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Citation	大阪大学, 2026, 博士論文
Version Type	VoR
URL	https://doi.org/10.18910/105564
rights	
Note	

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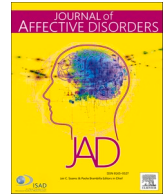
Reduced Functional Connectome Uniqueness on the Whole Brain and
Network Levels as a Clinically Relevant and Reproducible Neuroimaging
Marker in Major Depressive Disorder

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2026年1月 博士学位論文



Research paper

Reduced functional connectome uniqueness on the whole brain and network levels as a clinically relevant and reproducible neuroimaging marker in major depressive disorder

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A B S T R A C T

Background: Identifying reproducible neurobiological markers for Major Depressive Disorder (MDD) remains challenging due to methodological heterogeneity across neuroimaging studies. Functional connectome (FC) uniqueness, an individual-level metric derived from brain fingerprinting, quantifies the distinctiveness of intrinsic connectivity patterns and may offer a robust framework for biomarker discovery.

Methods: We analyzed multi-site resting-state fMRI data from healthy controls (HC) and patients with Major Depressive Disorder (MDD), aged 19–37 years. Individual functional connectomes were constructed using 300 regions of interest grouped into 14 canonical networks. FC uniqueness was defined as the ratio of self-similarity (calculated as Pearson correlation between connectomes from the same individual across different time points) to similarity-to-others (calculated as Pearson correlations between an individual's connectome and those of other participants at the next timepoint). An FC uniqueness index greater than one indicates successful individual identification, referred to as fingerprinting accuracy.

Results: Replicating prior studies, fingerprinting accuracy was highest at the whole-brain level, followed by the default mode and frontoparietal networks. MDD patients exhibited significantly lower FC uniqueness with pronounced reductions in frontoparietal and sensorimotor networks. Notably, reduced FC uniqueness was associated with higher PHQ-9 and BDI-II scores in this study.

Limitations: Comorbidity and age distribution differences may have introduced confounding effects.

Conclusions: Reduced FC uniqueness in frontoparietal and sensorimotor networks correlate with neurobiological organization in MDD and represents a reproducible, clinically interpretable neuroimaging marker with potential utility for diagnosis and stratification.

1. Introduction

A significant number of brain functional connectivity studies have been conducted since the emergence of blood oxygenation level-dependent (BOLD) analysis on MRI scans (Ogawa et al., 1990), specifically resting state functional MRI (Biswal et al., 1995). These studies are based on the conception that BOLD signals can be interpreted into neurophysiological condition, and that functional MRI reflects the summed synaptic activity of neuronal populations (Logothetis et al.,

2001). This neuroimaging technique possesses high spatiotemporal resolution covering the whole brain (Logothetis, 2008) while being noninvasive in nature and highly available both in research and clinical settings (Brown et al., 2014). It enables repetition for longitudinal study and provides objective quantification of neural dynamics (Buckner et al., 2013) as well as clinical relevance once it is combined with population neuroscience (Biswal and Uddin, 2025). Building on these foundations, extensive research has been conducted to provide insights into the brain functional and structural organization linked to a wide range of

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<https://doi.org/10.1016/j.jad.2025.121073>

Received 26 August 2025; Received in revised form 24 December 2025; Accepted 27 December 2025

Available online 4 January 2026

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psychiatric conditions, including Major Depressive Disorder (MDD).

MDD is an incapacitating condition that is very high in prevalence and imposing a major burden both on the individuals and the healthcare systems worldwide. It is estimated to affect 246 million people in the world with 3152.9 cases per 100,000 population, making it one of the most common psychiatric disorders globally (Zhang et al., 2025). It has extensive personal and economic burden including impaired daily functioning, reduced quality of life, and significant productivity losses (Proudman et al., 2021). Therefore, there is an urgent need for research into its neurobiological underpinnings to improve diagnosis and treatment strategies.

However, there has been no consistent neurobiological marker identified for MDD due to the heterogeneity of neuroimaging analytical methods and lack of standardized pipelines (Winter et al., 2024). Some common brain regions have been reported in several MDD functional connectivity studies, but detecting consistent patterns of network dysfunction in MDD is challenging because the results are often irreproducible due to methods heterogeneity (Kaiser et al., 2015). The study results are also contradictory at times, for instance Sheline et al. (2010) observed increased functional connectivity between the default mode network (DMN) and other networks via hyperconnected dorsal nexus in the dorsomedial prefrontal cortex, which implicates a role in the repetitive negative thinking seen in MDD. In contrast, Yang et al. (2021) reported reduced nodal efficiency within the DMN using graph theory analysis of a large multi-site dataset, particularly in recurrent MDD cases, indicating hypoconnectivity and diminished network integration in the DMN. This warrants the need for a standardized analytical pipeline to clarify the nature and distinct patterns of brain network alterations associated with psychiatric conditions.

Miranda-Dominguez et al. (2014) along with Finn et al. (2015) were the first to demonstrate that human brain functional connectivity is individually unique by leveraging pairwise correlations of regional BOLD time series to construct individual functional connectomes that could identify individuals from the data pool based on their unique functional connectivity patterns with over 90 % accuracy across sessions and termed it as brain fingerprinting. This uniqueness in brain functional connectivity is stable over years (Guo et al., 2012; Horien et al., 2019; Jalbrzikowski et al., 2020; Ousdal et al., 2020) and between scan conditions (Vanderwal et al., 2017). It is also preserved across life span, and the results can be replicated even when a different set of nodes is applied as region of interest (ROI) (St-Onge et al., 2023). This uniqueness may reflect neural maturation, while delays in network tuning are linked to poorer mental health since lower connectivity distinctiveness is associated with increased clinical symptom score (Kaufmann et al., 2017). Thus, brain fingerprinting has potential for a clear and meaningful method for indexing functional connectivity-based measurement (Ramduny and Kelly, 2024). Brain fingerprinting further develops into reproducible index termed as functional connectome (FC) uniqueness index, which is a promising neuroimaging marker with studies demonstrating its utility to index psychological distress and psychiatric vulnerability across development and diagnostic categories (Shan et al., 2022; Li et al., 2023).

While prior studies have shown FC uniqueness to be statistically robust, reliable, and reproducible, studies on its clinical validity in psychiatric conditions are very limited. Therefore, this study aims to examine whether standardized FC uniqueness pipelines can differentiate MDD patients from healthy controls (HC) and pinpoint potential brain connectivity patterns alteration that may serve as a consistent neurobiological marker for MDD. This study is the first to evaluate the clinical validity of FC uniqueness analysis as a reproducible indexing method by examining its association with depression severity. We computed FC uniqueness indices of MDD patients and HC at the whole brain and network levels, then correlated these indices with standardized clinical symptom scores to advance our understanding of the neurobiological basis of MDD, clarify its underlying mechanisms compared to the healthy population, and pave the way for personalized diagnosis and

treatment.

2. Methods

2.1. Participants and ethical clearance

Resting state functional MRI (rs-fMRI) scans of 35 patients with MDD as primary diagnosis and 42 HC aged 19–37 years old from the Chiba University Hospital and Hiroshima University Hospital via Brain/Minds Beyond Human Brain MRI (BMB-HBM) project database were analyzed in this study. All participants have been scanned two times in different sessions spanning from months to years apart, resulting in 154 rs-fMRI scans corresponding to 77 individuals included in this study. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) was used to determine diagnosis for MDD patients and to confirm the inexistence of psychiatric illness history in HC. Beck Depression Inventory Second Edition (BDI-II) (Beck et al., 1996; Kojima et al., 2002) and the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001; Muramatsu et al., 2018) were utilized to assess depression symptoms of MDD patients. The detailed demographic characteristics of participants in this study are presented in Table 1. The exclusion criteria set in this study are brain trauma, pregnancy, major physical illness, and illegal drug use.

2.2. MRI acquisition

At Chiba University Hospital, a 3.0 Tesla magnetic resonance Discovery MR750 scanner (GE Healthcare, Waukesha, WI, USA) equipped with a phased-array head coil (32-channel) was utilized to obtain brain images. A 3D magnetization-prepared rapid-acquisition gradient echo (MPRAGE) T1-weighted sequence covering the whole brain was collected with this settings: repetition time (TR = 8.128 or 8.168 ms), echo time (TE = 3.16 or 3.18 ms), flip angle (FA = 15° or 11°), inversion time (TI = 420 or 400 ms), acquisition matrix (256 × 256), slice thickness (1.0 or 1.2 mm), and voxel size (1 × 1 × 1 or 1.02 × 1.02 × 1.2 mm³). Gradient echo-planar imaging sequence was also used for resting-state functional BOLD images with following settings: repetition time at 2300 or 2500 ms, echo time at 30 ms, flip angle at 81° or 80°, slice thickness at 3.2–3.5 mm, 64 × 64 acquisition matrix, with 3.3 × 3.3 × 3.5 Or 3.3125 × 3.3125 × 3.2 mm³ voxel size.

At Hiroshima University BMB-HBM project, rs-fMRI scans were acquired using two machines of 3.0 Tesla MRI system: (1) Siemens MAGNETOM Verio and (2) Siemens MAGNETOM Skyra (Siemens, Erlangen, Germany). These machines were equipped with 32 or more channels head coil and ability to perform a multi band EPI sequence. The following scanning settings were used: slice number at 40, 64 × 64

Table 1
Clinical and demographic information of participants.

Characteristics	HC	MDD	Comparison Analysis	
			Statistics	p-val
Number of subjects	42	35	N/A	N/A
Sex(n) (F/M)	20/22	21/14	2.34 ^a	0.126
Age at first scan (years, means std)	21.17 ± 3.70	27.49 ± 4.98	40.705 ^b	<0.001*
Handedness(n)(R/L/B)	38/2/2	34/0/1	0.51 ^a	0.770
Comorbidity(n) (Y/N)	N/A	9/35	N/A	N/A
BDI-II Score (means std)	N/A	20.64 ± 11.39	N/A	N/A
PHQ-9 Score (means std)	N/A	12.47 ± 6.35	N/A	N/A
Fingerprinting accuracy (percent, means std)	58.83 ± 31.60	53.57 ± 27.20	114.5 ^c	0.462

Group comparisons were conducted using (a) chi-square tests (χ^2) for categorical variables, (b) one-way ANOVA (F) for continuous demographic measures, and (c) Mann–Whitney U test (U) for fingerprinting accuracy. Significant p-value are indicated by an asterisk (*).

acquisition matrix, FOV at 212 mm, $3.3 \times 3.3 \times 3.2$ mm (slice gap, 0.8 mm) voxel size, repetition time at 2500 ms; echo time at 30 ms, 80° flip angle. In addition, T1-weighted structural images were collected using a 3D magnetization-prepared rapid gradient echo sequence: 178 1-mm thick sagittal slices with a 256×256 acquisition matrix; FOV, 256 mm; TI/TR/TE = 900/2300/2.98 ms; flip angle, 9° . The acquisition time was 617 s for rs-fMRI scans and 312 s for T1-weighted structural images.

2.3. Image pre-processing

The scans are stored as raw Digital Imaging and Communications in Medicine (DICOM) images. For neuroimaging analysis in this study, these images are converted into the Neuroimaging Informatics Technology Initiative (NIFTI) format using the MRICroGL software (<https://www.nitrc.org/projects/mricroGL/>). Image pre-processing pipelines and functional connectivity analysis in this study were performed using CONN release 22.a (Nieto-Castanon and Whitfield-Gabrieli, 2022) and SPM (Penny et al., 2011) (RRID:SCR_007037) release 12.7771. To rigorously control motion-related confounds, we implemented a multi-tiered strategy. Framewise displacement (FD) was computed from rigid body realignment parameters, and scans exceeding a maximum FD of 1.5 mm or 1.5° were excluded. DVARS was used to detect motion spikes, applying a threshold defined as the 75th percentile plus 1.5 times the interquartile range. In the general linear model, we regressed out 24 Friston motion parameters along with principal components extracted from white matter and cerebrospinal fluid signals. Scrubbing was performed using scan-nulling regressors, with volume interpolation applied as an alternative when appropriate. Additionally, projection scrubbing based on ICA/PCA decomposition was used to remove residual artifacts in a data-driven manner, further enhancing the robustness of the functional connectivity estimates.

2.3.1. Realignment, slice-timing correction, normalization, and smoothing

Slice timing correction (FSL-slice timer), motion correction (FSL-mcflirt), skull stripping (SAL-bet), and resampling to 1.5 mm^3 voxels were conducted. Each subject's fMRI data was normalized to MNI space using their corresponding structural scan. T1-weighted images were co-registered to functional scans, corrected for field bias (N4BiasField), and segmented into gray matter, white matter, and CSF using SPM's unified segmentation. Functional and anatomical data were preprocessed using a flexible preprocessing pipeline (Nieto-Castanon, 2020) including realignment with correction of susceptibility distortion interactions, slice timing correction, outlier detection, direct segmentation and MNI-space normalization, and smoothing. Functional data were realigned using SPM realign and unwarp procedure (Andersson et al., 2001), where all scans were co-registered to a reference image (first scan of the first session) using a least squares approach and a 6 parameter (rigid body) transformation (Friston et al., 1995) and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Temporal misalignment between different slices of the functional data (acquired in interleaved top-down order) was corrected following SPM slice-timing correction (STC) procedure (Henson et al., 1999; Sladky et al., 2011), using Sinc-temporal interpolation to resample each slice BOLD time series to a common mid-acquisition time. Potential outlier scans were identified using ART as acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations (Power et al., 2014), and a reference BOLD image was computed for each subject by averaging all scans excluding outliers. Functional and anatomical data were normalized into standard MNI space, segmented into gray matter, white matter, and CSF tissue classes, and resampled to 2 mm isotropic voxels following a direct normalization procedure (Calhoun et al., 2017) using SPM unified segmentation and normalization algorithm (Ashburner and Friston, 2005; Ashburner, 2007) with the default ICI-549 tissue probability map template. Lastly, functional data was smoothed using spatial convolution with a Gaussian kernel of 6 mm full width half maximum (FWHM).

2.3.2. Denoising

Functional data were denoised using a standard denoising pipeline (Nieto-Castanon, 2020a) which include the regression of potential confounding effects characterized by white matter timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), filtered motion parameters and their first order derivatives (12 factors) (Friston et al., 1996), outlier scans (below 62 factors) (Power et al., 2014), session effects and their first order derivatives (2 factors), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD time series (Hallquist et al., 2013) between 0.007 Hz and 0.1 Hz. CompCor (Behzadi et al., 2007; Chai et al., 2012). Noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 73.6 to 310.8 (average 262.3) across all subjects.

2.3.3. First-level analysis

ROI-to-ROI connectivity (RRC) matrices were estimated by characterizing the functional connectivity between each pair of regions among 300 ROIs set developed at Greene Lab to define 300 nodes that were grouped into 14 networks (Seitzman et al., 2020). Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients from a general linear model (weighted-GLM) (Nieto-Castanon, 2020b), estimated separately for each pair of ROIs, characterizing the association between their BOLD signal time series. Individual scans were weighted by a boxcar signal characterizing each individual task or experimental condition convolved with an SPM canonical hemodynamic response function and rectified.

2.3.4. Group-level analyses

Group-level analyses were performed using a General Linear Model (GLM) (Nieto-Castanon, 2020c). For each individual connection, a separate GLM was estimated with first-level connectivity measures as dependent variables (one independent sample per subject and one measurement per task or experimental condition, if applicable), and groups or other subject-level identifiers as independent variables. Connection-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of similar connections). Cluster-level inferences were based on parametric statistics within and between each pair of networks (Functional Network Connectivity) (Jafri et al., 2008), using a complete-linkage hierarchical clustering procedure based on ROI-to-ROI anatomical proximity and functional similarity metrics (Nieto-Castanon, 2020d). Results were set on a threshold using the combination of a $p < 0.05$ connection-level threshold and a familywise corrected $p\text{-FDR} < 0.05$ cluster-level threshold (Benjamini and Hochberg, 1995). The time series of a node was extracted and averaged from each functional MRI data set. The Pearson correlation coefficients between each pair of node time series were calculated and normalized to Z scores by Fisher transformation generating functional matrix connectome of each data set.

2.4. Neuro harmonization

When MRI scans were acquired from several sites, site-linked effects may occur. Therefore, a harmonization step is essential to remove these potential effects in all data. In this study, harmonization was conducted based on the ComBat-GAM neuro-harmonization pipeline (<https://github.com/rpomponio/neuroHarmonize>) as previously published by Pomponio et al. (2019). In this study, the ComBat-GAM neuro-Harmonize pipeline was applied to the Fisher z-transformed functional

connectivity matrices (i.e., the derived connectivity features), not to the raw BOLD time series. This harmonization method preserves each subject's temporal signal structure while reducing site-related variance in the derived connectivity values by removing systematic differences that are attributable to site rather than biology.

2.5. Functional connectome uniqueness index

In-house MATLAB scripts (MATLAB R2023a, The MathWorks Inc., Natick, MA) were utilized to calculate functional connectome, connectome self-similarity, similarities-to-others, and FC uniqueness indices. The FC uniqueness analysis method used in this study is according to a study of Shan and colleagues (Shan et al., 2022) based on the foundational study of brain fingerprinting (Miranda-Dominguez et al., 2014; Finn et al., 2015). The 300 ROI set by Greene Lab used in this study was developed based on previous 264 ROIs (Power et al., 2011) added with nodes from subcortical and cerebellar structures. The 300 ROIs are nodes 4–5 mm in radius defined by a winner-take all partitioning method which are assigned into whole brain, meaning all ROIs included, and grouped into 14 networks: (1) Default Mode, (2) Visual, (3) Auditory, (4) Frontoparietal, (5) Reward, (6) Dorsal Attention, (7) Ventral Attention, (8) Salience, (9) Cingulo-opercular, (10) Somatomotor Dorsal, (11) Somatomotor Lateral, (12) Parieto-medial, (13) Medial Temporal Lobe, and (14) Unassigned. The unassigned network referred to regions that cannot be assigned to any specific network (Power et al., 2011). A notable limitation of widely used functional atlases is their focus on cortical regions, with minimal or absent representation of subcortical and cerebellar structures. In contrast, the Greene Lab 300 ROI atlas employed in this study was specifically designed to address this gap, providing functionally defined coverage of critical subcortical regions including the thalamus, basal ganglia, amygdala, hippocampus, and cerebellum. Nonetheless, Medial Temporal Lobe network was not included in the current study on the network level because it comprises very few nodes (only 4 nodes) and contains noise resulting in negative self-similarities values for multiple data sets. While this region was excluded from network-level analyses,

its corresponding nodes were retained in whole brain analyses, thereby preserving its contribution to functional connectome uniqueness on the whole brain level in this study. This reflects our use of the most comprehensive ROI set currently available. The connectome similarity in this study was calculated as the Pearson correlation between two vectors of edge values taken from two connectomes. Next, connectome similarity indices were calculated for (i) self-similarity, i.e. the calculated similarity between two connectomes from the same individual at different time points, and (ii) similarity-to-others, i.e. the calculated similarity between the connectome of a given individual to any connectome from a different individual at a different time point. As previously defined, uniqueness indices are the ratio of self-similarity to the maximal similarities-to-others (Shan et al., 2022). Uniqueness without modification applied in this study refers to uniqueness defined over the maximal similarity-to-others. This FC uniqueness calculation yields identification success that is termed as fingerprinting accuracy when the value is greater than one, which demonstrates that an individual connectome is distinct from others (Fig. 1).

2.6. Statistical analysis and nodes visualization

The chi-square (χ^2) test was employed to compare categorical variables such as gender and handedness between MDD and HC because it assesses independence between groups for nominal data. Age was compared with one-way ANOVA after confirming approximate normality and homogeneity of variance, since ANOVA provides an efficient test of mean differences for continuous variables when assumptions hold. The means value at 95 % Confidence Interval (95CI) of FC uniqueness indices of the whole brain and all networks between MDD patients and HC are compared using independent *t*-test after previously tested for homogeneity in variance with Levene's test. Then, an FDR correction at $q = 0.10$ Benjamini-Hochberg procedure was applied to control for multiple comparisons. This threshold is widely used in exploratory biomarker studies in brain imaging because it allows detection of potential neural markers while controlling the rate of false positives to a tolerable level (Genovese et al., 2002; Drysdale et al.,

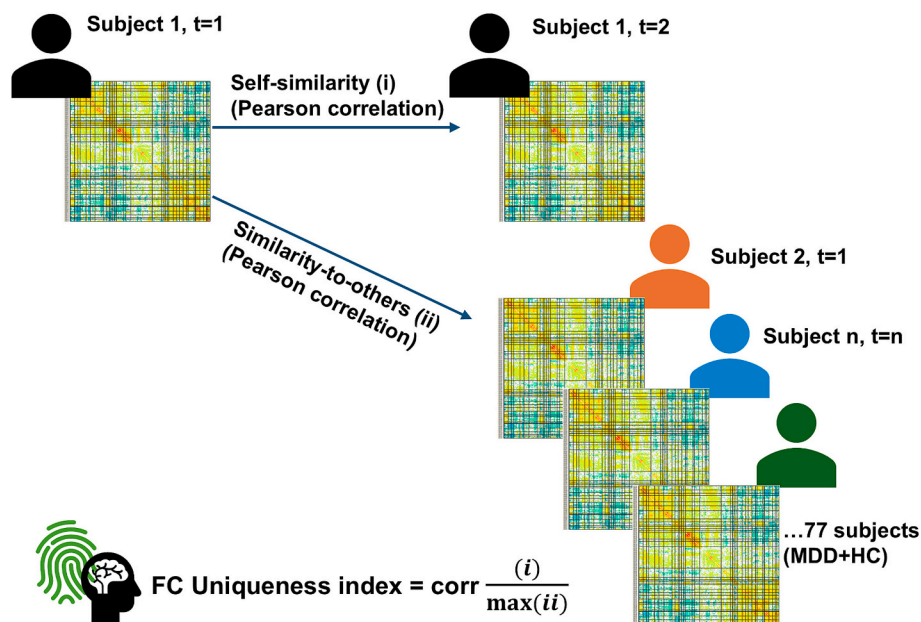


Fig. 1. Functional connectome uniqueness calculation method in this study. The functional matrix connectome at each time point (t) was derived by calculating Pearson correlations between the fMRI time series of all ROI pairs, followed by Fisher transformation. ROIs were defined using the 300 nodes ROI set and grouped into 14 functional networks (Seitzman et al., 2020). Self-similarity (i) refers to the correlation between connectomes from the same individual across different t; similarity-to-others (ii) refers to the correlations between an individual's connectome and those of other participants at the next t. FC Uniqueness was defined as the ratio of self-similarity to the highest similarity-to-others. FC Uniqueness indices greater than one indicates that an individual's connectome is more similar to their own at another t than to others in the group (Shan et al., 2022).

2017). We used a false discovery rate threshold of $q = 0.10$ for these exploratory network-level FC uniqueness comparisons analyses to balance sensitivity and control of false discoveries while prioritizing hypothesis generation and replication. With 13 brain networks tested, a more stringent family-wise correction would likely suppress true, moderate effects that are biologically plausible but underpowered in this sample. All reported p values are from two-tailed tests, and we also report q values (Benjamini–Hochberg at FDR $q = 0.05$) alongside raw p values. Furthermore, all reported findings meeting FDR $q \leq 0.10$ also exceeded the medium effect-size threshold (Cohen's $d > -0.5$). This combined criterion was used to prioritize results that are not only unlikely under the null after multiplicity correction but also exceed a minimally important magnitude in the observed direction. Fingerprinting accuracy as well as correlation of FC uniqueness indices and gender of each network between MDD patients and HC were analyzed using Mann–Whitney U test because these outcomes were non-normally distributed. Associations between uniqueness indices and age as well as depression score were assessed with Spearman's rank correlation to accommodate monotonic but nonparametric relationships. To assess potential confounding effects of age on FC uniqueness, we conducted two post hoc analyses. First, we performed Pearson correlation analyses between age and FC uniqueness within each group (HC and MDD) to evaluate within-group associations. Second, we ran a linear regression model with FC uniqueness as the dependent variable and group (MDD vs. HC) and age as predictors, allowing us to assess the group effect while adjusting for age. All statistical analyses and figure generation were performed in MATLAB (R2023a; The MathWorks, Natick, MA). ROI visualization on the whole brain and network level was produced with Netplotbrain (<https://www.netplotbrain.org/>) in Python (Spyder, Python 3.12). Analysis and visualization code are available from the corresponding author upon reasonable request.

3. Results

3.1. Participants demographic and clinical analysis

The participants of this study as shown in Table 1 comprised of a balanced gender ratio both in MDD and HC groups, and there was no significant association found between FC uniqueness and gender. However, the age distribution between the two groups was significantly different based on ANOVA analysis. Age distribution of HC was concentrated around the age of 21 years old, while in MDD group it was more spread out. Nevertheless, this study only included participants in the age range of 19–37 years old, a period when the human brain is maturing and experiencing only a slow wave of brain growth with no occurrence of brain tissue loss (Hedman et al., 2012). This approach mitigates confounding influences attributable to neurodevelopmental-related changes on the characterization of brain functional connectivity. Also, this age group represents the population with the highest risk and prevalence of MDD globally (Global Burden of Disease Collaborative Network, 2022). To further evaluate the potential influence of age, we conducted post hoc Pearson correlation analyses, which revealed no significant association between age and FC uniqueness within either group (MDD: $r = -0.13$, $p = 0.46$; HC: $r = 0.03$, $p = 0.83$). Detailed individual information on clinical demography and acquisition sites of the participants is provided in Supplementary Table 1. In addition, Supplementary Fig. 1 displays all FC uniqueness indices plotted against age at first scan on the whole brain level and across networks.

3.2. MDD patients showed significantly lower uniqueness indices means (95 CI) compared to HC

3.2.1. Functional connectome fingerprinting accuracy

FC uniqueness indices in this study were calculated based on the connectivity matrix of all participants, both MDD and HC groups, with no significant difference in terms of fingerprinting accuracy level

(Supplementary Fig. 2). The accuracy of brain fingerprinting in this study was found to be the highest in the whole brain, followed by default mode and frontoparietal network. This result was consistent both in MDD and HC even after group-wise separation and all participants accuracy recalculation (Fig. 2). Our findings are closely aligned with those of previous studies, supporting the reproducibility and robustness of FC uniqueness analysis as an indexing method for brain functional connectivity assessment.

3.2.2. Functional connectome uniqueness in whole brain

The FC uniqueness of MDD patients in the whole brain level was observed to be significantly lower than that of HC (Fig. 3a). All participants in HC group exhibited whole brain FC uniqueness indices above one, with a group mean of 1.513, 95CI [1.446, 1.580]. In contrast, the MDD patients demonstrated a lower score at 1.375, 95CI [1.244, 1.505], alongside slightly reduced fingerprinting accuracy. At the whole brain level, the HC and MDD FC Uniqueness indices differences yielded effect sizes in the medium range (Cohen's $d = -0.523$), supporting the interpretation that these findings are not only statistically detectable but also of potential biological signal.

3.2.3. Functional connectome uniqueness in 13 networks

We identified significantly lower FC uniqueness indices across three distinct brain networks in MDD patients compared to HC. The three networks were the frontoparietal, somatomotor dorsal, and somatomotor lateral networks (Fig. 3b–d). Moreover, fingerprinting accuracy in the somatomotor lateral network was consistently inferior both in MDD and HC, second only to the reward network that showed lowest fingerprinting accuracy overall. Aside from these three networks, the remaining networks did not survive FDR correction at $q = 0.10$ and thus remained statistically non-significant, despite a consistent trend toward lower FC uniqueness indices in MDD patients compared to HC (Fig. 3e–n). We also tested the results with more stringent FDR correction at 0.05. However, none survived false discovery rate correction at $q = 0.05$ although several comparisons yielded nominal significance. Nevertheless, the frontoparietal, somatomotor dorsal, and somatomotor lateral networks yielded effect sizes in the medium range (Cohen's $d = -0.520$; -0.661 ; -0.544 respectively). These findings should be interpreted cautiously and may reflect trends warranting further investigation in larger cohorts.

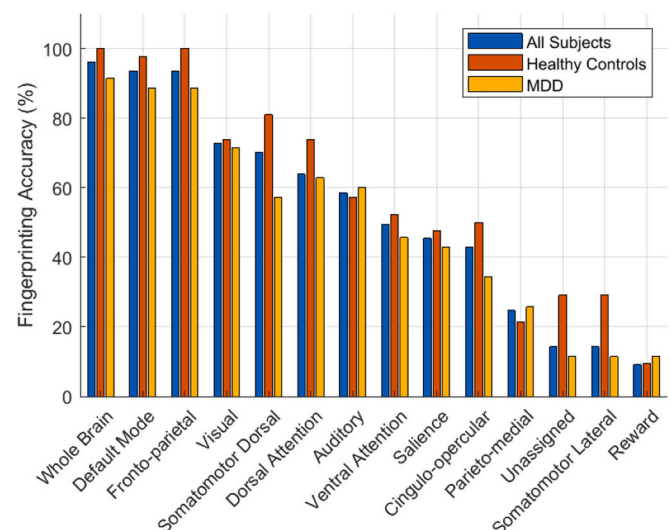


Fig. 2. Fingerprinting accuracy by network and diagnostic group. The Y-Axis represents fingerprinting accuracy (%) calculated separately for the whole brain and each network (X-axis) in all participants, HC, and MDD. Fingerprinting accuracy is defined as the FC uniqueness score equal to 1 or higher.

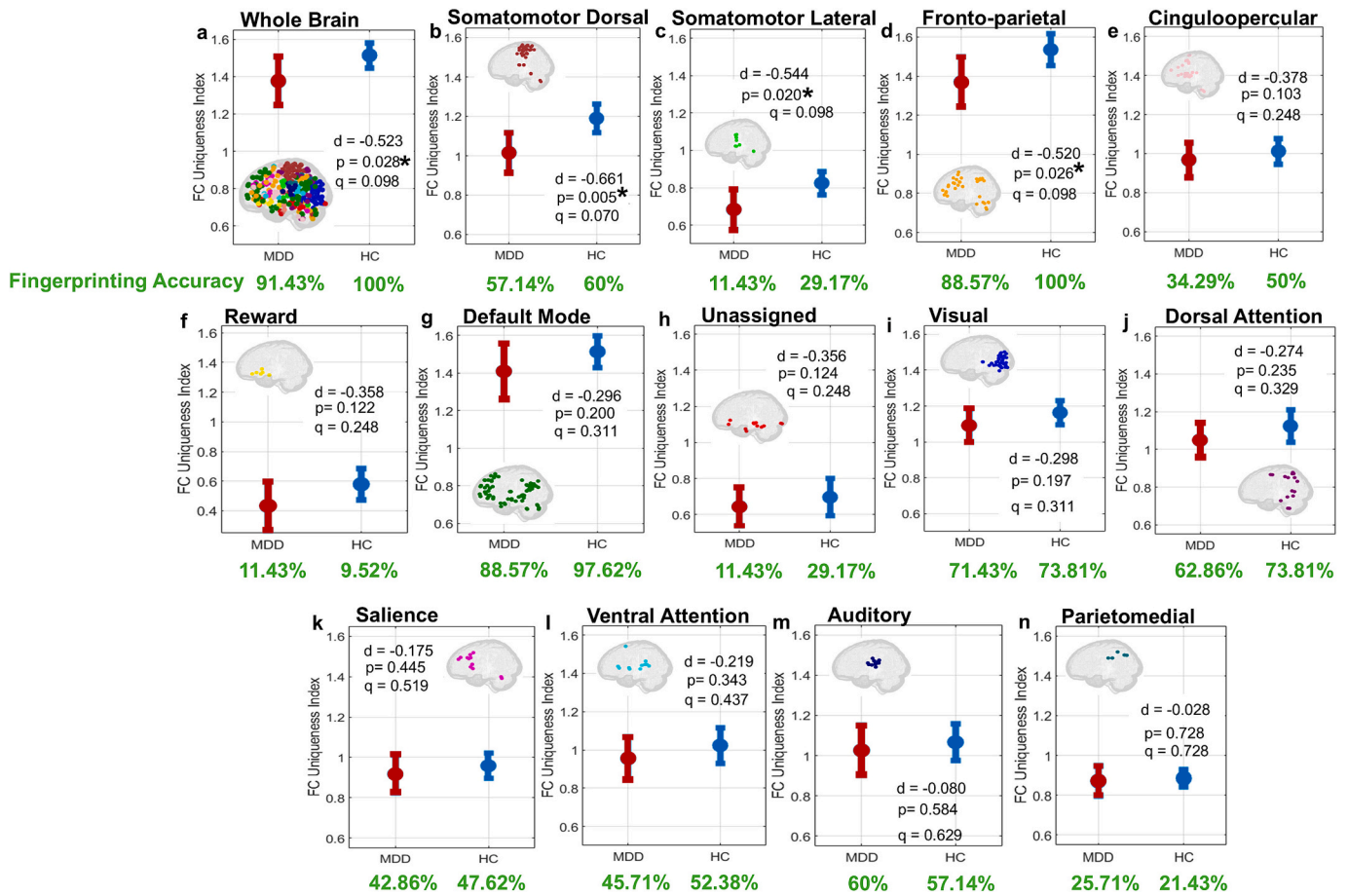


Fig. 3. Comparisons of functional connectome uniqueness indices between MDD individuals and HC on the whole brain level and all networks. The means (95 % CI) of the whole-brain and network FC uniqueness indices were compared between MDD patients and healthy controls. The results show a trend toward lower uniqueness scores in MDD across all networks and the whole brain. All reported p values in this figure are raw p values from two-tailed tests. For each comparison, Cohen's d value (effect size) and the q value (Benjamini–Hochberg FDR-adjusted p at $q < 0.05$) are also reported. FC uniqueness is significantly lower in MDD at the whole-brain level and in several networks; comparisons significant at FDR $q < 0.10$ are marked with an asterisk (*). However, none remained significant at $q < 0.05$.

3.2.4. Post hoc analysis

A covariate-adjusted regression analysis showed that the group effect was not statistically significant when controlling for age ($p = 0.1167$), suggesting that age-related variance may partially account for the observed group differences. The attenuation of the group effect after adjustment for age warrants a cautious reinterpretation of our primary finding. Although unadjusted analyses indicate reduced FC uniqueness in MDD, the loss of statistical significance when controlling for age suggests that at least part of the observed difference may reflect age-related variance rather than diagnosis alone.

3.3. Correlation between depression severity and FC uniqueness score

The Spearman correlation analysis revealed a strong and expected relationship between BDI-II and PHQ-9 scores ($\rho = 0.89$, $p < 0.0001$), confirming that both measurements are highly overlapping in capturing the characteristics of depressive symptom severity. Importantly, both BDI-II and PHQ-9 scores exhibited moderate and statistically significant inverse relationship with FC uniqueness at the whole brain level ($\rho = -0.52$, $p = 0.005$; and $\rho = -0.45$, $p = 0.017$, respectively), as demonstrated by the pairwise relationships plot matrix in Fig. 4. No other statistically significant correlations between BDI-II scores and FC Uniqueness indices were observed at network levels as shown in Table 2. However, significant negative associations between PHQ-9 scores and FC uniqueness were found within the auditory and ventral attention networks ($\rho = -0.53$, $p = 0.003$; and $\rho = -0.44$, $p = 0.018$,

respectively).

3.4. Correlation between age and FC uniqueness at whole brain level and all networks

In HC, Spearman's rank correlations between age and FC uniqueness indices were mostly weak and non-significant (Table 3), except for the frontoparietal network, which showed a strikingly significant positive association with age ($\rho = 0.57$, $p = 0.001$). Conversely, MDD patients exhibited stronger negative associations between age and FC uniqueness within the reward, salience, and unassigned networks ($\rho = -0.48$, $p = 0.027$; $\rho = -0.46$, $p = 0.027$; $\rho = -0.46$, $p = 0.027$ respectively). However, no significant correlation of FC uniqueness and age was observed at the whole brain level across MDD patients and HC.

4. Discussions

We investigated FC uniqueness indices in MDD patients compared to HC across multiple acquisition sites and demonstrated that FC uniqueness is a reproducible and clinically sensitive marker of brain connectivity distinctiveness. Importantly, we found that MDD patients exhibited significantly lower FC uniqueness compared to HC, specifically in the frontoparietal and sensorimotor networks. Furthermore, our findings revealed a significant inverse relationship between depression severity and FC uniqueness.

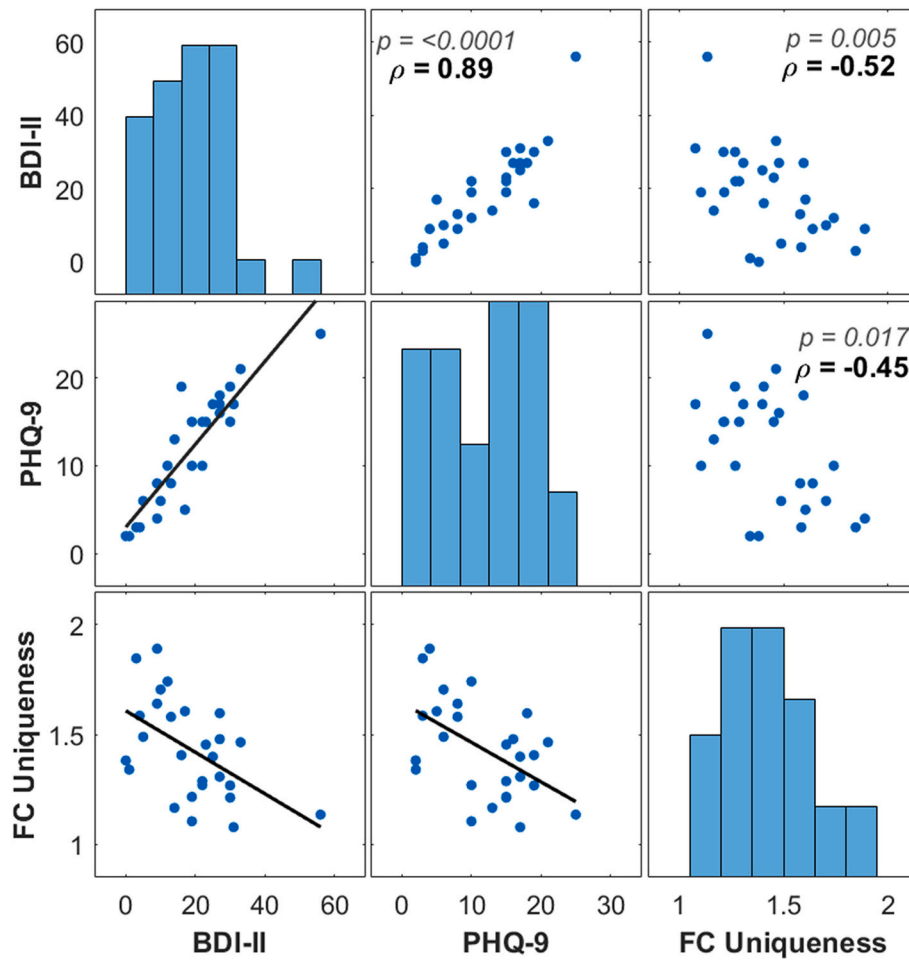


Fig. 4. Plot matrix depicting pairwise relationships among BDI-II, PHQ-9, and whole-brain functional connectivity (FC) uniqueness indices. Diagonal histograms represent the univariate distribution of FC Uniqueness, BDI-II, and PHQ-9 scores without any comparisons. Lower triangle scatter plots display bivariate relationships between FC Uniqueness indices and clinical assessment scores. Upper triangle is annotated with Spearman's rank rho (ρ) as correlation estimates. BDI-II and PHQ-9 showed a strong positive association ($p < 0.0001$), whereas both symptom scales were negatively correlated with FC uniqueness (BDI-II: $p = 0.005$; PHQ-9: $p = 0.017$).

Table 2

Spearman's rank correlation test results between FC Uniqueness indices and depression assessment.

Networks	FC uniqueness & BDI-II		FC uniqueness & PHQ-9	
	ρ	p-val	ρ	p-val
Whole Brain	-0.52	0.005*	-0.45	0.017*
Default Mode	-0.10	0.588	-0.25	0.190
Frontoparietal	-0.23	0.239	-0.35	0.061
Visual	-0.29	0.125	-0.38	0.042
Dorsal Attention	-0.10	0.622	-0.20	0.307
Ventral Attention	-0.29	0.121	-0.44	0.018*
Auditory	-0.26	0.178	-0.53	0.003*
Salience	0.18	0.347	-0.03	0.889
Cingulo-opercular	0.22	0.257	-0.11	0.556
Parietomedial	-0.21	0.270	-0.16	0.400
Somatomotor Lateral	0.25	0.190	0.10	0.591
Somatomotor Dorsal	-0.10	0.593	-0.32	0.086
Reward	0.28	0.148	0.15	0.452
Unassigned	-0.05	0.783	-0.26	0.166

Spearman's rank correlations (ρ) between FC uniqueness indices and depression assessment scores across the whole brain and 13 networks. Negative values indicate an inverse association between FC uniqueness and clinical severity. Significant p -values are indicated by an asterisk (*).

Table 3

Spearman's rank correlation test results between FC uniqueness indices and age.

Networks	HC		MDD	
	ρ	p-val	ρ	p-val
Whole brain	-0.14	0.674	0.01	0.963
Default mode	-0.21	0.523	-0.19	0.485
Frontoparietal	0.57	0.001*	-0.32	0.162
Visual	0.03	0.833	0.01	0.963
Dorsal attention	0.03	0.833	0.06	0.963
Ventral attention	0.22	0.523	-0.22	0.462
Auditory	-0.11	0.728	0.20	0.479
Salience	-0.16	0.674	-0.46	0.027*
Cingulo-opercular	-0.04	0.833	-0.35	0.129
Parietomedial	0.10	0.728	-0.16	0.542
Somatomotor dorsal	-0.21	0.523	0.01	0.963
Somatomotor lateral	0.25	0.523	0.03	0.963
Reward	0.14	0.674	-0.48	0.027*
Unassigned	0.09	0.728	-0.46	0.027*

Spearman's rank correlations (ρ) between FC uniqueness indices and age across the whole brain and 13 networks for HC and MDD. Positive values indicate greater FC uniqueness indices with increasing age, while negative values indicate reduced FC uniqueness indices. Significant negative correlations with age emerged in the reward, salience, and unassigned networks for MDD, while for HC a significant positive correlation emerged in the frontoparietal network. Significant p -values are indicated by an asterisk (*).

4.1. Reduced FC uniqueness in the frontoparietal and sensorimotor networks correlates with major depressive disorder

This study reinforces the robustness of functional connectome uniqueness as an individual-level biomarker. High fingerprinting accuracy in the whole brain, default mode, and frontoparietal networks are consistently observed across both MDD patients and HC. This replicates prior findings (Finn et al., 2015; Shan et al., 2022) despite the smaller sample size and multiple fMRI acquisition sites in this study. This alignment suggests that FC uniqueness is a reproducible and reliable neurobiological index, offering a promising avenue for future research into brain individuality and its relevance to psychiatric conditions. In addition, the significant reduction in whole brain FC uniqueness among MDD patients supports the hypothesis that depressive pathology is associated with less distinctive functional brain organization. The lower uniqueness indices in MDD patients relative to the HC benchmark implies reduced network individuality and may reflect disrupted processes of network maturation or tuning, echoing themes from Kaufmann et al. (2017), Li et al. (2023), and Shan et al. (2022). Notably, reduced FC uniqueness in the frontoparietal, somatomotor dorsal, and somatomotor lateral highlights specific network-level vulnerability in pathophysiology of MDD. The frontoparietal network, which is characterized by high inter-individual variability and a central role in cognitive control (Mueller et al., 2013; Yeo et al., 2011), exhibited reduced FC uniqueness indices and less fingerprinting accuracy in MDD patients of this study. This is consistent with prior evidence implicating lower distinctiveness of this network in depression (Kaiser et al., 2015). This finding may explain the altered executive function and lower degree of subject-specific functional specialization found in individuals with depression. The uniformly low fingerprinting accuracy of the somatomotor lateral network in HC and MDD relative to other networks assessed in this study implies a stable and conserved functional architecture developmental characteristics of somatomotor lateral network indicated by early stabilization of its connectivity profiles (Tu et al., 2025), but a further fingerprinting accuracy reduction and lower FC uniqueness indices of this network in MDD could signal lateral portions of motor or somatosensory dysfunction tied to the disorder (Ray et al., 2021). Although not passing FDR correction, marginal lower FC uniqueness indices in the cingulo-opercular and reward networks invite closer scrutiny because of its size effects. It suggests a subtle effect that may become significant in larger cohorts and longitudinal designs given the involvement of these networks in affect regulation, depression, and anhedonia (Höflich et al., 2019; Shan et al., 2022).

4.2. Depression severity is inversely correlated with FC uniqueness

The negative correlation between FC uniqueness indices and depression assessment scores conveys a meaningful clinical pattern; greater symptom burden relates to less differentiated individual brain connectivity organization. This reduced uniqueness may reflect a loss of specialized functional connectivity patterns in MDD patients that normally aid adaptive cognitive and affective function in HC (Yang et al., 2021a). This indicates that brain FC uniqueness indices may serve as a dimensional neurobiological marker for psychiatric disorder, capturing not only group-level differences but also potentially the individual spectrum of symptom severity. In other words, individuals exhibiting higher depressive symptoms tend to have less unique functional connectome profiles, potentially reflecting a convergence toward less differentiated network configurations in the presence of psychopathology. This pattern supports the growing notion that FC uniqueness may serve as a neural marker of psychological resilience or vulnerability (Fu et al., 2023; Shan et al., 2022; Sun et al., 2024; Zhou et al., 2025). While our findings suggest that FC uniqueness may differentiate MDD patients from HC, we emphasize that this study is exploratory in nature. The observed group differences are correlational and derived from a modest sample size, without predictive modeling or classification validation.

Accordingly, we propose FC uniqueness as a candidate systems-level marker that warrants further investigation. Future studies with larger cohorts and dedicated stratification frameworks will be essential to assess its clinical relevance and predictive value.

4.3. Age-related trajectories of FC uniqueness in individuals aged 19–37 years old

We found a positive association between FC uniqueness and age in the frontoparietal network of HC. This finding suggests that frontoparietal connectivity distinctiveness increases with age in healthy individuals aged 19 to 37 years old, possibly reflecting this network's lifelong differentiation and maturation process which is crucial for successful aging from the perspective of cognitive performance (Nolin et al., 2025). This positive association of FC uniqueness and age was not found in frontoparietal network of MDD patients. In contrast, MDD patients exhibited negative correlations between FC uniqueness indices and age in the reward, salience, and unassigned networks, suggesting that depressive pathology may reflect impaired age-related connectivity refinement in these regions (Wang et al., 2024). Importantly, the non-significant age-adjusted results for comparison of FC uniqueness indices between MDD and HC ($p = 0.1167$) does not rule out a disease effect but suggests that age may account for part of the observed difference. Consequently, we have tempered claims to reflect the study's limitations and present effect sizes and 95 % confidence intervals alongside significance tests to convey magnitude and precision. Future studies should use age-balanced or longitudinal designs to separate aging from illness effects. Additional strategies to strengthen causal inference include formal matching or propensity-score methods, larger cohorts to increase power for adjusted models, and explicit modeling of age-dependent trajectories. These steps are necessary to determine whether reduced FC uniqueness reflects MDD itself, age-related change, or an interaction between the two.

4.4. Functional connectome uniqueness may reflect macro-level signatures of synaptic tuning and pruning underlying normal brain maturation

Our findings contribute to the growing evidence that FC uniqueness index can quantify the distinctiveness of an individual's brain functional connectivity pattern. The relatively higher HC FC uniqueness in comparison to MDD patients suggests a more individualized and stable neural pattern in healthy brain function. This neural distinctiveness may represent a macro-scale reflection of synaptic tuning and pruning processes that shape micro-scale connectivity during brain maturation (Liu et al., 2023; Park and Poo, 2013). During development and adaptation, synaptic pruning eliminates redundant or less-used connections, while synaptic tuning reinforces specific, efficient pathways (Faust et al., 2021; Huttenlocher and Dabholkar, 1997; Sakai, 2020; Scelfo and Buffelli, 2009). These microstructural refinements contribute to more streamlined and specialized functional networks over time (Estévez-Priego et al., 2020; Sadeh et al., 2015). Importantly, emerging evidence suggests that these synaptic refinement processes may be disrupted in MDD. Postmortem and in vivo studies have reported altered synaptic density, reduced dendritic spine complexity, and impaired plasticity in individuals with depression (Holmes et al., 2019; Kang et al., 2012), potentially leading to less differentiated or less stable functional architectures. While our study does not directly assess synaptic mechanisms, we propose that reduced FC uniqueness in MDD may serve as a systems-level correlation of these microstructural alterations. We emphasize that this interpretation is hypothesis-generating and warrants further investigation using multimodal approaches that integrate functional imaging with molecular or histological markers of synaptic integrity.

4.5. Limitations

Despite alignment with prior findings, this study generalizability is constrained by a modest sample size. The existence of comorbidity and age distribution differences between HC and MDD patients may also introduce confounding effects. Post hoc analyses for age-related confounding suggested age-related variance may partially account for the observed difference in this study. Therefore, we recommend that future studies use age-matched samples or covariate-adjusted models to further clarify the relationship between age and FC uniqueness in MDD patients. Furthermore, the medial temporal lobe network was not included in this study due to limitations in ROI coverage. This exclusion is notable given that the amygdala, a key structure within the medial temporal lobe, is strongly implicated in affective processing and depression-related pathology. Therefore, this exclusion constrains interpretation with respect to core affective circuits implicated in MDD. Future work should address this gap using higher-resolution parcellations or medial temporal lobe focused acquisitions, larger samples, and targeted analyses to determine whether and how this network circuitry contributes to altered FC uniqueness in MDD.

5. Conclusions

Our findings demonstrate that FC uniqueness index is reproducible and clinically relevant. We observed high fingerprinting accuracy across the whole brain and within the default mode and frontoparietal networks in both HC and MDD patients. Notably, MDD patients exhibited significantly lower FC uniqueness scores than HC at the whole brain level and sensorimotor networks. We also revealed that greater depression severity was inversely associated with FC uniqueness, highlighting the potential of FC uniqueness index as a neurobiological marker for clinical status in MDD. Finally, FC uniqueness analysis may serve as a robust and reliable method to reconcile the contradictory findings within a single neurobiological phenotype in brain functional connectivity studies.

CRedit authorship contribution statement

Siti Nurul Zhahara: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yusuke Sudo:** Writing – review & editing, Software, Methodology. **Kohei Kurita:** Writing – review & editing, Software, Methodology, Funding acquisition. **Eri Itai:** Resources, Investigation, Data curation. **Toshiharu Kamishikiryo:** Resources, Data curation. **Hitomi Kitagawa:** Resources, Data curation. **Tokiko Yoshida:** Resources, Data curation. **Junbing He:** Resources, Investigation, Funding acquisition, Data curation. **Rio Kamashita:** Resources, Investigation, Data curation. **Yuko Isobe:** Resources, Investigation, Data curation. **Yuki Ikemizu:** Writing – review & editing, Software, Methodology. **Koji Matsumoto:** Resources, Investigation, Data curation. **Go Okada:** Supervision, Resources, Funding acquisition, Data curation. **Eiji Shimizu:** Supervision, Resources, Funding acquisition, Data curation. **Yoshiyuki Hirano:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization.

Statement of ethics

Ethical approval for the study was obtained from the Research Ethics Committee of the Graduate School of Medicine, Chiba University (M10545) and from the Hiroshima University Ethical Committee (No. E-172). The study was conducted after sufficient explanation had been carried out and written informed consent was obtained from all participants. Methods employed in this study were performed in accordance with relevant guidelines and regulations.

Funding sources

This work was supported by the AMED Brain/MINDS Beyond Program (Grant Number: JP18dm0307002 and JP24wm0625204), JSPS KAKENHI (Grant Numbers: JP19K03309, JP21K03084, JP23K22361, JP24K21493, JP25K00879, JP25K06842, and JP25H01085).

Declaration of competing interest

The authors declare no competing interest.

Acknowledgements

The authors wish to thank Saori C Tanaka PhD at ATR and Shinsuke Koike MD, PhD at the University of Tokyo for their generous support. We also thank Dr. Kiagus Aufa Ibrahim at Chiba University Graduate School of Science and Engineering for his valuable help. We gratefully acknowledge all participants in this study from Brain/Minds Beyond Human MRI Project, Hiroshima University and Research Center for Child Mental Development, Chiba University.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jad.2025.121073>.

Data availability

Data and codes supporting this article are available to interested researchers from the corresponding author upon reasonable requests.

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