

Energy inefficiency underpinning brain state dysregulation in individuals with major depressive disorder

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Supplementary Methods

Participants selection process

The UK Biobank (UKB) serves as the world's largest neuroimaging resource, comprising approximately 45,000 imaging sessions from ~40,000 participants recruited across the United Kingdom (age range: 40-69 years at baseline) up to 2023 [1-5]. The UKB protocol was approved by the North West Multi-centre Research Ethics Committee (11/NW/0382), and all participants provided written informed consent for data provision and linkage. Data in the present study were accessed under UKB application #88660. This study included 38,979 participants with complete imaging data across three MRI modalities: T1-weighted structural MRI, resting-state functional MRI (rs-fMRI), and diffusion-weighted MRI (dMRI). Below, we have outlined the criteria and screening processes used to define the MDD group as well as a well-matched healthy control group from the UKB dataset.

Participants with self-reported neurological conditions known to affect cognitive function [6], or those with diagnoses of bipolar disorder, schizophrenia, Parkinson's disease, stroke, dementia, autism spectrum disorder, psychosis, Alzheimer's disease, multiple sclerosis, epilepsy, or intellectual disability (ICD-10), were first excluded from the study (Fig. S1). After this process, 37,963 participants remained.

MDD status was then determined using a two-step screening process. First, participants were identified as having a history of depression (UKB Data-Fields: 2090/2100, collected during the first neuroimaging visit; Table S3) [7]. The validity of this broad classification has been supported by genetic analyses demonstrating strong genetic correlations with formally diagnosed MDD [8]. Next, among participants with positive lifetime depression, we identified those who reported experiencing at least one core depressive symptom: depressed mood (Data Field: 2050) or unenthusiasm / disinterest (Data Field: 2060), for the majority or all days in the last two weeks prior to MRI acquisition. These two self-reported symptoms correspond to the 2-item Patient Health Questionnaire (PHQ-2), which reliably captures concurrent mood states during MRI assessment. This two-step screening process initially identified 890 MDD cases. From this group, we further excluded participants who did not complete the PHQ-2 questionnaire during the neuroimaging visit or for whom data on key covariates (smoking and alcohol consumption status) were unavailable. This resulted in a final study sample of 850 MDD cases. Although a conventional MDD diagnosis requires meeting five of nine DSM criteria (PHQ-9) [9], there are variable time lags of up to two years between neuroimaging scans and symptom assessment using PHQ-9 for the UKB dataset. Besides, complete PHQ-9 data were only available for 524 of 850 MDD participants (61.6%). The PHQ-2 has demonstrated comparable diagnostic utility, with both measures showing sensitivities of 98% and specificities of 80% in MDD screening [10]. This supports our MDD phenotype definition using PHQ-2.

For the healthy controls (HCs), we applied strict criteria to ensure they were free from any history or symptoms of depression. Specifically, the participants were required to meet the following criteria: They had never seen a general practitioner (GP) or psychiatrist for nerves, anxiety, tension, or depression (Data-Fields: 2090/2100); PHQ-2 scores < 1 at the time of the MRI visit; and they reported no prior week-long episodes of either depressed mood (Data-Field: 4598) or anhedonia (Data-Field:

4631).

From this pool of eligible individuals, a case control dataset of 850 healthy controls was formed by the following process. Each participant with MDD was matched with all the individuals that had the same age in years (Data-Field: 21003), sex (Data-Field: 31), and assessment center (Data-Field: 54). Then for each MDD patient, a matched healthy control was randomly chosen from the matching pool. In addition, information on smoking status (Data-Field: 20116) and alcohol consumption status (Data-Field: 20117) was also collected for all participants and included as covariates in subsequent analyses to account for potential group differences.

The final sample comprised 850 individuals with MDD and 850 well-matched healthy controls. A detailed flowchart outlining the participant selection process was provided in Fig. S2. The two groups were matched on age (mean [SD]: 60.59 [7.30] years), sex (33.88% male), and assessment center (Cheadle/Reading/Newcastle: 60.12%/12.94%/26.94%). The detailed demographic and clinical characteristics of the selected sample, including key covariates such as smoking and alcohol consumption status, were presented in Table 1.

Group-consensus SC construction

Individual structural connectomes were first derived from each participant's diffusion MRI data. To generate group-representative structural connectivity matrices for the MDD and HC groups, we employed a distance-dependent consensus approach that preserves both edge density and the distribution of connection lengths within and between hemispheres [11]. This method generates a binary consensus network that determines which connections should be retained. For these preserved connections, the edge weights in the final group-consensus matrices (A_{MDD} and A_{HC}) were computed by averaging the corresponding non-zero weights across the individuals within each diagnostic group. This approach ensures that the resulting group-consensus connectomes maintain the spatial characteristics of individual brain networks while addressing potential inconsistencies in individual connectome reconstruction.

The third-party Python software used to generate the uniform and distance-dependent group-representative networks is available at <https://github.com/netneurolab/netneuroltools>.

Network null models

To investigate whether the brain structure, as reflected by the empirical structural connectome in this case, is optimized for energy-efficient state transitions, we compared the mean energy cost (including persistence energy) between all possible state pairs under the empirical connectivity and two null network models (Fig. S4). Specifically, the first null model utilized Maslov-Sneppen rewiring, which preserves both the binary degree of each node and the distribution of the connection weights while randomizing the connectivity pattern [12]. The second, more conservative model, not only maintained the degree sequence and edge weight distribution but also approximately preserved the edge length distribution (based on inter-regional Euclidean distances) and the relationship between connection weights and lengths [13].

For both the MDD and HC groups, we generated 1,000 surrogate networks for each null model based on their respective group-consensus structural connectomes (see the "Group-consensus structural connectome construction" section). Using group-averaged brain states derived from all subjects within each group, we calculated the transition and persistence energies between all possible state pairs for each null network. This computational procedure followed the same approach used with the empirical connectomes and allowed us to compare the mean energy costs obtained from null models with those from the empirical connectomes.

Neurotransmitter profiles and rERC *t*-map

A comprehensive cortical profile of neurotransmitter receptor densities was obtained from a database compiling PET imaging data from over 1,200 healthy participants across multiple studies [14]. Mean tracer maps were extracted from each study, with detailed methodological information available in [15]. PET images were registered to a normalization template (MNI-ICBM 152 nonlinear 2009 template) and then parcellated according to our 210 cortical regions based on the Brainnetome atlas [16]. The receptor density values were normalized using min-max scaling across all regions. A total of 19 neurotransmitter receptor and transporter maps across 9 different neurotransmitter systems—including dopamine, norepinephrine, serotonin, acetylcholine, glutamate, GABA, histamine, cannabinoid, and opioid—were obtained. The spatial correspondence between these receptor distributions and the rERC *t*-map was assessed using Spearman correlations across the 210 cortical regions, with spin tests applied to account for spatial autocorrelation.

Gene expressions and rERC *t*-map

a) Estimation of regional gene expressions

Brain-wide gene expression profiles were obtained from the Allen Human Brain Atlas (AHBA) [17, 18], which contains gene expression data from post-mortem brain tissues of six neurologically healthy donors (age = 42.50 ± 13.38 years; male/female = 5/1): a 24-year-old African American male (H0351.2001), a 39-year-old African American male (H0351.2002), a 57-year-old European-ancestry male (H0351.1009), a 31-year-old European-ancestry male (H0351.1012), a 49-year-old Hispanic female (H0351.1015), and a 55-year-old European-ancestry male (H0351.1016).

Microarray expression data provided by Arnatkevičiūtė et al. [19] were first processed using the abagen toolbox (version 0.1.1; <https://github.com/rmarkello/abagen>). This involved a series of quality control and processing steps, as detailed below: (1) Microarray probes were reannotated based on current genomic data, and probes were filtered to remove those lacking valid Entrez IDs or showing below-background intensity in the majority of samples [20], (2) For genes with multiple probes, we selected the probe demonstrating the highest consistency of regional variation across donors, as quantified by the differential stability index [21]. (3) Tissue samples were initially assigned to brain regions based on their MNI coordinates, with unassigned samples excluded from further analysis; (4) Sample-to-region mapping was refined through two steps: updating sample MNI coordinates using nonlinear registration and constraining the matching process by hemisphere and structural divisions (cortex and subcortex) [19]. (5) Expression values were normalized within distinct brain structures using a robust sigmoid transformation followed by unit-interval rescaling [22].

To ensure data quality, genes with low similarity across donors ($r < 0.2$) were excluded from further analysis. Finally, by averaging the expression values of samples assigned to the same region (cortical regions only) in each donor and then across donors, a regional expression matrix with 199 rows (cortical brain regions) and 5,826 columns (the remaining genes) was obtained.

b) PLS regression analysis

Partial least squares (PLS) regression [23] was employed to investigate the spatial association between the rERC t -map and gene expression profiles of 5,826 genes across 199 cortical regions. In this analysis, gene expression data served as predictor variables, while the rERC t -values served as the response variable. The significance of the PLS components was evaluated through permutation testing, which assessed whether the components explained more covariance between the rERC t -map and gene expression patterns than expected by chance [24]. Spatial autocorrelation was addressed using spin tests. For significant PLS components, bootstrapping (5,000 iterations) was performed to estimate the reliability of each gene's contribution. Gene-specific Z-scores were calculated as the ratio of each gene's PLS weight to its bootstrap standard error, enabling the ranking of genes based on their contribution to significant PLS components [25]. Genes exceeding a threshold of $|Z| > 3$ were selected for further enrichment analysis.

c) Gene enrichment analysis

Gene enrichment analysis was performed using Metascape [26], an automated meta-analysis tool that provided a comprehensive functional enrichment analysis across 40 independent knowledge bases. The genes list generated from the PLS analysis was input into the Metascape analysis. The enrichment analysis was carried out using multiple ontology sources, including GO Biological Processes, KEGG pathways, and DisGeNET. The statistical significance was established using a threshold of $q < 0.05$, with false discovery rate correction for multiple comparisons. Kappa scores were used as the similarity metric when performing hierarchical clustering on the enriched terms, and sub-trees with a similarity of > 0.3 were considered a cluster.

Spin tests

To assess the statistical significance of spatial correlations between different brain maps, we employed a non-parametric spatial permutation test, commonly known as the 'spin test', to account for their inherent spatial autocorrelation [27, 28]. This method works by projecting the cortical surface onto a sphere and applying a large number of random rotations to one of the maps. A critical advantage of this approach over simple value shuffling is that it preserves the spatial covariance structure of the data. This generates a more realistic and conservative null distribution, thereby minimizing the risk of false positives. For our analysis, we generated 10,000 such random rotations to create a null distribution of correlation values. The significance of the empirically observed correlation (p_{spin}) was then determined by its percentile rank within this null distribution.

Supplementary Results

PLSC analysis between rERC and depressive symptom severity

To examine the relationship between rERC patterns and depressive symptoms, we conducted a partial least squares correlation (PLSC) analysis [29]. The analysis incorporated two sets of variables: brain variables (rERC values across 210 cortical regions of MDD) and behavioral variables (PHQ-2 scores, with age, sex, assessment center, smoking and alcohol consumption status as covariates). A correlation matrix was first computed between these two variable sets, followed by singular value decomposition to identify latent components representing optimal combinations of brain and behavioral patterns. This analysis yielded three significant latent components (LC1, LC2, and LC3), explaining 31.70%, 24.72%, and 18.34% of the total covariance, respectively (Fig. S8a). The significance of each component was assessed through permutation testing (10,000 permutations, all $p < 0.0001$). The stability of brain and behavioral weights was evaluated using bootstrapping (5000 iterations).

A further analysis of LC3 revealed: (1) a significant correlation between component scores for brain and behavioral variables ($r = 0.380, p < 0.0001$; Fig. S8b), indicating a robust relationship between the rERC patterns and the severity of depressive symptoms; (2) significant PHQ-2 variable loading ($p < 0.0001$; Fig. S8c), suggesting that depressive symptom severity substantially contributes to this brain-behavior relationship; and (3) a positive correlation between rERC scores and PHQ-2 scores ($r = 0.190, p < 0.0001$; Fig. 4f).

The spatial relationship between LC3 rERC loadings and the case-control rERC t -map was examined using spin tests to account for spatial autocorrelation, revealing a significant negative correlation ($r = -0.183, p_{spin} = 0.0079$; Fig. 4g). After applying Bonferroni correction ($p < 0.05$) to the LC3 rERC loadings, seven brain regions showed significant contributions (Table S2). Notably, the most contributing region INS_R_6_3 overlapped with regions showing significant rERC group differences in the main analysis (Table S1).

Validation of dominance metrics against signal-to-noise ratio

The dominant network approach used here to extract brain states [30] could potentially be influenced by signal dropout, a concern particularly relevant for the limbic network which consistently scored low in measures of brain state dominance (Fig. 2b).

To examine the influence of signal quality, we calculated a network-level inverted temporal signal-to-noise ratio (tSNR). First, tSNR was computed for each of the 210 brain regions from the preprocessed fMRI time series (mean signal intensity / temporal standard deviation). A single tSNR value was then derived for each network by taking the median tSNR of all its constituent regions. Finally, this network-wise tSNR was inverted, creating a metric where a higher value indicates poorer signal quality. Across subjects, while the limbic (LIM) network showed relatively lower signal quality than other networks (Fig. S10a), correlations between its signal quality and dominance metrics were either negligible (Appearance Rate $r = 0.03, p = 0.212$; Fig. S10d) or weakly positive (Fractional Occupancy, $r = 0.14, p < 0.0001$; Dwell Time, $r = 0.124, p < 0.0001$; Fig. S10b, c). These initial results suggest that poorer signal quality is not systematically associated with lower dominance scores at the cross-

subject level.

To further probe this relationship on a network-by-network basis within each subject, we performed a within-subject correlation analysis. Specifically, for each subject, we correlated the inverted tSNR across the seven functional networks with the corresponding values for Fractional Occupancy (FO), Dwell Time (DT), and Appearance Rate (AR). Given the small number of data points (seven networks), we used Kendall's rank correlation (τ) as a robust measure. Using Spearman's correlation yielded highly consistent results.

At the individual level, the proportion of subjects exhibiting a significant correlation was very small (<4%), with these correlations being mixed in direction (Fig. S10e (i)). Across the entire cohort ($N = 1700$), we observed a subtle negative trend, though the magnitude of the mean correlation was small (mean Kendall's τ values of -0.116 for FO, -0.099 for DT, and -0.137 for AR; Fig. S10f (i)). This suggested that networks with poorer signal quality might tend to have slightly lower dominance scores. We hypothesized that this weak trend might be disproportionately influenced by the limbic network, which exhibits both the lowest signal quality and consistently low dominance scores.

To test this hypothesis, we conducted a follow-up analysis by excluding the limbic network and repeating the correlations across the remaining six networks. While the proportion of subjects with significant correlations remained rare (less than 2%) (Fig. S10e (ii)), the group-level distribution of correlation coefficients shifted markedly to the positive, with mean Kendall's τ values becoming positive for FO (0.150) and DT (0.184), and near zero for AR (0.017) (Fig. S10f (ii)). A positive correlation implies that networks with poorer signal quality tend to have larger dominance scores. This result confirms that the initial, subtle negative trend was probably driven by the limbic network, rather than being a systematic property of our dominance metrics across the cortex.

Robustness of main findings after excluding limbic network

To formally test the robustness of our findings against any potential influence from the limbic network, we conducted a "leave-one-network-out" analysis by completely excluding it. Dominant brain states were re-defined at each time point based on the remaining brain regions, yielding six new brain states for each subject.

The obtained results were highly consistent with our initial findings. The core temporal dynamics were preserved, with MDD patients still exhibiting significantly shorter average dwell time ($t = -3.557$, $p = 0.0004$) and a higher average appearance rate ($t = 6.144$, $p < 0.0001$) (Fig. S11a). Furthermore, the key finding of energy inefficiency in MDD was also fully replicated. That is, transitions between states demanded more energy in MDD patients, resulting in increased average energetic cost and reduced control stability (Fig. S11b).

This stringent validation demonstrates that our key findings regarding altered brain state dynamics in MDD are robust to the exclusion of the limbic network. The replication of both temporal and energetic patterns strengthens our main results.

Sensitivity analysis for anxiety comorbidity

Given the common comorbidity between MDD and anxiety disorders, and since our two-step screening process did not exclude anxiety cases, we performed a comprehensive sensitivity analysis to assess its potential influence on our findings.

We first identified anxiety comorbidity in our final MDD sample (N=850), using both self-report data (UKB Data-Field: 20002) and formal clinical ICD-10 diagnoses (codes F40, F41; Table S4). This identification approach, combining self-report and formal diagnostic codes, was consistent with the methodology used for our primary comorbidity exclusions (e.g., bipolar disorder, schizophrenia). Of the 850 MDD participants, 128 (15.1%) had a record of anxiety disorder (Table S5). To test anxiety's potential impact, we re-ran all primary analyses on a refined subsample of 722 MDD patients (i.e., excluding 128 comorbid cases) and their matched HCs.

Results showed remarkable consistency with our main findings. Patterns of altered temporal brain dynamics remained clearly evident, i.e., shorter average dwell time and higher average appearance rate in MDD (Fig. S12a, i-ii). The key findings of increased average energetic cost and decreased control stability in MDD were also preserved (Fig. S12a (iii-iv), b). Moreover, a highly spatial concordance of the case-control rERC t-maps between the full (N=850) and non-comorbid subgroup (N=722) was obtained (Spearman's $r = 0.942$, $p_{spin} < 0.0001$; Fig. S12c). Though some measures like control stability ($p = 0.0647$) showed reduced statistical significance due to reduced sample size (Fig. S12a, iv), these analyses confirmed that our main results reflect fundamental neural dynamic alterations in MDD rather than driven by anxiety comorbidity.

In addition, further investigation revealed important clinical differences. We found that the excluded anxiety-comorbid subgroup (N=128) had significantly more severe depressive symptoms (PHQ-2 scores) than the non-comorbid MDD subgroup (N=722) (mean $\pm$ SD: 4.13 ± 1.24 vs. 3.84 ± 1.27 ; $t = 2.49$, $p = 0.0139$). This suggests that removing anxiety-comorbid cases didn't isolate anxiety-specific effects, but rather excluded more symptomatic individuals. Including MDD participants with anxiety-comorbid actually preserved both statistical power and clinical representativeness of our sample. Based on this comprehensive sensitivity analysis, we retained the full cohort of 850 MDD participants in our main analyses to best reflect real-world MDD presentations.

Validation of our MDD identification procedure against ICD-10 diagnoses

As described above, our work focused on current depression. This section detailed the validation of our two-step procedure (Fig. S13) using self-reported PHQ-2 for identifying 'current MDD' against formal clinical ICD-10 diagnoses of depressive disorders (F32/F33) [31] from the UK Biobank health registry (ICD-10 diagnosis, Data-Field: 41280). The objective was to ensure that our method is both sensitive to formal diagnostic history and specific to the current depressive state required for our brain dynamics analyses.

Our first step identified individuals with a history of "broad depression", a definition adapted from prior work [7] that uses UKB self-report data (Data-Fields 2090 and 2100; see Table S3 for details).

This "broad depression" construct has been validated against genetic data that show a high genetic correlation between broad depression status and formally assessed major depression [8]. Of the 38,979 participants with full imaging data, 804 had an ICD-10 diagnosis of depression (Table S6). Our "broad depression" criterion identified 12,133 individuals, including 752 of the 804 ICD-10 cases (93.5%). This high sensitivity demonstrates that our initial screening step is highly effective at capturing individuals with a formal ICD-10 diagnosis history.

Next, we validated the second step of our procedure, which filtered for *current* depressive state at the time of imaging scanning, using PHQ-2 [32]. This step is critical because ICD-10 diagnosis from UK Biobank do not align with the timing of imaging visit, making it an unreliable indicator of a participant's depressive state at the time of the scan (Fig. S14, Table S7). The specificity of our "current state" filter was evident in the ICD-10 cohort: only 132 of the original 804 individuals with a historical depression diagnosis were retained after applying the current-symptom criteria. This validated our procedure's ability to distinguish lifetime diagnoses from current symptomatic states, a crucial requirement for our studies of brain dynamics.

In conclusion, our two-step identification procedure effectively balanced sensitivity to past depression diagnoses with specificity for current symptoms. The final analytic sample including 850 individuals with validated current MDD after further standard exclusions, was applied in this study (Fig. S2).

Validation of network dominance using cosine similarity

To validate our operationalization of "network dominance," we compared our amplitude-based method [30] to an established pattern-matching approach using cosine similarity [33].

First, a state-level comparison was performed by correlating our seven derived brain states for each subject with the canonical templates of Resting State Networks (RSNs) [34]. This revealed a precise one-to-one mapping, where the positive components of each state showed the highest cosine similarity with its corresponding RSN template. Fig. S15 provided a representative example of this mapping.

Next, a timepoint-by-timepoint comparison was conducted for each subject across the entire dataset. The network identified as dominant by our amplitude-based method agreed with the cosine similarity method in 82.16% of cases, demonstrating strong concordance between these two independent methods. This high agreement between methods provided strong empirical support for the validity of identifying dominant networks using the amplitude-based approach.

Together, these results supported that our amplitude-based operationalization of network dominance reliably captures established functional network organization, validating its use for characterizing dynamic brain states.

Supplementary Figures

UK Biobank Field Codes and values

- Field 6150 = 3
- Field 20001 = 1031 OR 1032
- Field 20002 = 1082 1083 1086 1524 1262 1397 1683
1245 1246 1491 1425 1433 1258 1263 1264 1266 1244
1583 1659 1259 1240 1434

Corresponding condition titles

- Brain cancer/primary malignant tumour
- Brain haemorrhage
- Brain/intracranial abscess
- Cerebral aneurysm
- Cerebral palsy
- Chronic/degenerative neurological problem
- Dementia/Alzheimer's disease/cognitive impairment
- Encephalitis
- Epilepsy
- Head injury
- Infection of nervous system
- Ischaemic stroke
- Meningeal cancer/malignant meningioma
- Meningioma (benign)
- Meningitis
- Motor neurone disease
- Multiple sclerosis
- Neurological injury/trauma
- Neuroma (benign)
- Other demyelinating condition
- Other neurological problem
- Parkinson's disease
- Spina bifida
- Stroke
- Subarachnoid haemorrhage
- Subdural haematoma
- Transient ischaemic attack

Fig. S1. Neurological conditions considered during the exclusion of unsuitable participants.

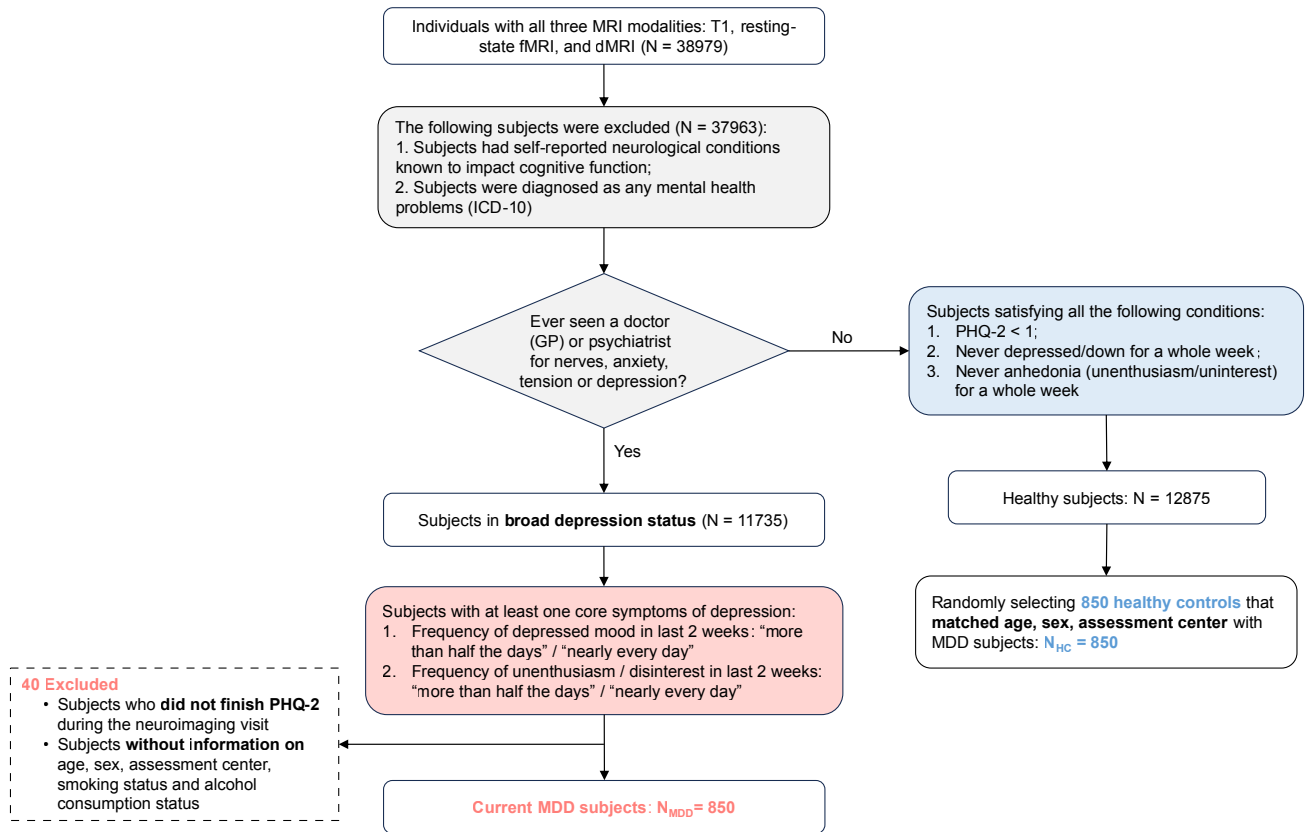


Fig. S2. Flowchart of the participant selection process from the UK Biobank dataset. MDD, major depressive disorder; HC, healthy control; dMRI, diffusion magnetic resonance imaging; fMRI, functional magnetic resonance imaging; PHQ-2, 2-item Patient Health Questionnaire.

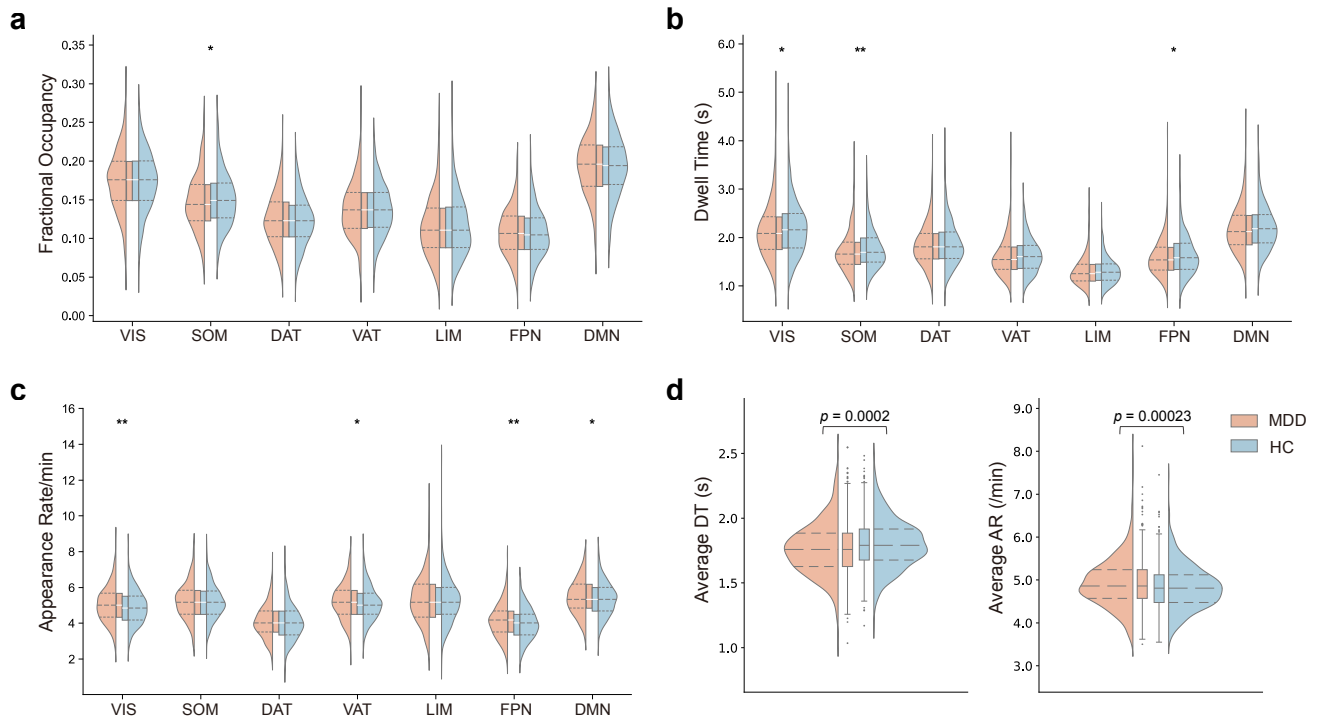


Fig. S3. Comparison of temporal brain dynamics between the MDD patients and the HCs. Same as Fig. 2b, but no thresholding was applied when extracting recurrent brain states (see Methods). Our key results were robust to changing this threshold for brain state extraction. Comparisons were made using two-sided ANCOVA ($df=1690$, $n=850$ independent participants per group; see Methods) and p-values were corrected for multiple comparisons (false discovery rate, FDR) where indicated. *uncorrected $p<0.05$, **corrected $p<0.05$. Data are presented as split violin plots to show the probability density of the data, with box plots overlaid. In the box plots, the center line is the median, the box limits are the 25th and 75th percentiles, and the whiskers extend to $1.5\times$ the interquartile range, with outliers shown individually. MDD, major depressive disorder; HC, healthy control; VIS, visual network; SOM, somatomotor network; DAT, dorsal attention network; VAT, ventral attention network; LIM, limbic network; FPN, frontoparietal network; DMN, default mode network; DT, dwell time; AR, appearance rate. Exact P-values and test statistics are provided in the Supplementary Data file.

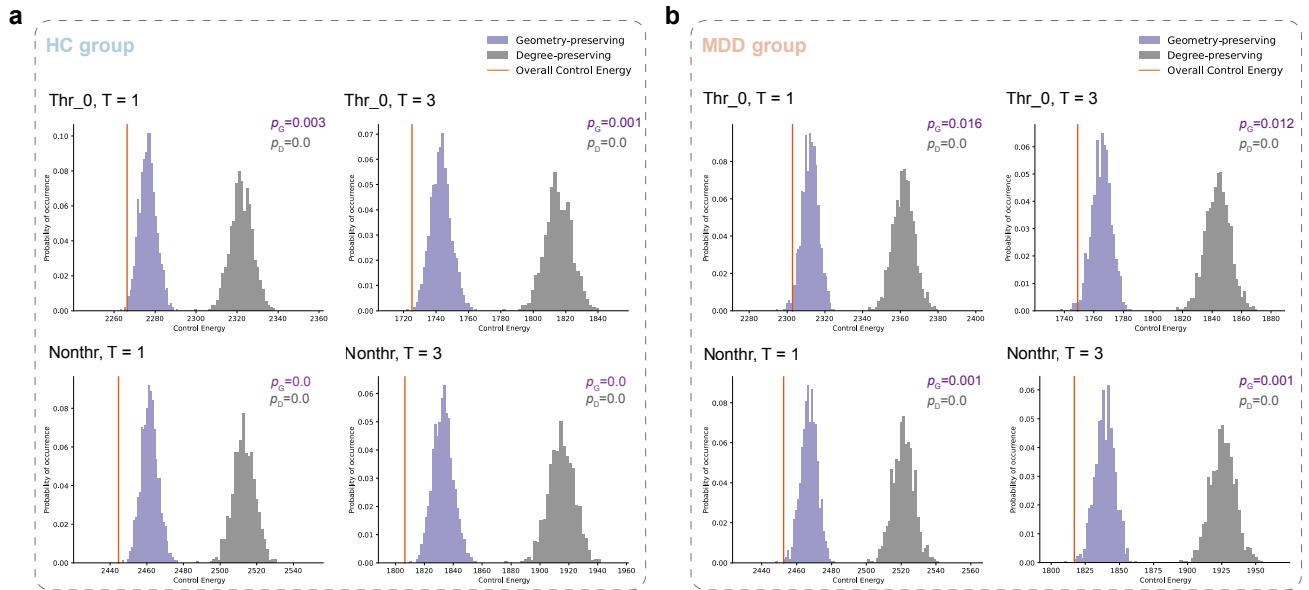


Fig. S4. Role of structural network topology in supporting effective transitions between brain states. Distributions of mean control energy (including transition energy and persistence energy) for geometry-preserving (purple, $n=1,000$ surrogate networks) and degree-preserving (grey, $n=1,000$ surrogate networks) null models are shown for (a) healthy control (HC) and (b) major depressive disorder (MDD) groups. The vertical red line in each subplot indicates the overall control energy calculated using the empirical structural connectome. In all conditions for both groups, the empirical control energy was found to be significantly lower than that of both the geometry-preserving and degree-preserving null models (all $p < 0.05$), confirming that the structural connectome wiring is highly optimized for energetic efficiency. Further details regarding these null models were provided in Supplementary Methods. P-values were calculated as the fraction of times that the null models resulted in a lower energy than the empirical structural connectome. ‘Thr_0’ represents the threshold used in the main analysis (see Methods: Extraction of brain states); ‘Nonthr’ indicates no threshold was applied. T refers to the control horizon ($T=1,3$).

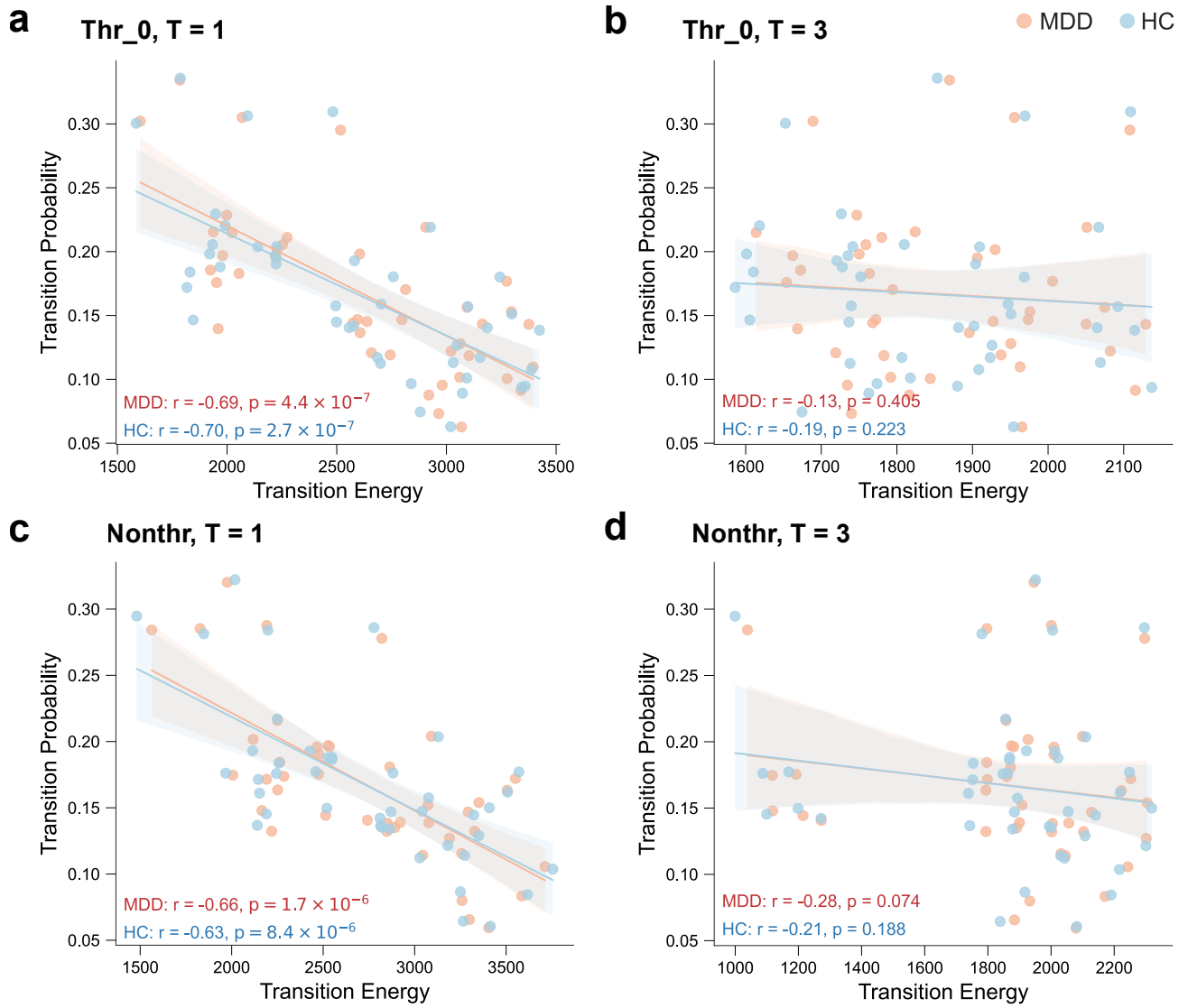


Fig. S5. Spearman correlation analysis between transition energy and transition probability for both the MDD patients and the HCs. Each data point represents a specific transition between two brain states, resulting in $n = 42$ state pairs for each group. Shaded regions represent 95% confidence intervals. ‘Thr_0’/‘Nonthr’ refers to the extracted recurrent brain states with/without thresholding (see Methods). T refers to the control horizon, and $T=1,3$ were considered. Transitions were more strongly associated with control energy at $T=1$ compared to $T=3$, thus we focused on $T=1$. MDD, major depressive disorder; HC, healthy control. Source data are provided in the Supplementary Data.

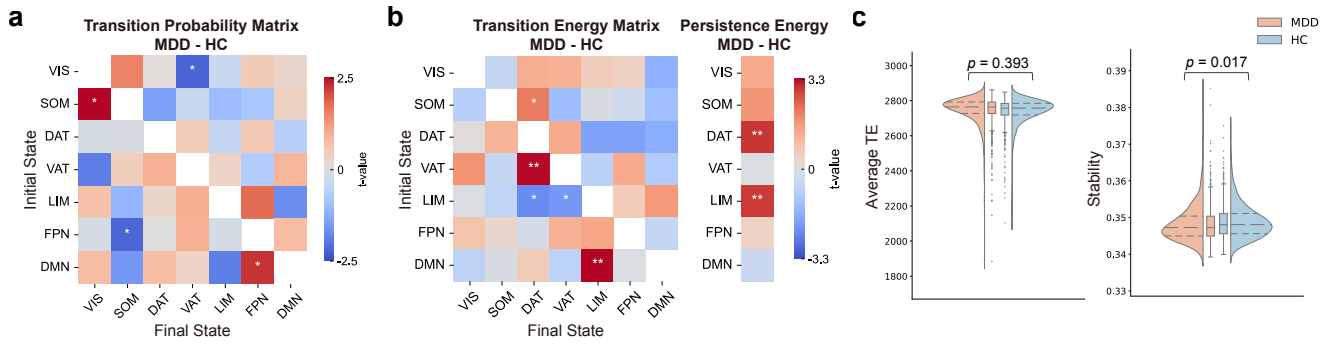


Fig. S6. Case-control comparison of the empirically observed transition probabilities and control energies of different state pairs. Same as Fig. 3, but no thresholding was applied when extracting the recurrent brain states. Our key results were robust without thresholding for brain state extraction. Comparisons were made using two-sided ANCOVA (df=1690, n=850 independent participants per group; see Methods) and p-values were corrected for multiple comparisons (false discovery rate, FDR) where indicated. *uncorrected $p < 0.05$, **corrected $p < 0.05$. Data in (c) are presented as split violin plots to show the probability density of the data, with box plots overlaid. In the box plots, the center line is the median, the box limits are the 25th and 75th percentiles, and the whiskers extend to $1.5 \times$ the interquartile range, with outliers shown individually. MDD, major depressive disorder; HC, healthy control; VIS, visual network; SOM, somatomotor network; DAT, dorsal attention network; VAT, ventral attention network; LIM, limbic network; FPN, frontoparietal network; DMN, default mode network; TP, transition probability; TE, transition energy. Exact P-values for the matrix elements are provided in the Supplementary Data.

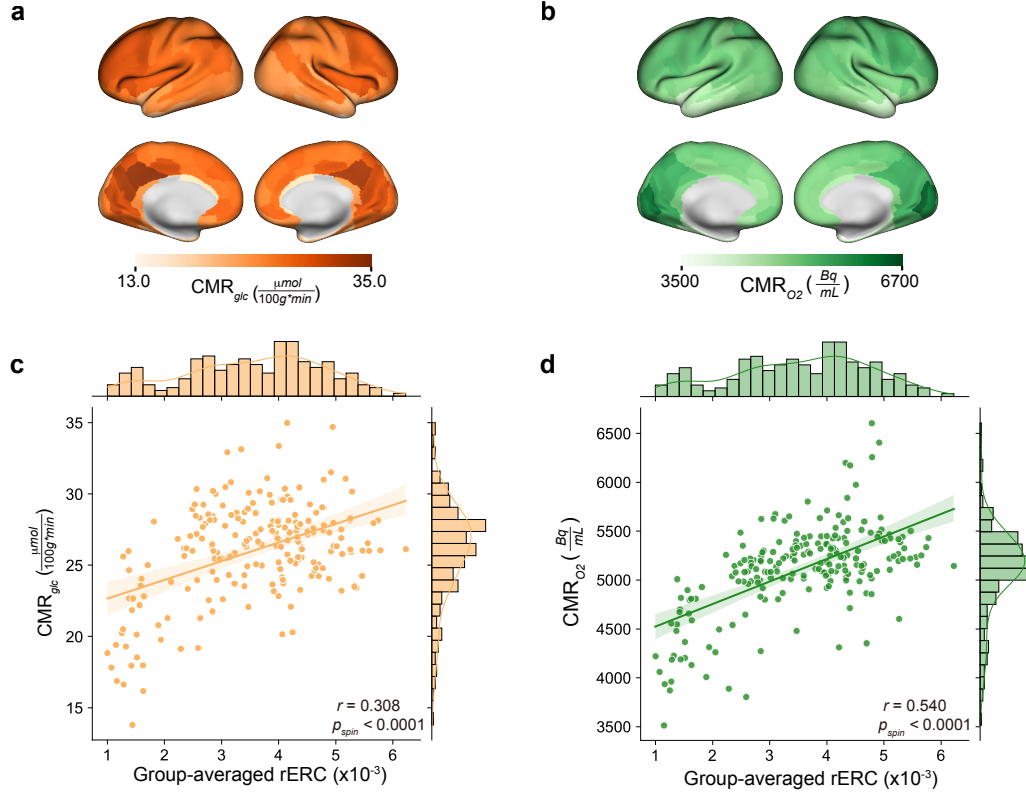


Fig. S7. Spatial correspondence between regional energy regulation capacity (rERC) and brain metabolism in HCs. (a-b) Cortical surface maps of the publicly available, normative templates for (a) cerebral glucose metabolism (CMR_{glc}) and (b) cerebral oxygen metabolism (CMR_{O_2}). The sources and processing of these normative maps are described in Methods. (c-d) Scatter plots illustrating the spatial correlation across 210 cortical regions between the group-averaged rERC map (derived from $n=850$ HCs) and the normative maps of (c) CMR_{glc} ($r=0.308$, $p_{spin} < 0.0001$) and (d) CMR_{O_2} ($r=0.540$, $p_{spin} < 0.0001$). Each point represents a brain region. P-values were derived from non-parametric spin tests ($N_{perm}=10,000$) to account for spatial autocorrelation. In (c) and (d), shaded regions represent 95% confidence intervals.

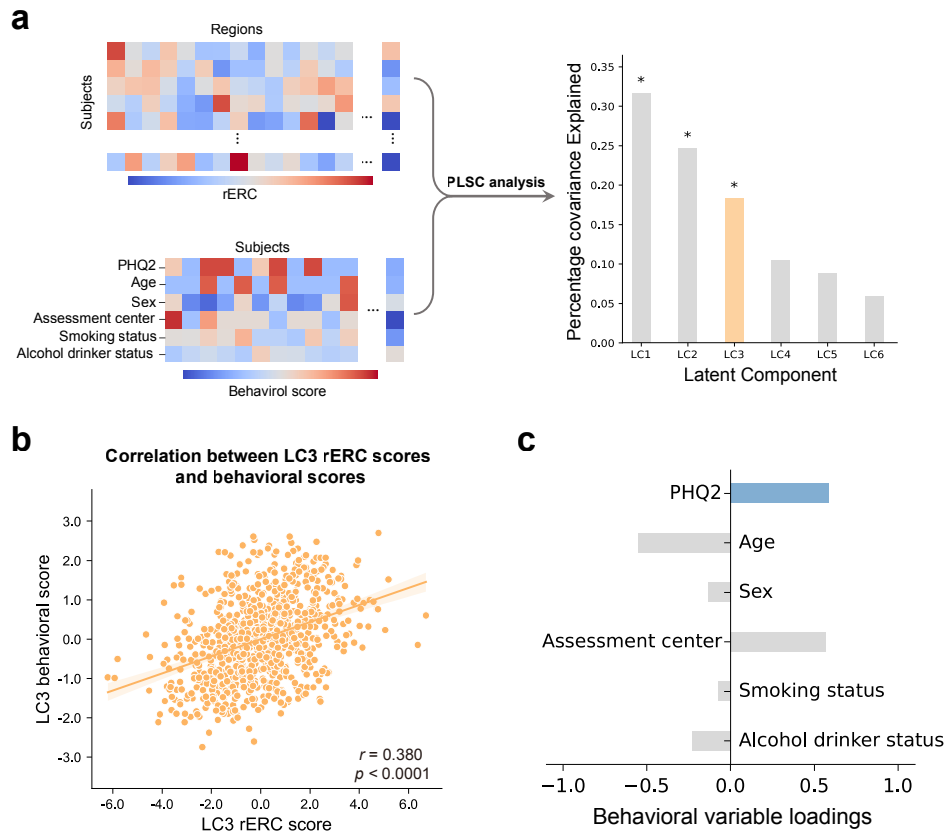
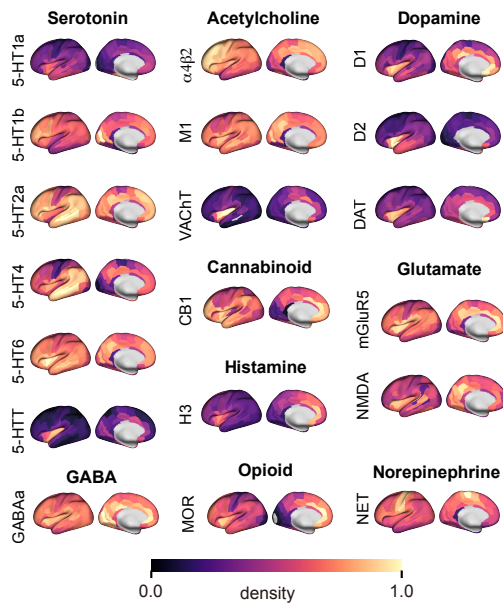


Fig. S8. PLSC analysis between MDD rERC and depressive symptom severity (n=850 patients). (a) Covariance explained by latent components (LC). The first three components LC1, LC2, and LC3 showed significance. $*p < 0.0001$. (b) Pearson correlation analysis showed that the LC3 rERC scores were significantly correlated with the LC3 scores of the behavioral variables ($r=0.380$, $p=1.37 \times 10^{-30}$). Each data point represents an individual subject. Shaded regions represent 95% confidence intervals. (c) Behavioral variable LC3 loadings. PHQ-2 showed significance ($p < 0.0001$). rERC, regional energy regulation capacity; PLSC, partial least squares correlation; LC, latent component. Detailed statistical results, are provided in the Supplementary Data file.

a Cortical neurotransmitter density maps



b Correlation between MDD-HC rERC tmap and neurotransmitter maps

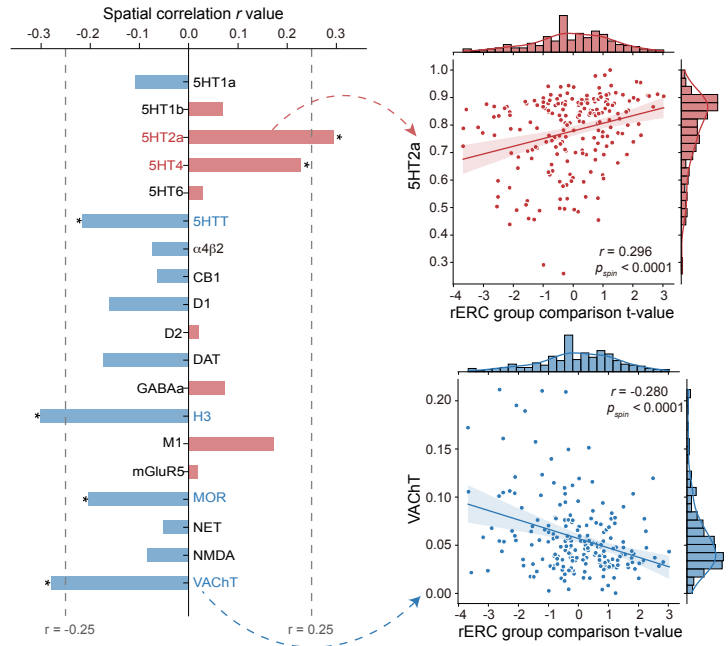


Fig. S9. Association between brain-wide neurotransmitter distribution and energy regulation deficits in MDD. (a) The empirical spatial distribution of receptors and transporters across nine neurotransmitter systems, mapped to the cortical surface using Brainnetome atlas. These include serotonin (5-HT1a, 5-HT1b, 5-HT2a, 5-HT4, 5-HT6, 5-HTT), GABA (GABAA), acetylcholine ($\alpha 4\beta 2$, M1, VAcHT), dopamine (D1, D2, DAT), cannabinoid (CB1), histamine (H3), glutamate (mGluR5, NMDA), opioid (MOR) and noradrenaline (NET). The raw PET data were obtained from [14]. (b) Summary of spatial correlations between the rERC group comparison t-map (derived from $n=850$ MDD and $n=850$ HCs) and each neurotransmitter map from (a). The bar plot displays the resulting correlation coefficients. The scatter plots provide illustrative examples for the 5-HT2a (top) and VAcHT (bottom) systems, where each point represents one of the 210 cortical regions. Statistical assessments: All spatial correlations in (b) were quantified using two-sided Spearman correlation tests ($n=210$ regions) with significance assessed via non-parametric spin tests (10,000 permutations). Specific statistics for the illustrative examples are: 5-HT2a ($r=0.296$, $p_{spin} < 0.0001$) and VAcHT ($r=-0.280$, $p_{spin} < 0.0001$). * $p < 0.05$ after Bonferroni correction. In (b), shaded regions represent 95% confidence intervals. MDD, major depressive disorder; HC, healthy control; rERC, regional energy regulation capacity. Exact statistics are provided in the Supplementary Data.

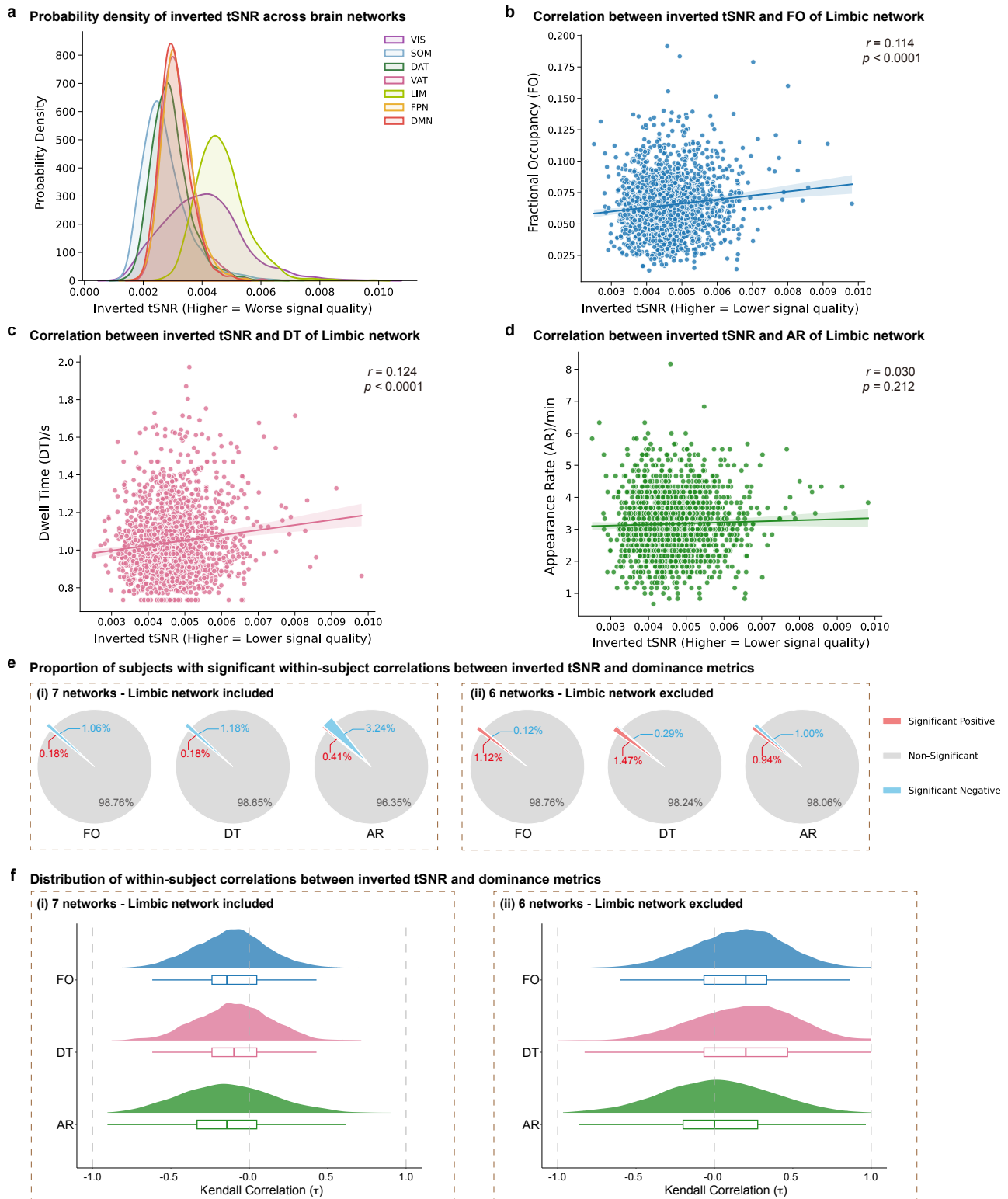


Fig. S10. Cross-subject and within-subject analyses of the relationship between dominance metrics and signal quality. Analyses were performed on $n=1700$ participants (MDD: $n=850$, HC: $n=850$). (a) Probability density of the inverted temporal signal-to-noise ratio (inverted tSNR; a higher value indicates poorer signal quality) across the seven resting-state networks (RSNs). (b-d) Cross-subject Pearson correlations between the limbic (LIM) network's inverted tSNR and its dominance metrics (Fractional Occupancy, Dwell Time, and Appearance Rate). Each data point represents an individual subject. (e) Proportion of subjects with significant positive, significant negative, or non-significant within-subject Kendall correlations between network-level tSNR and dominance metrics. (f) Distribution of these within-subject Kendall correlation (τ) coefficients across all subjects, visualized using raincloud plots. For both (e) and (f), analyses are shown for the full set of (i) seven networks and (ii) six networks after excluding the limbic network. In (b), (c), and (d), shaded regions represent 95% confidence intervals. VIS, visual network; SOM, somatomotor network; DAT, dorsal attention network; VAT, ventral attention network; LIM, limbic network; FPN, frontoparietal network; DMN, default mode network.

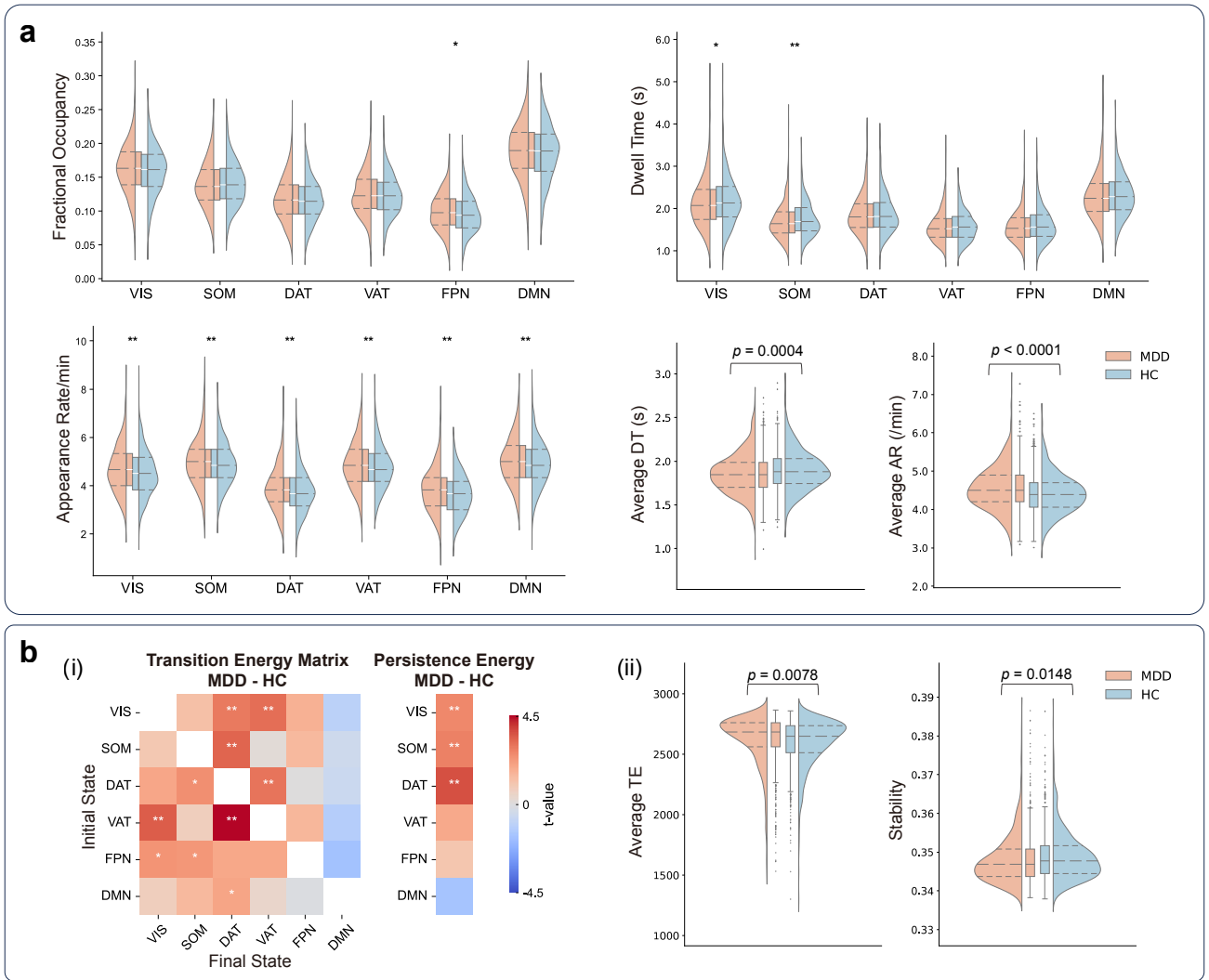


Fig. S11. Robustness of key findings after excluding Limbic network. (a) Comparison of temporal brain dynamics between MDD patients (n=850) and HCs (n=850), including (top left) fractional occupancy, (top right) dwell time, and (bottom left) appearance rate. (bottom right) Average dwell time and average appearance rate across seven states were also compared. (b) i Case-control comparison of the transition and persistence energies of different state pairs using uniformly-weighted whole-brain inputs; ii Case-control comparison of average transition energies across different states pairs and global control stability. Comparisons were made using two-sided ANCOVA (df=1690, n=850 independent participants per group; see Methods) and p-values were corrected for multiple comparisons (false discovery rate, FDR) where indicated. *uncorrected $p < 0.05$, **corrected $p < 0.05$. Data are presented as split violin plots to show the probability density of the data, with box plots overlaid. In the box plots, the center line is the median, the box limits are the 25th and 75th percentiles, and the whiskers extend to $1.5 \times$ the interquartile range, with outliers shown individually. MDD, major depressive disorder; HC, healthy control; VIS, visual network; SOM, somatomotor network; DAT, dorsal attention network; VAT, ventral attention network; LIM, limbic network; FPN, frontoparietal network; DMN, default mode network; TE, transition energy. Exact P-values and test statistics are provided in the Supplementary Data file.

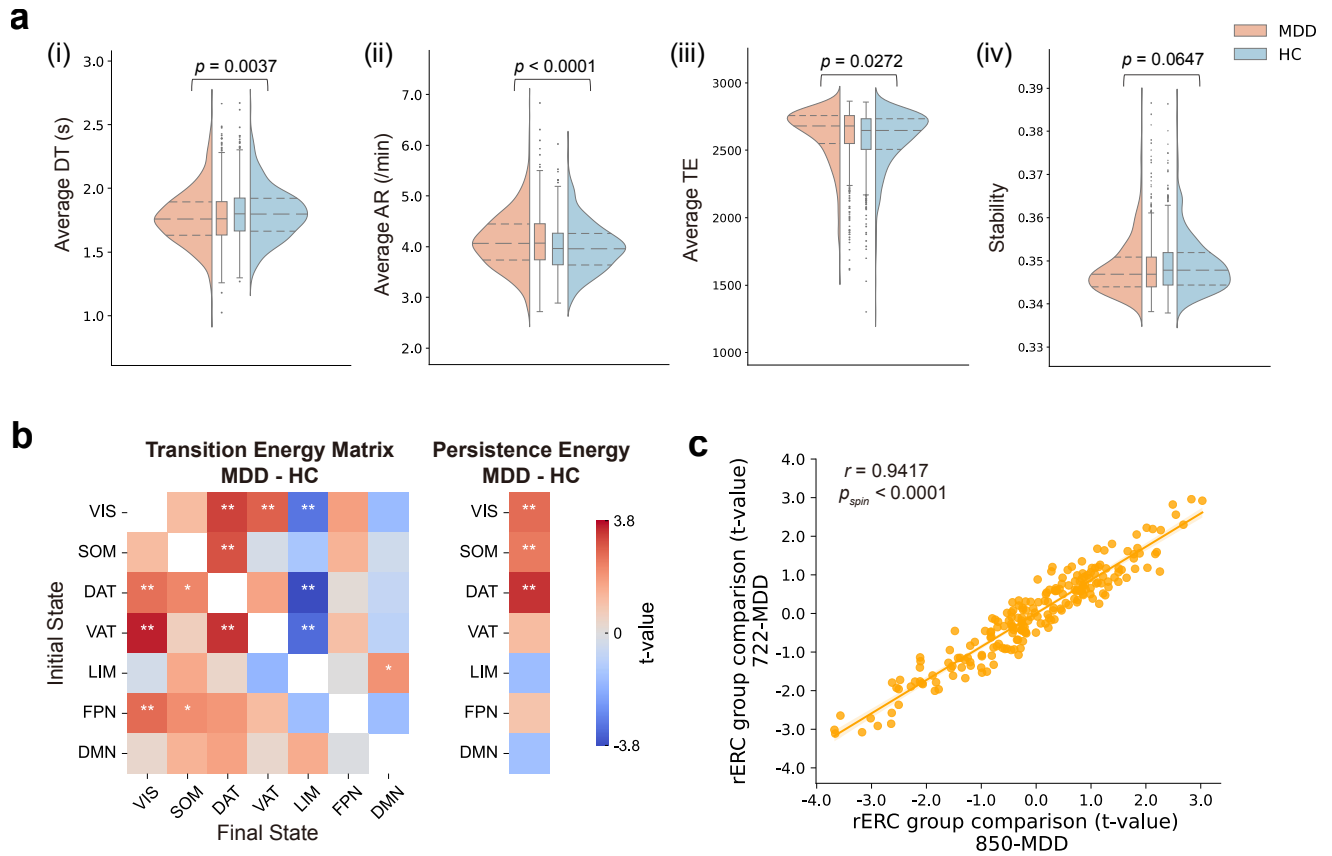


Fig. S12. Robustness of key findings after excluding anxiety comorbidity. (a) Case-control comparison between non-comorbid MDD patients ($n=722$) and HCs ($n=722$) of (i) average dwell time (DT), (ii) average appearance rate (AR), (iii) average transition energy (TE) and (iv) global control stability. (b) Case-control comparison of the transition and persistence energies of different state pairs using uniformly-weighted whole-brain inputs. (c) Spearman correlation of case-control rERC t -maps between the full ($n=850$) and non-comorbid MDD subgroup ($n=722$). Comparisons in (a) and (b) were made using two-sided ANCOVA ($df=1434$, $n=722$ independent participants per group; see Methods) and p -values were corrected for multiple comparisons (false discovery rate, FDR) where indicated. *uncorrected $p<0.05$, **corrected $p<0.05$. Data in (a) are presented as split violin plots to show the probability density of the data, with box plots overlaid. In the box plots, the center line is the median, the box limits are the 25th and 75th percentiles, and the whiskers extend to $1.5\times$ the interquartile range, with outliers shown individually. In (c), each data point represents a brain region ($n=210$) and shaded regions represent 95% confidence intervals. MDD, major depressive disorder; HC, healthy control; VIS, visual network; SOM, somatomotor network; DAT, dorsal attention network; VAT, ventral attention network; LIM, limbic network; FPN, frontoparietal network; DMN, default mode network; TE, transition energy; spin, spin test. Exact P -values and test statistics are provided in the Supplementary Data file.

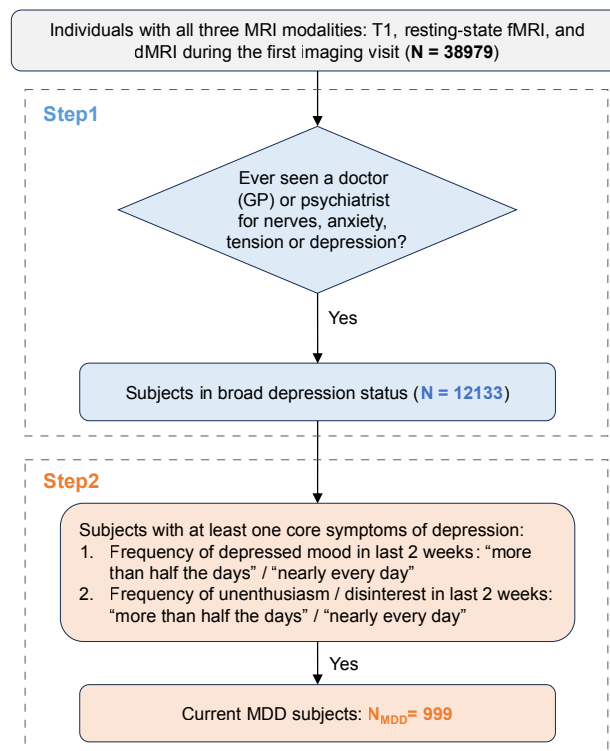


Fig. S13. Flowchart of the two-step procedure for MDD cohort identification. This flowchart specifically illustrated the outcome of our two-step symptom-based screening criteria. To demonstrate the maximum potential pool of MDD candidates based on symptomatology alone, this process was applied directly to all participants with the requisite imaging data, without yet accounting for other exclusion criteria such as comorbidities or data processing. This screening identified a pool of 999 potential MDD cases. The complete, multi-stage participant selection pipeline, which incorporated all exclusion criteria and results in the final analytic sample, was detailed in Figure S2.

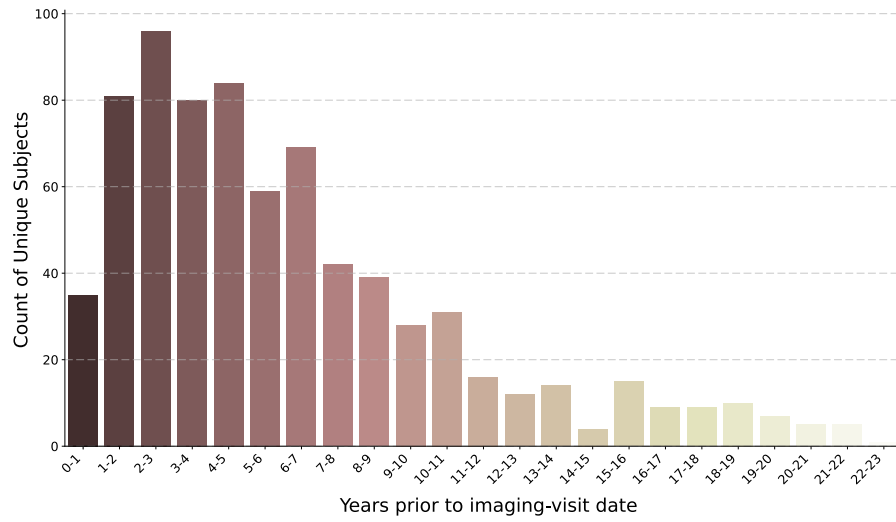


Fig. S14. Timing discrepancy between the date of nearest ICD-10 diagnosis of depressive disorders and date of neuroimaging scan (n=751 subjects).

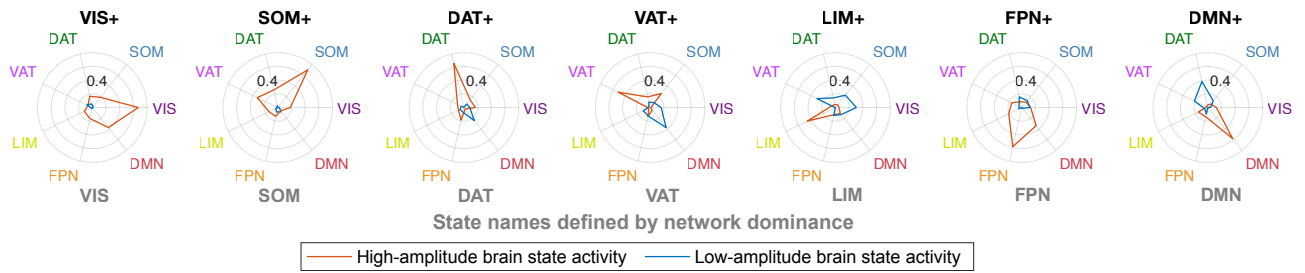


Fig. S15. Validation of amplitude-based state definition using cosine similarity. Radar plots for one subject showing the cosine similarity between the positive (red)/negative (blue) components of each derived state and the RSNs template. The top label corresponds to the RSN with the most similarity to the positive components of each state. Larger radial values correspond to higher cosine similarity. VIS, visual network; SOM, somatomotor network; DAT, dorsal attention network; VAT, ventral attention network; LIM, limbic network; FPN, frontoparietal network; DMN, default mode network.

Supplementary Tables

Table S1. Significant regions showing diminished rERC in individuals with MDD compared with healthy controls ($p_{FDR} < 0.05$).

Gyrus	Label	Name	Anatomical and modified cyto-architectonic descriptions	Intrinsic network	t -value	$p_{uncorrected}$	p_{FDR}
Superior frontal gyrus	5	SFG_L_7_3	A9l, lateral area 9	DMN	-3.5676	0.0004	0.0259
Insular gyrus	168	INS_R_6_3	dIa, dorsal agranular insula	VAT	-3.6624	0.0003	0.0259
	174	INS_R_6_6	dId, dorsal dysgranular insula	VAT	-3.6769	0.0002	0.0259

The t -values and corresponding p -values represent the group differences in rERC between individuals with MDD and healthy controls. These statistics were derived from a two-sided one-way analyses of covariance (ANCOVA), with age, sex, assessment center, smoking status, and alcohol drinker status included as covariates. P -values were corrected for multiple comparisons across all 210 cortical regions using the false discovery rate (FDR) method. For full details, see Methods. VAT, ventral attention network; LIM, limbic network; DMN, default mode network; FDR, false discovery rate.

Table S2. Brain regions significantly contributing to the brain-symptom relationship in MDD ($p_{bonf} < 0.05$).

Gyrus	Label	Name	Anatomical and modified Cyto-architectonic descriptions	Intrinsic network	Z score	p_{bonf} ($\times 10^{-4}$)
Middle frontal gyrus	28	MFG_R_7_7	A10l, lateral area10	FPN	4.9091	4.8037
Inferior frontal gyrus	38	IFG_R_6_5	A44op, opercular area 44	VAT	4.5516	1.1182
Orbital gyrus	41	OrG_L_6_1	A14m, medial area 14	DMN	4.6235	1.1182
	44	OrG_R_6_2	A12/47o, orbital area 12/47	DMN	4.2201	4.2733
	47	OrG_L_6_4	A11m, medial area 11	LIM	4.5651	1.1182
	48	OrG_R_6_4		LIM	4.0081	9.1805
Insular gyrus	168	INS_R_6_3	dIa, dorsal agranular insula	VAT	5.5319	<1.0

The table lists brain regions whose regional energy regulation capacity (rERC) values reliably contributed to the third latent component (LC3) of the PLSC analysis linking brain patterns to symptom severity. The Z-score reflects the bootstrap ratio for each region's weight, with higher absolute values indicating a more stable contribution. P -values were corrected for multiple comparisons across all 210 cortical regions using Bonferroni correction. Only regions with a significant contribution ($p_{bonf} < 0.05$) are shown. MDD, major depressive disorder; PLSC, partial least squares correlation; VIS, visual network; SOM, somatomotor network; DAT, dorsal attention network; VAT, ventral attention network; LIM, limbic network; FPN, frontoparietal network; DMN, default mode network.

Table S3. Description of UK Biobank data-fields used for MDD cohort identification.

Data Field	Description
53	Date of attending assessment center
2090	Seen doctor (GP) for nerves, anxiety, tension or depression
2100	Seen a psychiatrist for nerves, anxiety, tension or depression
2050	Frequency of depressed mood in last 2 weeks
2060	Frequency of unenthusiasm / disinterest in last 2 weeks
41270	Diagnoses - ICD10
41280	Date of first in-patient diagnosis - ICD10

Table S4. Breakdown of ICD-10 diagnoses for anxiety disorders in the imaging sample

Anxiety disorder	ICD-10 codes	Subjects Num
F40 Phobic anxiety disorders	F40.0 Agoraphobia	1
	F40.1 Social phobias	1
	F40.2 Specific (isolated) phobias	32
	F40.8 Other phobic anxiety disorders	3
	F40.9 Phobic anxiety disorder, unspecified	0
F41 Other anxiety disorders	F41.0 Panic disorder [episodic paroxysmal anxiety]	37
	F41.1 Generalized anxiety disorder	11
	F41.2 Mixed anxiety and depressive disorder	97
	F41.3 Other mixed anxiety disorders	1
	F41.8 Other specified anxiety disorders	0
	F41.9 Anxiety disorder, unspecified	371

Table S5. Comorbidity of Anxiety Disorders in the MDD Samples.

Anxiety disorders	Total cases in full imaging sample (N=38,979)	Comorbid cases in final MDD sample (N=850) (n, %)
Self-report neurological condition	1,074	91 (10.7%)
ICD-10 diagnosis (F40/F41)	515	47 (9.1%)
Any anxiety diagnosis (combined)	1,484	128 (15.1%)

Table S6. Breakdown of ICD-10 diagnoses for depressive disorders in the imaging sample.

Depressive Disorder	ICD-10 codes	<i>N</i>_{Subjects}
F32 Depressive episode	F32.0 Mild depressive episode	10
	F32.1 Moderate depressive episode	13
	F32.2 Severe depressive episode without psychotic symptoms	18
	F32.3 Severe depressive episode with psychotic symptoms	13
	F32.8 Other depressive episodes	1
	F32.9 Depressive episode, unspecified	769
F33 Recurrent depressive disorder	F33.0 Recurrent depressive disorder, current episode mild	1
	F33.1 Recurrent depressive disorder, current episode moderate	5
	F33.2 Recurrent depressive disorder, current episode severe without psychotic symptoms	4
	F33.3 Recurrent depressive disorder, current episode severe with psychotic symptoms	2
	F33.4 Recurrent depressive disorder, currently in remission	0
	F33.8 Other recurrent depressive disorders	1
	F33.9 Recurrent depressive disorder, unspecified	16

Table S7. Time intervals between the nearest ICD-10 diagnosis of depressive disorders and the neuroimaging visit.

ICD-10 diagnosis timing	Number of Unique Subjects
Before Image visit (within 1 year)	35
Before Image visit (within 2 years)	116
Before Image visit (within 3 years)	212
Before Image visit (over 3 years)	539
After Image visit	53

Table S8. Meta-analytic functional decoding of the left superior frontal gyrus (SFG_L_7_3).

Term	pReverse	zReverse	probReverse
terms_abstract_tfidf_mental states	6.250E-27	10.745	0.8087
terms_abstract_tfidf_mind tom	3.409E-11	6.628	0.7870
terms_abstract_tfidf_tom	4.151E-11	6.599	0.7818
terms_abstract_tfidf_medial pfc	9.481E-10	6.118	0.7762
terms_abstract_tfidf_theory mind	6.913E-17	8.349	0.7624
terms_abstract_tfidf_dorsomedial prefrontal	2.365E-16	8.202	0.7611
terms_abstract_tfidf_mental state	8.610E-11	6.490	0.7561
terms_abstract_tfidf_mentalizing	1.284E-12	7.096	0.7525
terms_abstract_tfidf_speaker	4.341E-07	5.053	0.7497
terms_abstract_tfidf_default network	2.842E-08	5.551	0.7489
terms_abstract_tfidf_inferences	7.497E-08	5.379	0.7430
terms_abstract_tfidf_inference	3.912E-09	5.888	0.7412
terms_abstract_tfidf_autobiographical	4.647E-10	6.231	0.7392
terms_abstract_tfidf_cortex dmpfc	3.663E-06	4.630	0.7387
terms_abstract_tfidf_cortex mpfc	1.584E-16	8.250	0.7386
terms_abstract_tfidf_mind	6.791E-19	8.878	0.7379
terms_abstract_tfidf_dorsal medial	1.672E-06	4.790	0.7349
terms_abstract_tfidf_social cognition	2.480E-13	7.320	0.7339
terms_abstract_tfidf_infer	6.588E-06	4.507	0.7337
terms_abstract_tfidf_mpfc	9.542E-18	8.579	0.7316
terms_abstract_tfidf_medial prefrontal	1.593E-41	13.499	0.7308
terms_abstract_tfidf_young older	3.445E-05	4.142	0.7296
terms_abstract_tfidf_recollection	3.176E-09	5.922	0.7272
terms_abstract_tfidf_dorsomedial	1.047E-14	7.733	0.7268
terms_abstract_tfidf_belief	1.499E-05	4.329	0.7264
terms_abstract_tfidf_negative neutral	1.943E-05	4.271	0.7240
terms_abstract_tfidf_uniquely	9.222E-07	4.908	0.7223
terms_abstract_tfidf_beliefs	1.231E-04	3.840	0.7161
terms_abstract_tfidf_thinking	8.161E-08	5.364	0.7151
terms_abstract_tfidf_dorsolateral pfc	2.955E-05	4.177	0.7151
terms_abstract_tfidf_autobiographical memory	1.120E-04	3.863	0.7116
terms_abstract_tfidf_subsequent memory	6.436E-06	4.512	0.7114
terms_abstract_tfidf_concrete	3.329E-05	4.150	0.7093
terms_abstract_tfidf_tpj	3.324E-06	4.650	0.7092
terms_abstract_tfidf_dmpfc	1.380E-05	4.347	0.7089
terms_abstract_tfidf_temporoparietal junction	7.153E-08	5.387	0.7079
terms_abstract_tfidf_thoughts	9.883E-06	4.420	0.7078
terms_abstract_tfidf_track	4.225E-04	3.526	0.7072
terms_abstract_tfidf_medial superior	3.006E-04	3.615	0.7056
terms_abstract_tfidf_cortex superior	3.981E-07	5.070	0.7001

terms_abstract_tfidf_emotional information	3.875E-04	3.548	0.6971
terms_abstract_tfidf_reasoning	6.927E-07	4.963	0.6965
terms_abstract_tfidf_anterior medial	6.671E-04	3.403	0.6955
terms_abstract_tfidf_read	2.909E-07	5.129	0.6948
terms_abstract_tfidf_fronto temporal	3.284E-04	3.592	0.6942
terms_abstract_tfidf_temporal pole	4.019E-06	4.610	0.6922
terms_abstract_tfidf_task demands	4.776E-06	4.574	0.6910
terms_abstract_tfidf_remembering	1.648E-03	3.147	0.6883
terms_abstract_tfidf_self referential	1.124E-05	4.392	0.6871
terms_abstract_tfidf_sentences	3.729E-10	6.265	0.6866
terms_abstract_tfidf_class	2.818E-03	2.987	0.6857
terms_abstract_tfidf_situation	2.686E-05	4.199	0.6857
terms_abstract_tfidf_memory retrieval	4.554E-07	5.044	0.6856
terms_abstract_tfidf_intentions	1.586E-04	3.777	0.6855
terms_abstract_tfidf_details	6.631E-04	3.404	0.6855
terms_abstract_tfidf_social	3.413E-26	10.587	0.6847
terms_abstract_tfidf_match	6.419E-05	3.997	0.6841
terms_abstract_tfidf_deactivated	1.611E-03	3.154	0.6831
terms_abstract_tfidf_final	2.317E-03	3.046	0.6830
terms_abstract_tfidf_neutral pictures	2.317E-03	3.046	0.6830

The table lists the top 60 associated terms generated by the Neurosynth chi-square method, ranked by reverse inference probability. probReverse is the posterior probability of a term being present in a study, given activation in the specified brain region ($P(\text{Term}|\text{Activation})$). zReverse is the Z-score associated with this probability, indicating the strength and reliability of the association. pReverse is the corresponding p-value.

Table S9. Meta-analytic functional decoding of the right insula gyrus (INS_R_6_3).

Term	pReverse	zReverse	probReverse
terms_abstract_tfidf_insula anterior	1.438E-21	9.539	0.7668
terms_abstract_tfidf_anterior insular	2.084E-10	6.355	0.7409
terms_abstract_tfidf_anterior insula	1.811E-54	15.542	0.7377
terms_abstract_tfidf_insula inferior	2.065E-08	5.606	0.7308
terms_abstract_tfidf_signal task	3.975E-09	5.885	0.7299
terms_abstract_tfidf_noxious	7.929E-09	5.770	0.7294
terms_abstract_tfidf_stop signal	6.074E-08	5.417	0.7151
terms_abstract_tfidf_task difficulty	3.209E-10	6.288	0.7075
terms_abstract_tfidf_pre sma	5.717E-09	5.825	0.7005
terms_abstract_tfidf_calculation	8.311E-05	3.935	0.6919
terms_abstract_tfidf_choose	8.311E-05	3.935	0.6919
terms_abstract_tfidf_likelihood	3.711E-06	4.627	0.6913
terms_abstract_tfidf_painful	1.335E-09	6.063	0.6908
terms_abstract_tfidf_insula	3.516E-56	15.792	0.6888
terms_abstract_tfidf_autonomic	1.216E-05	4.375	0.6796
terms_abstract_tfidf_frontal operculum	2.485E-05	4.216	0.6793
terms_abstract_tfidf_stop	1.131E-06	4.867	0.6776
terms_abstract_tfidf_risk taking	3.906E-04	3.546	0.6754
terms_abstract_tfidf_flexibly	8.071E-04	3.350	0.6747
terms_abstract_tfidf_pre supplementary	1.503E-05	4.328	0.6729
terms_abstract_tfidf_middle cingulate	4.925E-04	3.485	0.6727
terms_abstract_tfidf_motor pre	1.017E-03	3.286	0.6717
terms_abstract_tfidf_insular	1.999E-15	7.941	0.6707
terms_abstract_tfidf_taste	8.856E-04	3.325	0.6694
terms_abstract_tfidf_response inhibition	8.760E-08	5.351	0.6682
terms_abstract_tfidf_matrix	7.676E-04	3.364	0.6674
terms_abstract_tfidf_insular cortex	6.526E-08	5.404	0.6669
terms_abstract_tfidf_15 healthy	6.628E-04	3.405	0.6656
terms_abstract_tfidf_arithmetic	6.992E-04	3.390	0.6616
terms_abstract_tfidf_pain	1.506E-13	7.387	0.6594
terms_abstract_tfidf_implementation	2.911E-03	2.977	0.6572
terms_abstract_tfidf_control processes	4.117E-05	4.101	0.6562
terms_abstract_tfidf_reversal	4.163E-03	2.866	0.6558
terms_abstract_tfidf_memory wm	2.712E-07	5.142	0.6547
terms_abstract_tfidf_contingent	5.957E-03	2.750	0.6543
terms_abstract_tfidf_time task	5.029E-03	2.805	0.6529
terms_abstract_tfidf_high functioning	7.179E-03	2.688	0.6511
terms_abstract_tfidf_disturbed	7.179E-03	2.688	0.6511
terms_abstract_tfidf_depended	3.009E-03	2.967	0.6495
terms_abstract_tfidf_sustained attention	8.597E-03	2.628	0.6480

terms_abstract_tfidf_congruency	4.264E-03	2.858	0.6479
terms_abstract_tfidf_rt	1.792E-03	3.123	0.6471
terms_abstract_tfidf_salience network	7.584E-04	3.368	0.6466
terms_abstract_tfidf_opercular	5.062E-03	2.803	0.6453
terms_abstract_tfidf_changing	1.618E-04	3.772	0.6448
terms_abstract_tfidf_equal	4.242E-03	2.860	0.6446
terms_abstract_tfidf_flexible	3.192E-04	3.599	0.6444
terms_abstract_tfidf_published	5.981E-03	2.749	0.6427
terms_abstract_tfidf_maintenance	2.551E-07	5.154	0.6399
terms_abstract_tfidf_cortex ventral	4.903E-03	2.813	0.6393
terms_abstract_tfidf_dissociated	3.423E-03	2.927	0.6386
terms_abstract_tfidf_regulatory	3.986E-03	2.879	0.6365
terms_abstract_tfidf_probability	4.040E-04	3.537	0.6365
terms_abstract_tfidf_nociceptive	2.009E-02	2.325	0.6362
terms_abstract_tfidf_load	4.162E-07	5.061	0.6359
terms_abstract_tfidf_conflicting	4.624E-03	2.832	0.6345
terms_abstract_tfidf_difficulty	1.730E-07	5.226	0.6338
terms_abstract_tfidf_separable	1.942E-02	2.337	0.6329
terms_abstract_tfidf_memory load	1.612E-02	2.406	0.6328
terms_abstract_tfidf_operculum	8.779E-05	3.922	0.6327

The table lists the top 60 associated terms generated by the Neurosynth chi-square method, ranked by reverse inference probability. probReverse is the posterior probability of a term being present in a study, given activation in the specified brain region ($P(\text{Term}|\text{Activation})$). zReverse is the Z-score associated with this probability, indicating the strength and reliability of the association. pReverse is the corresponding p-value.

Table S10. Meta-analytic functional decoding of the right insula gyrus (INS_R_6_6).

Term	pReverse	zReverse	probReverse
terms_abstract_tfidf_painful	8.586E-37	12.671	0.8302
terms_abstract_tfidf_noxious	1.303E-15	7.994	0.8169
terms_abstract_tfidf_sensation	1.061E-17	8.567	0.8153
terms_abstract_tfidf_primary secondary	1.050E-15	8.021	0.8137
terms_abstract_tfidf_nociceptive	1.005E-11	6.806	0.8091
terms_abstract_tfidf_pain	5.171E-58	16.056	0.8077
terms_abstract_tfidf_sii	7.369E-11	6.513	0.8006
terms_abstract_tfidf_secondary somatosensory	1.877E-17	8.501	0.7926
terms_abstract_tfidf_sensations	2.033E-08	5.609	0.7830
terms_abstract_tfidf_insula	1.502E-80	19.007	0.7750
terms_abstract_tfidf_chronic pain	2.575E-08	5.568	0.7705
terms_abstract_tfidf_cortex thalamus	8.969E-08	5.346	0.7681
terms_abstract_tfidf_insular cortex	6.686E-17	8.352	0.7677
terms_abstract_tfidf_insular	5.684E-30	11.373	0.7647
terms_abstract_tfidf_electrical	2.794E-09	5.943	0.7602
terms_abstract_tfidf_intense	1.420E-06	4.822	0.7601
terms_abstract_tfidf_insula anterior	7.801E-10	6.149	0.7589
terms_abstract_tfidf_somatosensory cortices	1.433E-07	5.261	0.7547
terms_abstract_tfidf_discriminative	6.253E-06	4.518	0.7542
terms_abstract_tfidf_anterior insula	5.549E-32	11.770	0.7512
terms_abstract_tfidf_taste	1.058E-05	4.405	0.7495
terms_abstract_tfidf_posterior insula	2.370E-10	6.335	0.7480
terms_abstract_tfidf_medial pfc	2.635E-05	4.203	0.7475
terms_abstract_tfidf_experiencing	5.900E-06	4.530	0.7425
terms_abstract_tfidf_muscle	7.437E-06	4.481	0.7404
terms_abstract_tfidf_s1	1.441E-05	4.338	0.7403
terms_abstract_tfidf_anterior insular	1.441E-05	4.338	0.7403
terms_abstract_tfidf_matrix	3.507E-05	4.138	0.7378
terms_abstract_tfidf_autonomic	1.999E-06	4.754	0.7358
terms_abstract_tfidf_12 healthy	2.065E-05	4.258	0.7257
terms_abstract_tfidf_emotional responses	6.325E-05	4.000	0.7255
terms_abstract_tfidf_secondary	1.757E-13	7.366	0.7214
terms_abstract_tfidf_cortical subcortical	6.734E-09	5.797	0.7183
terms_abstract_tfidf_somatosensory	1.375E-19	9.054	0.7165
terms_abstract_tfidf_men women	2.550E-04	3.657	0.7156
terms_abstract_tfidf_index finger	1.276E-03	3.221	0.7142
terms_abstract_tfidf_ventral tegmental	1.276E-03	3.221	0.7142
terms_abstract_tfidf_risk taking	7.888E-04	3.357	0.7139
terms_abstract_tfidf_somatosensory cortex	2.237E-10	6.344	0.7132
terms_abstract_tfidf_unpleasant	3.342E-05	4.149	0.7115

terms_abstract_tfidf_tegmental	1.517E-03	3.171	0.7115
terms_abstract_tfidf_emotional information	5.794E-04	3.441	0.7114
terms_abstract_tfidf_negative affect	3.591E-04	3.568	0.7113
terms_abstract_tfidf_salience network	6.312E-05	4.001	0.7098
terms_abstract_tfidf_nervous	1.631E-04	3.770	0.7095
terms_abstract_tfidf_primary somatosensory	1.242E-06	4.849	0.7089
terms_abstract_tfidf_designs	1.795E-03	3.122	0.7088
terms_abstract_tfidf_intensity	2.428E-12	7.007	0.7084
terms_abstract_tfidf_skin	9.518E-06	4.428	0.7067
terms_abstract_tfidf_reveals	9.422E-04	3.307	0.7045
terms_abstract_tfidf_age healthy	1.781E-03	3.125	0.7016
terms_abstract_tfidf_frontal operculum	4.902E-04	3.486	0.7015
terms_abstract_tfidf_depicting	7.909E-04	3.356	0.7008
terms_abstract_tfidf_factorial	2.538E-04	3.658	0.6993
terms_abstract_tfidf_cortex insula	1.137E-04	3.859	0.6992
terms_abstract_tfidf_disgust	9.166E-04	3.315	0.6988
terms_abstract_tfidf_sustained attention	5.467E-03	2.778	0.6970
terms_abstract_tfidf_cortex dorsal	2.396E-03	3.036	0.6968
terms_abstract_tfidf_ranging	2.396E-03	3.036	0.6968
terms_abstract_tfidf_insula inferior	3.887E-03	2.887	0.6956

The table lists the top 60 associated terms generated by the Neurosynth chi-square method, ranked by reverse inference probability. probReverse is the posterior probability of a term being present in a study, given activation in the specified brain region ($P(\text{Term}|\text{Activation})$). zReverse is the Z-score associated with this probability, indicating the strength and reliability of the association. pReverse is the corresponding p-value.

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