive and manic state of BD patients (67), suggesting set state-specific psychotherapeutic targets.

Neural dysfunctions during emotional memory intersected cross different mental disorders with co-hyperactivation in the right amygdala, left insula and right supramarginal gyrus, indicating the transdiagnostic neural substrates of emotional memory bias (Figure S9). The amygdala has been widely reported to be involved in emotional activation and response to external negative stimuli, which are emphasized as underlying emotional impairments (8, 68). The insula is associated with disrupted working memory, facilitated by inflexible update and preferential maintenance of negative or threatening stimuli (69, 70). The co-activation of amygdala and insula indicates that excessive attention to negative stimulation, mediated by hyper-activation of amygdala, may produce interference effect, contributing to systematic distortions

in emotional information processing in mental disorders. Additionally, the supramarginal gyrus, part of default mode network, is linked to self-focused rumination and abnormal self-referential processes (71, 72). Growing evidences suggests that emotional memory bias is not limited to attention and memory-related problems but is embedded in stable negative self-referential schemas (17, 73). Abnormal functional activation of the supramarginal gyrus may explain the neural underpinnings of interpretive biases driven by weakened cognitive structure in mental disorders (57). These results support the idea that common disrupted processing related to emotional memory also exists in psychiatric disorders.

Further analyses revealed regions with infra-normal or supra-normal functional activation of emotional memory might be a promising predictor for affective symptom dimension in specific disorder condition, diagnosis-specific emotional regulation network exhibited maximum predictive weight in midst of each predictive model. Accumulating studies highlighted that emotional dysregulation was associated with psychopathology and increased difficulties in controlling emotional responses contributing to affect-related disorders with intense emotional distress (74). Growing maladaptive strategies of emotional regulations, such as emotional suppression or rumination, could be a cause of developing affective symptoms in different psychiatric disorder (75, 76). Prior studies suggest that reducing emotional memory bias may be the basis for rehabilitation of emotional disturbances and is closely related to the reduced recurrence rate after cognitive behavioural therapy (62, 63). Many antidepressant treatments are considered effective by reversing these cognitive

emotional biases (77). Our findings indicate that parallel deficits in large-scale emotional regulation networks are associated with affective symptoms in specific psychiatric condition, thereby guiding the optimization of clinical treatment strategies.

Several issues need to be considered. First, the clinical sample in the current dataset was relatively small. Although we used a nonparametric group-based permutation test to identify statistically significant deviation in each case group relative to healthy controls, which is not affected by sample size, a larger clinical sample would help to better disentangle intersubject heterogeneity. Second, data of depressive severity in BD patients was partially missing, making it impossible to calculate the anxiety/somatization factor score of HAMD to represent affective symptom in BD. Additionally, a greater number and more comprehensive assessment scales for emotional symptoms will help better characterize the affective symptoms of different mental disorders. Finally, most BD patients in this study were in the euthymic stage, further study with more patients in different stages are imperative to assess the reproducibility of our findings.

Conclusion

To summarize, this study proposed a stable and cross-sample verifiable normative model representing the potential link between emotional episodic memory and brain functional activation based on a task-based fMRI design. Individualized measures of normative model enabled to delineate neural correlates underlying disrupted emotional memory were linked to diagnosis-specific emotional dysregulation network and clinical

affective symptom in three major psychiatric disorder. These findings step forward in understanding unique neuropsychological representation underlying basic dimensions of affectivity and provide a novel insight for the prevention and treatment of psychiatric disorder.

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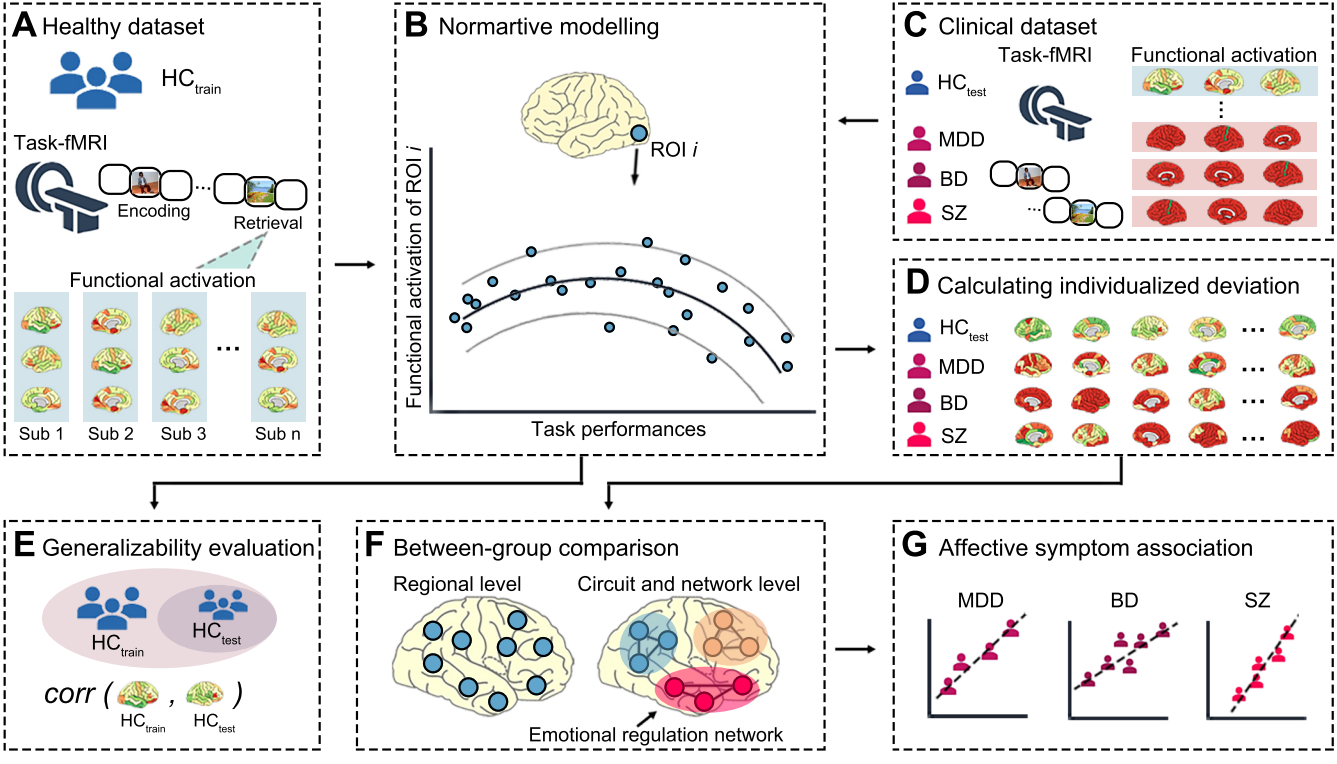
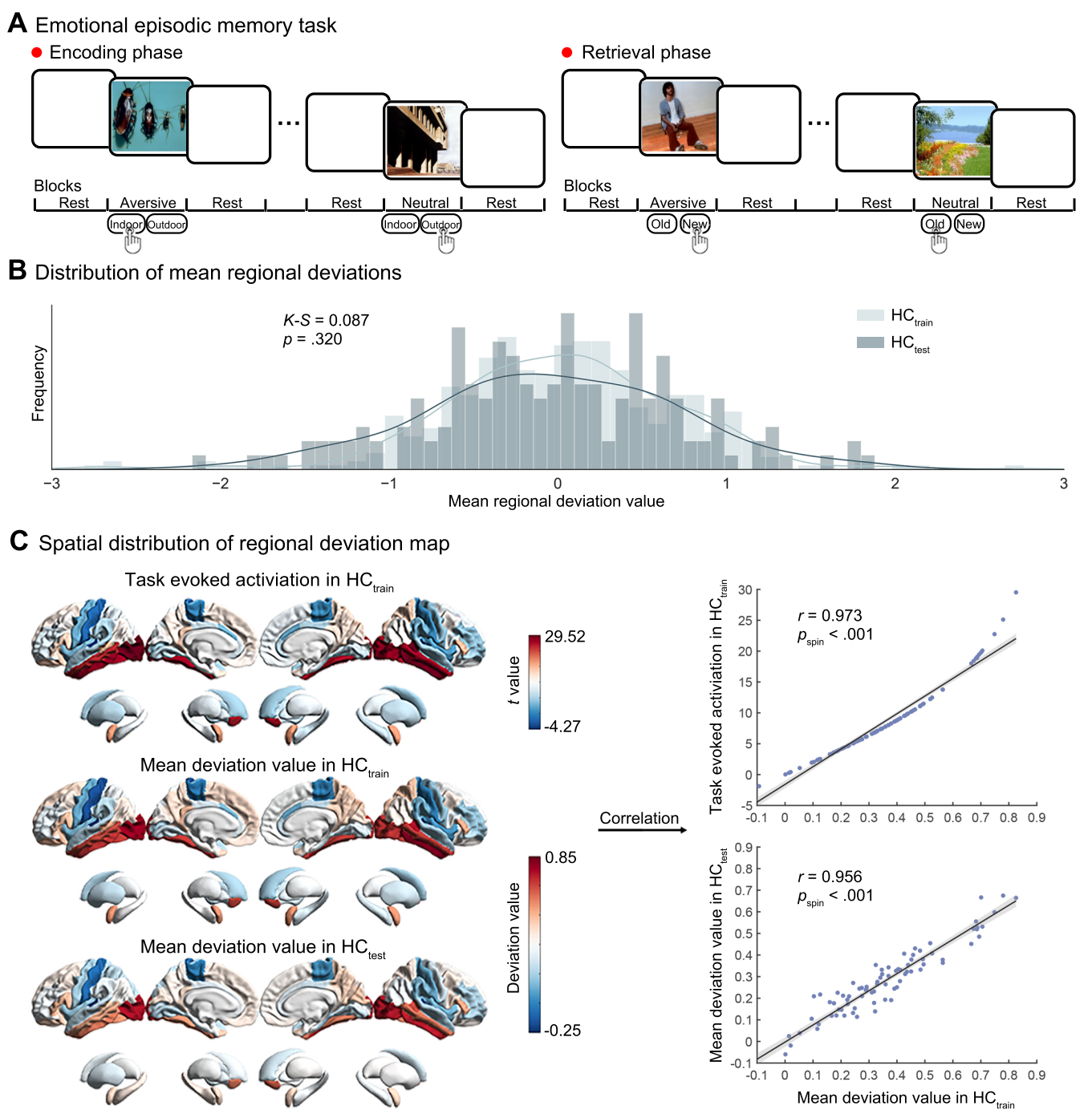
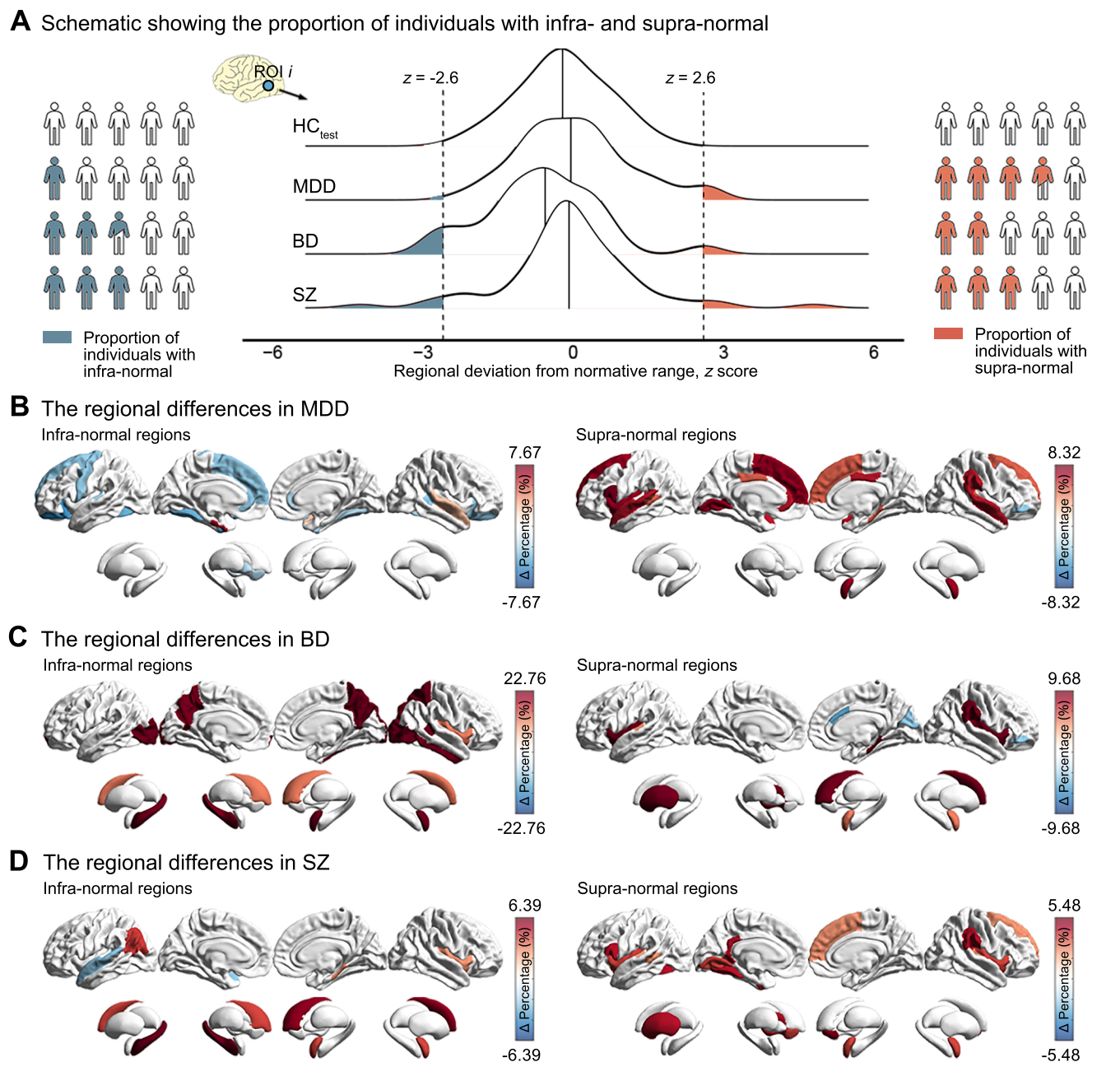
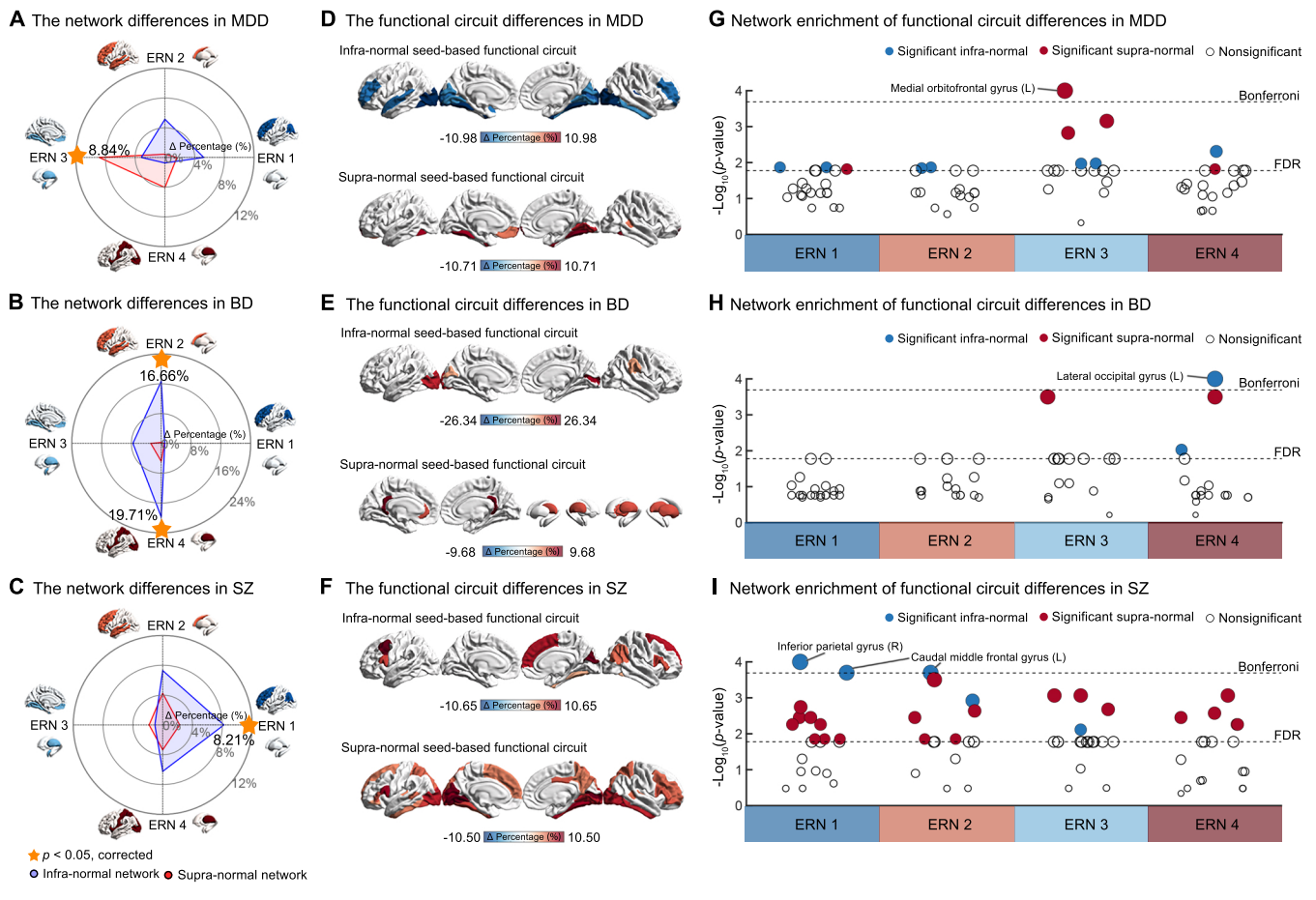
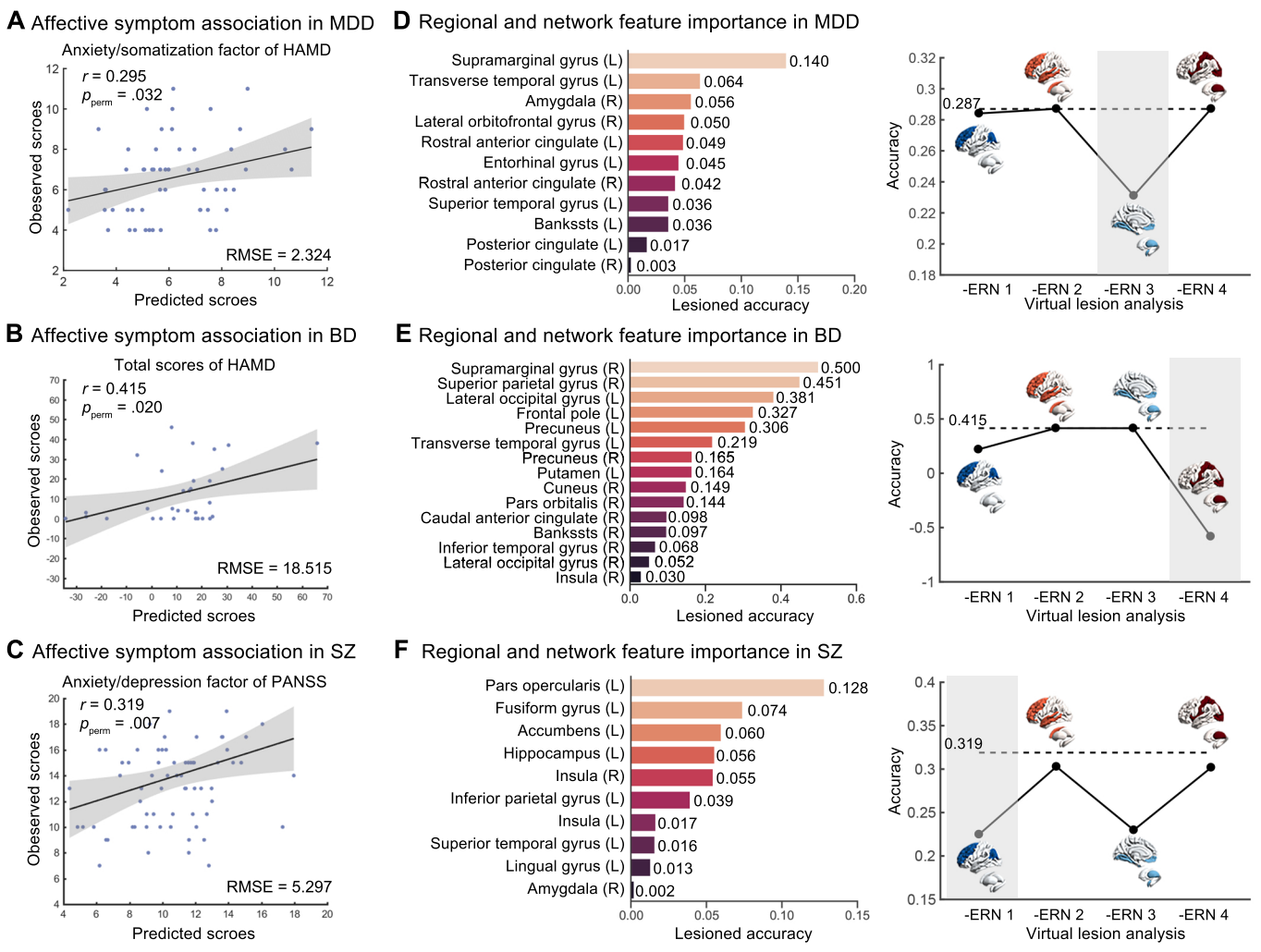

A Healthy dataset
HC train
Task-fMRI
Encoding
Retrieval
Functional activation
Sub 1
Sub 2
Sub 3
Sub n
B Normartive modelling
ROI i
Functional activation of ROI i
Task performances
C Clinical dataset
Task-fMRI
Functional activation
HC test
MDD
BD
SZ
D Calculating individualized deviation
HC test
MDD
BD
SZ
E Generalizability evaluation
HC train
HC test
corr (,)
HC train
HC test
F Between-group comparison
Regional level
Circuit and network level
Emotional regulation network
G Affective symptom association
MDD
BD
SZ


A Emotional episodic memory task
Encoding phase
Retrieval phase
Blocks
Rest
Aversive
Rest
Rest
Neutral
Rest
Indoor
Outdoor
Indoor
Outdoor
Blocks
Rest
Aversive
Rest
Rest
Neutral
Rest
Old
New
Old
New
B Distribution of mean regional deviations
K-S = 0.087
p = .320
HCtrain
HCtest
Frequency
−3
−2
−1
0
1
2
3
Mean regional deviation value
C Spatial distribution of regional deviation map
Task evoked activiation in HCtrain
29.52
-4.27
t value
Mean deviation value in HCtrain
0.85
-0.25
Deviation value
Mean deviation value in HCtest
Correlation
r = 0.973
pspin < .001
Task evoked activiation in HCtrain
r = 0.956
pspin < .001
Mean deviation value in HCtest
Mean deviation value in HCtrain


A Schematic showing the proportion of individuals with infra- and supra-normal
ROI i
z = -2.6
z = 2.6
HC test
MDD
BD
SZ
Proportion of individuals with infra-normal
Proportion of individuals with supra-normal
−6
−3
0
3
6
Regional deviation from normative range, z score
B The regional differences in MDD
Infra-normal regions
7.67
-7.67
Supra-normal regions
8.32
-8.32
C The regional differences in BD
Infra-normal regions
22.76
-22.76
Supra-normal regions
9.68
-9.68
D The regional differences in SZ
Infra-normal regions
6.39
-6.39
Supra-normal regions
5.48
-5.48
Δ Percentage (%)


A The network differences in MDD
ERN 2
ERN 1
ERN 3
ERN 4
8.84%
Δ Percentage (%)
0%
4%
8%
12%
B The network differences in BD
ERN 2
ERN 1
ERN 3
ERN 4
16.66%
19.71%
Δ Percentage (%)
0%
8%
16%
24%
C The network differences in SZ
ERN 2
ERN 1
ERN 3
ERN 4
8.21%
Δ Percentage (%)
0%
4%
8%
12%
p < 0.05, corrected
Infra-normal network
Supra-normal network
D The functional circuit differences in MDD
Infra-normal seed-based functional circuit
-10.98 Δ Percentage (%) 10.98
Supra-normal seed-based functional circuit
-10.71 Δ Percentage (%) 10.71
E The functional circuit differences in BD
Infra-normal seed-based functional circuit
-26.34 Δ Percentage (%) 26.34
Supra-normal seed-based functional circuit
-9.68 Δ Percentage (%) 9.68
F The functional circuit differences in SZ
Infra-normal seed-based functional circuit
-10.65 Δ Percentage (%) 10.65
Supra-normal seed-based functional circuit
-10.50 Δ Percentage (%) 10.50
G Network enrichment of functional circuit differences in MDD
Significant infra-normal
Significant supra-normal
Nonsignificant
Medial orbitofrontal gyrus (L)
Bonferroni
FDR
-Log10(p-value)
ERN 1
ERN 2
ERN 3
ERN 4
H Network enrichment of functional circuit differences in BD
Significant infra-normal
Significant supra-normal
Nonsignificant
Lateral occipital gyrus (L)
Bonferroni
FDR
-Log10(p-value)
ERN 1
ERN 2
ERN 3
ERN 4
I Network enrichment of functional circuit differences in SZ
Significant infra-normal
Significant supra-normal
Nonsignificant
Inferior parietal gyrus (R)
Caudal middle frontal gyrus (L)
Bonferroni
FDR
-Log10(p-value)
ERN 1
ERN 2
ERN 3
ERN 4


A Affective symptom association in MDD
Anxiety/somatization factor of HAMD
r = 0.295
p_perm = .032
RMSE = 2.324
Obeserved scroes
Predicted scroes
B Affective symptom association in BD
Total scores of HAMD
r = 0.415
p_perm = .020
RMSE = 18.515
Obeserved scroes
Predicted scroes
C Affective symptom association in SZ
Anxiety/depression factor of PANSS
r = 0.319
p_perm = .007
RMSE = 5.297
Obeserved scroes
Predicted scroes
D Regional and network feature importance in MDD
Supramarginal gyrus (L) 0.140
Transverse temporal gyrus (L) 0.064
Amygdala (R) 0.056
Lateral orbitofrontal gyrus (R) 0.050
Rostral anterior cingulate (L) 0.049
Entorhinal gyrus (L) 0.045
Rostral anterior cingulate (R) 0.042
Superior temporal gyrus (L) 0.036
Bankssts (L) 0.036
Posterior cingulate (L) 0.017
Posterior cingulate (R) 0.003
Lesioned accuracy
0.287
Accuracy
-ERN 1
-ERN 2
-ERN 3
-ERN 4
Virtual lesion analysis
E Regional and network feature importance in BD
Supramarginal gyrus (R) 0.500
Superior parietal gyrus (R) 0.451
Lateral occipital gyrus (L) 0.381
Frontal pole (L) 0.327
Precuneus (L) 0.306
Transverse temporal gyrus (L) 0.219
Precuneus (R) 0.165
Putamen (L) 0.164
Cuneus (R) 0.149
Pars orbitalis (R) 0.144
Caudal anterior cingulate (R) 0.098
Bankssts (R) 0.097
Inferior temporal gyrus (R) 0.068
Lateral occipital gyrus (R) 0.052
Insula (R) 0.030
Lesioned accuracy
0.415
Accuracy
-ERN 1
-ERN 2
-ERN 3
-ERN 4
Virtual lesion analysis
F Regional and network feature importance in SZ
Pars opercularis (L) 0.128
Fusiform gyrus (L) 0.074
Accumbens (L) 0.060
Hippocampus (L) 0.056
Insula (R) 0.055
Inferior parietal gyrus (L) 0.039
Insula (L) 0.017
Superior temporal gyrus (L) 0.016
Lingual gyrus (L) 0.013
Amygdala (R) 0.002
Lesioned accuracy
0.319
Accuracy
-ERN 1
-ERN 2
-ERN 3
-ERN 4
Virtual lesion analysis