NeuroImage: Clinical 52 (2026) 104073

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Depression: higher temporal variability of the functional connectivity of the ventromedial prefrontal cortex and hippocampal system

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ARTICLE INFO

Keywords:
Major depressive disorder
Ventromedial prefrontal cortex
Orbitofrontal cortex
Anterior cingulate cortex
Functional connectivity
HCP-MMP
hippocampus

ABSTRACT

It is important to understand the brain differences found in depression in the first episode untreated state, to ensure that differences related to depression and not to the treatments or long-term effects of being depressed are identified. Resting state functional connectivity was measured in 172 patients with not yet treated first-episode major depressive disorder (MDD) with a mean age of 22 years, and 237 healthy controls (HC), using the Human Connectome Project Multimodal Parcellation atlas. Higher temporal variability of resting state functional connectivity was found in depression of ventromedial prefrontal cortex (vmPFC) and medial orbitofrontal cortex regions including 10r, 10v and OFC implicated in reward, and the medial temporal lobe / hippocampal memory system, and for some lateral orbitofrontal cortex regions, in the right hemisphere. These functional differences in depression were found with only two significant differences between the MDD patients and the controls in the volumes of cortical regions, and no significant differences in the weighted streamline numbers between cortical regions measured with diffusion tractography, so functional measures of cortical function are more revealing in this first-episode cohort about brain differences in depression than anatomical differences. The results greatly extend by use of a young first-episode cohort not yet receiving medication our understanding of how a ventromedial prefrontal cortex (vmPFC) reward-related region with major connectivity with orbitofrontal cortex emotion systems and hippocampal memory systems have increased temporal variability and reduced stability in depression, and have implications for treatment, including that this vmPFC reward system should be treated.

1. Introduction

Major depressive disorder (MDD) is a prevalent and debilitating psychiatric disorder associated with high rates of suicide and significant family and social burdens (Hamilton et al., 2013; The Lancet Global, 2020; Xiao et al., 2025). MDD is a heterogeneous disease that typically is accompanied by symptoms such as anhedonia (i.e., amotivation and loss of interest/pleasure); depressed mood (i.e., feelings of sadness); rumination, diminished concentration (i.e., deficits in attention and memory); thoughts of death/suicide; unpleasant bodily feelings including somatosensory problems of discomfort, loss of energy, and fatigability; and memory problems (Johnson et al., 2024; Xu et al.,

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https://doi.org/10.1016/j.nicl.2026.104073
Received 5 July 2026; Received in revised form 7 September 2026; Accepted 27 September 2026
Available online 1 October 2026
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2025). To pave the way for treatment, there have been many investigations of brain differences in depression including of functional connectivity (Du et al., 2026; Lynch et al., 2024; Rolls, 2023b; Rolls et al., 2020; Tozzi et al., 2024; Xia et al., 2022; Yan et al., 2019; Yang et al., 2021; Yuan et al., 2020; Zhang et al., 2024a; Zhang et al., 2024b), and of structure e.g. volume (Chen et al., 2023; Schmaal et al., 2020). However, it is important to measure these differences in untreated patients because treatment with drugs can affect functional connectivity; and in first-episode young patients to ensure that years of multi-episode depression and the associated problems do not contribute to the differences found (Rolls et al., 2020).

The aim of the present study was therefore to measure functional and structural differences in the brains of young first-episode as yet untreated patients with MDD compared to controls. The mean age of the new patient cohort investigated here was 22 years, and was chosen in part because the 20s is an important time for development of the reward system (Sowell et al., 1999) which is related to emotion and depression (Rolls, 2023b; Rolls et al., 2020), and age 20.5 is the peak onset age of mood disorders including depression (Solmi et al., 2022). The functional differences measured here were in the temporal variability of the functional connectivity, which measures how the functional connectivity of a brain region with other brain regions alters across different time windows, which may reflect the dynamical reconfiguration of a brain region into different functional modules at different times (Sun et al., 2019; Zhang et al., 2016). Differences in the temporal variability of functional connectivity have been found to be related to creativity (Sun et al., 2019) and for particular cortical regions to mental disorders such as ADHD and schizophrenia (Rolls et al., 2021; Zhang et al., 2016). Previous studies on the temporal variability of functional connectivity in depression have found some increases, for example of a medial prefrontal cortex seed region with the insula (Kaiser et al., 2016), and of the default mode network (Long et al., 2020; Xie et al., 2026). The current investigation adds to previous research by use of a large young first-episode untreated group, by comparing differences in the temporal variability of functional connectivity with structural differences in the same cohort, and by use of the Human Connectome Project Multimodal Parcellation (Glasser et al., 2016) in which many cortical regions have known functions and connectivity as described below. Increased temporal variability of a cortical region may be interpreted as not being stably locked to other cortical regions and across time, reflecting weaker influences on other cortical regions and instability across time. The structural differences measured were the volumes of cortical regions, the numbers of streamlines measured with diffusion tractography between cortical regions, and fractional anisotropy.

It is emphasized that the temporal variability of the functional connectivity is a very different measure to the functional connectivity. The functional connectivity is a static measure for the mean connectivity between each pair of cortical regions, in a 180 × 180 symmetric matrix for each of the left and right hemispheres with the parcellation utilized here. (The functional connectivity is measured as the mean correlation across the whole of the timeseries of the BOLD signals between each pair of cortical regions.) In contrast, the temporal variability of the functional connectivity measure defined here is a dynamical measure of the variability across time of the functional connectivity for each of the 180 cortical regions, in a 180 element vector for each hemisphere given the 180 cortical regions in each hemisphere in the parcellation described here. The dynamic measure thus can have a very different interpretation and utility to the static measure, with the dynamic measure for example relating to how unstable the activity of a brain region is across time, and any corresponding associated symptomatology. The dynamic measure could in principle be unrelated to the static measure, but depending on the dynamical architecture of the brain, a change in the dynamical measure could be produced by a difference in the static measure. In attractor networks, which are a key feature of the neocortex (Rolls, 2026a), a reduction of the connection strength between the excitatory neurons does produce a decrease in stability, which means more temporal variability (Loh et al., 2007a; Loh et al., 2007b; Rolls, 2026a; Rolls and Deco, 2010). In this investigation we examine this issue of whether the dynamic measure can be related in part to a change in the static measure.

An additional key feature of the design of the present study with a new cohort of more than 400 participants is the use of the Human Connectome Project Multimodal Parcellation atlas (HCP-MMP) (Glasser et al., 2016), for this atlas defines each cortical region by several measures, including cortical myelin and thickness, functional connectivity, and functional magnetic resonance imaging (fMRI) activations in 7 tasks, so provides a very useful framework with which to understand human cortical function in health and disease, with much evidence of the connectivity between cortical regions in HCP participants now available (Rolls, 2023a, 2024, 2026a; Rolls et al., 2022a, 2023a, 2023b; Rolls et al., 2022b, 2022c, 2023c, 2023d, 2024a; Rolls et al., 2023e; Rolls et al., 2023f; Rolls et al., 2023g; Rolls et al., 2024c). The cortical regions in this parcellation are shown in Fig. 4, and the abbreviations are provided in Table S1. A further key feature of the present design is focus on brain systems known to be involved in emotion such as the orbitofrontal cortex (OFC), and the vmPFC region which connects the OFC to the hippocampal memory system (Rolls et al., 2022c). The medial orbitofrontal cortex is involved in emotion in that it is activated by all rewarding stimuli (which produce positive emotion and mood) (Grabenhorst and Rolls, 2011; Rolls, 2018, 2023b), and has been shown in depression to have lower functional connectivity (Cheng et al., 2016; Rolls et al., 2020), and lower activation by rewarding stimuli in individuals with depressive symptoms (Xie et al., 2021). The lateral orbitofrontal cortex is involved in emotion in that it is activated by punishing and non-rewarded stimuli (which produce negative emotion) (Grabenhorst and Rolls, 2011; Rolls, 2018, 2023b), and has been shown in depression to have higher functional connectivity (Cheng et al., 2016; Rolls et al., 2020), and higher activation by non-reward stimuli in individuals with depressive symptoms (Xie et al., 2021).

2. Methods

2.1. Participants

185 patients with major depressive disorder (MDD) and 240 healthy controls (HC) were recruited from the Second Xiangya Hospital of Central South University, China. Diagnoses of MDD were made using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), based on the Structured Clinical Interview for DSM-5 Disorders (SCID-5) (APA, 2022) and confirmed by two psychiatrists at or above the attending physician level. Depression severity and symptom profiles were assessed using the 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1960). All patients were drug-naïve at recruitment and during the neuroimaging. 240 HCs were recruited from the local community. These participants were matched with the MDD group in terms of sex and age. Demographic information is summarized in Table 1. This study used data from a multicenter cohort of patients with MDD, the Zhangjiang International Brain Bank (ZIB)-MDD cohort (https://zib.fudan.edu.cn/). The data collection was approved by the

Table 1
Population information.

Diagnosis	MDD (n = 172)		HC (n = 237)		Test	
	Mean	SD	Mean	SD	t	p
Age	21.83	6.12	21.33	3.6	1.03	0.30
Mean FD	0.08	0.04	0.08	0.04	0.04	0.97
Education	3.65	0.71	4.15	0.45	−8.70	<0.01
HAMD	22.85	4.71	–	–	–	–
	N	%	N	%	χ^2	P
Female	127	73.84	176	74.26	0.01	0.92

(An education score of 3 is high school, and of 4 is university.)

corresponding ethics committee (ClinicalTrials.gov identifier: the ZIB-MDD cohort (ChiCTR2000031931)). All participants provided written informed consent after information on the research procedures had been provided by the study team.

Further details follow. Recruitment criteria for the outpatients included first-episode major depressive disorder; to have not received antidepressant treatment; to be aged 16–46 years; HAMD-17 ≥ 17; IQ $>$ 70; $>$9 years of education; and Han Chinese ethnicity. Major alternative psychiatric diagnoses, including bipolar disorder, were exclusionary. Anxiety comorbidity, however, was very common in this cohort, occurring in more than 90% of the patients. No illness-duration variable is available in the current dataset, because all patients were first-episode and drug-naïve. The age range for the MDD group was 16–46 years, and for the HC group was 17–42 years, with further details in Table 1. The 21-item Beck Depression Inventory (Beck et al., 1961) score was 31.6 $\pm$ 8.9 (mean $\pm$ sd) for the MDD group.

2.2. Image acquisition and preprocessing

The participants were scanned on a SIEMENS MAGNETOM Skyra scanner with 32-channel head coil. High-resolution T1-weighted structural images were acquired using a 3D MPRAGE sequence with a repetition time (TR) of 3000 ms, an echo time (TE) of 2.14 ms, a flip angle (FA) of 9°, a field of view (FOV) of 256 $\times$ 256 mm^2, and a voxel size of 0.8 $\times$ 0.8 $\times$ 0.8 mm^3. Resting state functional connectivity data were collected with a TR of 2500 ms, a TE of 30 ms, a FA of 77°, a FOV of 220 $\times$ 220 mm^2, and a voxel size of 3.4 $\times$ 3.4 $\times$ 3.4 mm^3 for 8 min and 29 s. The scanning instructions were not to think about anything with a specific theme, and to keep the eyes open, with a fixation cross on the screen for participants to look at. Foam padding was used to minimize head motion during scanning. Data preprocessing was performed using an in-house MATLAB-based package that integrates FSL, AFNI, and the BrainWavelet toolbox that is available (https://github.com/weikanggong/Resting-state-fMRI-preprocessing). This preprocessing pipeline includes brain extraction, slice timing correction, motion correction, spatial smoothing (6 mm FWHM), wavelet despiking, regression of white matter, CSF, and motion parameters, temporal band-pass filtering (0.01–0.08 Hz), and registration to individual T1 images followed by normalization to 3 mm standard space. Framewise displacement (FD) was calculated to evaluate head motion, and scans with mean FD $>$ 0.3 mm were excluded, leaving 172 MDD and 237 HC with data for temporal variability analysis.

The fMRI time series were analyzed with the global signal retained (Cheng et al., 2015; Cheng et al., 2016) (see Supplementary Material section S6). ROI-level time series were derived using the HCP-MMP atlas (Glasser et al., 2016) in its extended version that can be used if volumetric rather than surface-based data are available (HCPex) (Huang et al., 2022), obtained by averaging voxel-wise signals within each parcellated region. The ordering of the brain regions in this atlas (Huang et al., 2022) is shown in Table S1, and coronal slices to show the locations of the 360 cortical regions are shown in Fig. S1. The locations of these cortical regions are shown in Fig. 4 on a view of the human brain with the sulci unfolded, and in Fig. S1–5 with the sulci folded as the human brain is normally viewed.

2.3. Temporal variability of the functional connectivity profile of a brain region

The temporal variability of a brain region was obtained by correlating the functional connectivity (FC) profile of a brain region across different time windows, which reflects the dynamical reconfiguration of a brain region into distinct functional modules at different times (Zhang et al., 2016). To characterize the temporal variability of the functional connectivity of a given HCPex brain region, we first segmented all BOLD signals into n non-overlapping windows with length l. The whole-brain FC network F_i (an m*m matrix, with $m = 180$ nodes in each hemisphere) in the ith time window was then constructed, with the Pearson correlation being the measure of FC. The FC profile of region k at time window i is denoted by F_i (k,:) (shortened as $F_{i,k}$), which is an m-dimensional vector that represents all the functional connections of region k. The variability of a region k is defined as:

$$V_k = 1 - \overline{corrcoef\left(F_{i,k}, F_{j,k}\right)}\ i,j = 1,2,3,\ldots,n, i \neq j.$$

We calculated V_k at a number of different window lengths (l = equal to 20, 25, … 40 TR) and confirmed that the results presented for a window length of 35 TR are representative of those at other window lengths. The reliability of the estimate of V_k was shown to be high (r $\geq$0.915) as shown by a leave-one-out analysis for the time windows as reported in the Supplementary Material section S3. The temporal variability of the functional connectivity key results were also confirmed at the longer window length of 40 TR as reported in the Supplementary Material section S4.

2.4. Voxel-based morphometry analysis

VBM from the SPM Toolbox (http://www.fil.ion.ucl.ac.uk/spm/) was used for the processing. The volume of each cortical region in the left and the right hemisphere in the HCPex atlas (Huang et al., 2022) was extracted for each individual. A total of 421 participants (HC:240; MDD:181) had volumetric data available. After applying QC criteria in the VBM analysis, retaining only scans rated better by VBM than C− (Gaser et al., 2024), 13 participants were excluded. The final sample comprised 408 participants (HC:235; MDD:173). Differences between the MDD and Control group were assessed with a linear regression analysis with the covariates regressed out being age, sex, education, and TIV (total intracranial volume, which was not statistically different between the groups).

2.5. Diffusion tractography for streamline number and fractional anisotropy

Diffusion-weighted images were obtained with the following parameters: repetition time (TR) = 9400 ms; echo time (TE) = 89.0 ms; field of view (FOV) = 256 $\times$ 256 mm^2; matrix size = 122 $\times$ 122; slice thickness = 2.0 mm; slice number = 70; and b-values of 0 and 1000 s/mm^2, with details in the Supplementary Material.

A Multi-Shell Multi-Tissue Constrained Spherical Deconvolution (MSMT-CSD) combined with anatomically constrained tractography (ACT) was performed to reconstruct fibre orientation distribution (FOD) using the iFOD2 method (Hsu et al., 2023). A dynamic seeding algorithm was employed, generating 20 million streamlines (maximum tract length = 250 mm, minimal tract length = 5 mm, FOD amplitude = 0.05, curve angle = 45°) (Smith et al., 2015; Tournier et al., 2010). The registered 5tt image was used as prior biological information to ensure that the streamlines terminated at the GM-WM interface (Smith et al., 2012). To improve the estimation of structural connection density and to reduce false-positive streamlines, the spherical-deconvolution informed filtering of tractography (SIFT) was then applied, resulting in 2 million streamlines per participant (Smith et al., 2013). Further details are in the Supplementary Material, including that no differences in fractional anisotropy were found.

For the DTI dataset, a total of 434 participants had diffusion data available with both AP and PA directions and successfully completed preprocessing. After applying a mean head motion threshold of 2 mm, 20 subjects were excluded, leaving 414 subjects in total (HC: 235; MDD: 179). The HCPex parcellation (Huang et al., 2022) was used.

2.6. Statistical analysis

Regression analyses with a general linear model were used to test

whether cortical divisions and individual cortical regions had different temporal variability of functional connectivity in major depressive disorder, with age, sex, education and meanFD regressed out as covariates of no interest. The resulting t values for the comparisons had 403 degrees of freedom, given that there were 172 individuals in the MDD group, and 237 individuals in the HC group, and that there were 6 estimated parameters. Correction for multiple comparison was made using FDR (Benjamini and Hochberg, 1995), based on the 22 cortical divisions in each hemisphere. Where significant differences were found at the cortical division level after FDR correction for multiple comparisons, follow up tests were performed to test within divisions with significant differences after FDR correction which individual cortical regions within such divisions had significant differences. As set out in the Introduction, the medial OFC has connectivity via the vmPFC with the hippocampal memory system, and the functional connectivity between the medial OFC and hippocampal system is lower in depression, so the preplanned focus was on the temporal variability of FC between MDD and controls for key regions within these systems. In that context, the following three sets of cortical regions were defined for further statistical analysis, and exact p values are provided for these three comparisons. Composite 1 for emotion and depression: 10r, 10v, p32, OFC (Rolls, 2023b; Rolls et al., 2026a; Rolls et al., 2022c). Composite 2 for ventromedial visual cortical pathway cortical regions providing spatial inputs to the hippocampal memory system VMV1, VMV2, VMV3, VVC, PHA1, PHA2, PHA3 (Rolls, 2026a, 2026b; Rolls et al., 2023b; Rolls et al., 2024c). Composite 3 for cortical regions implicated in episodic memory: Hipp, EC, 31pd, 31 pv, 7 m (Ma et al., 2022; Rolls et al., 2023g). The results were analyzed separately for the two hemispheres, as the right hemisphere shows greater differences in functional connectivity in this cohort (Rolls et al., 2026a) and previous depression cohorts (Rolls et al., 2020).

To evaluate whether the higher temporal variability of the functional connectivity could be explained purely by regional signal quality differences, participant-specific temporal signal-to-noise ratio (tSNR) was calculated for all cortical regions, defined as the mean BOLD signal divided by the temporal standard deviation of the signal. Regional tSNR values were compared between MDD and HC groups using linear models controlling for age, sex, education, and mean FD. Because the primary temporal variability findings were based on cortical divisions, division-level mean tSNR was calculated by averaging ROI-level tSNR values within each cortical division. Division-level tSNR differences were similarly assessed between groups. No significant group differences in tSNR were observed in the key regions implicated by the temporal variability findings after FDR correction. Finally, ROI-level and division-level temporal variability analyses were repeated with ROI-level or division-level tSNR included as additional covariates to determine whether group differences in temporal variability remained after accounting for regional signal quality. Additional tests also confirmed that head motion variability differences did not account for the results that were found, as set out in Supplementary Material section S8.

Regression analyses with a general linear model were used to test whether the number of streamlines between all pairs of cortical regions in each hemisphere were different in major depressive disorder, with age, sex, education and meanFD regressed out as covariates of no interest. Correction for multiple comparison was made using FDR, based on the 180 cortical regions in each hemisphere.

3. Results

3.1. Higher temporal variability of the functional connectivity of the ventromedial prefrontal cortex, and hippocampal memory system, in major depressive disorder

Fig. 1 shows for reference the functional connectivity in the MDD

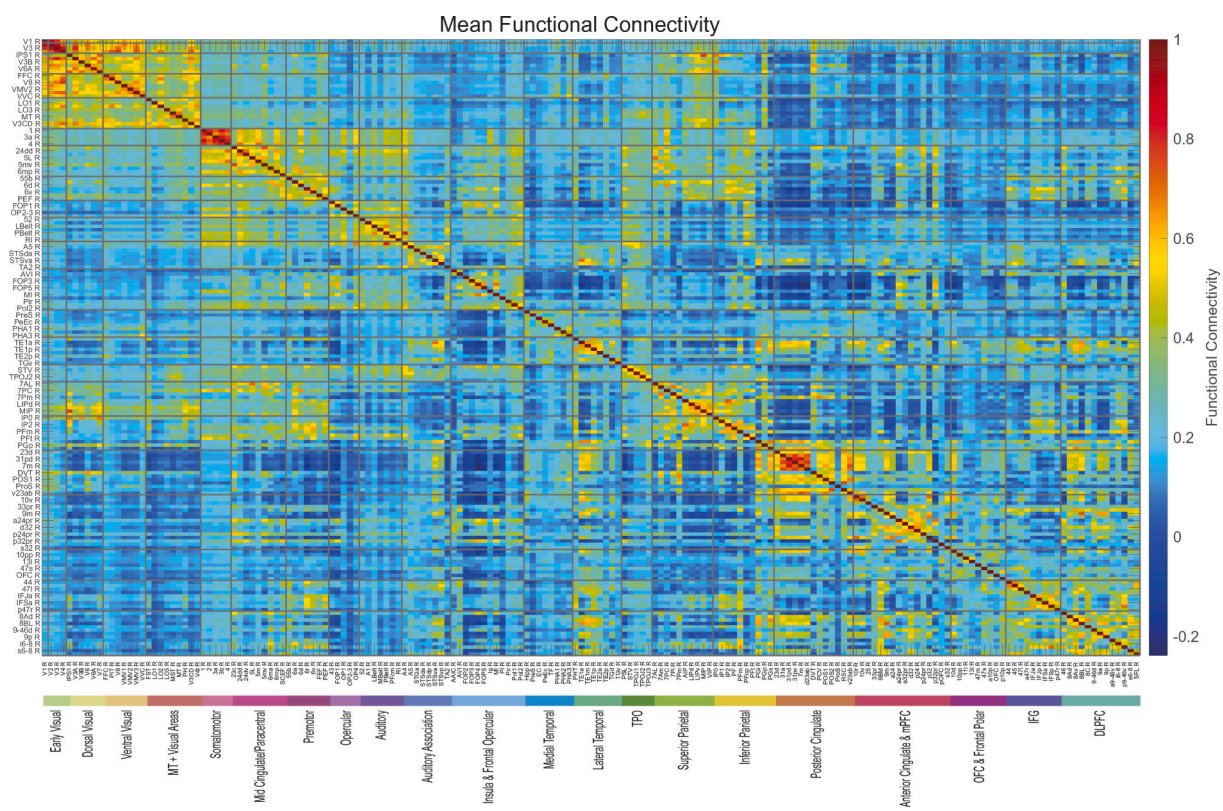

Fig. 1. Mean functional connectivity in the right hemisphere across the Major Depressive Disorder (MDD) group ($n = 172$) and the Control group ($n = 237$). The labels for the Human Connectome Project Multimodal Parcellation atlas (Glasser et al., 2016) are in the order for the extended version (Huang et al., 2022) and are provided in Table S1, as are the cortical division labels shown below. The horizontal and vertical black lines separate the divisions in the atlas (see Table S1).

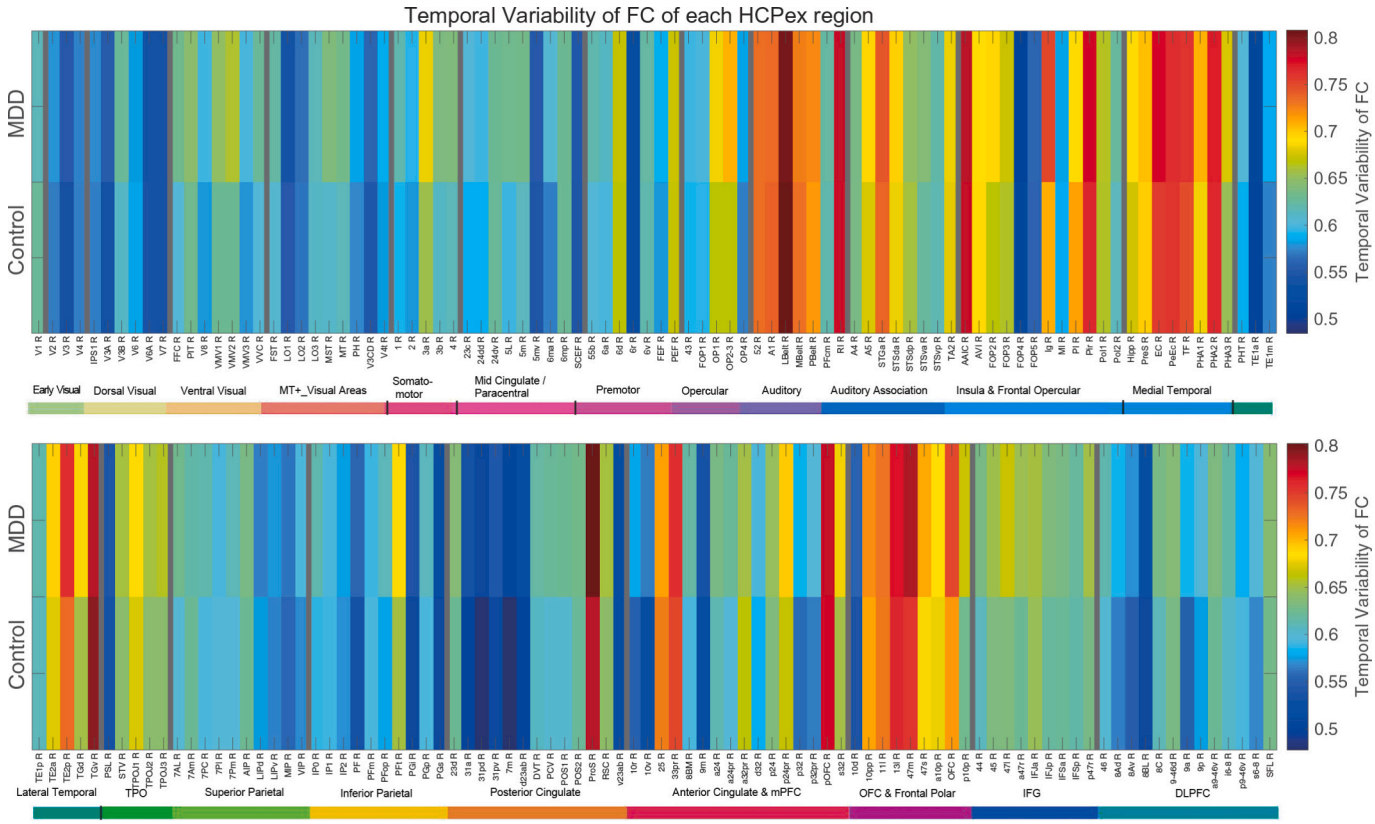

Fig. 2. Temporal variability of the functional connectivity in the right hemisphere for the Major Depressive Disorder (MDD) group ($n = 172$), and for the Control group ($n = 237$). The window length was 35 with a TR of 2.5 s and 200 volumes in the timeseries. The temporal variability of the functional connectivity for the first set of cortical regions in the HCPex atlas is shown in the top panel; and for the second set of regions in the lower panel. The labels of the regions in the HCPex atlas are provided in Table S1, and the cortical divisions in this atlas are named below. The vertical black lines separate the divisions in the HCP-MMP atlas. Significantly higher temporal variability of the functional connectivity for some cortical regions in MDD is described in the text.

group in the right hemisphere. Fig. 2 shows higher temporal variability of the functional connectivity in some cortical regions in the MDD group vs the control group. Statistical analyses showed that the following cortical divisions in the HCP-MMP atlas (see Table S1) have significantly higher temporal variability, with window length = 35 (fdr corrected for multiple comparisons $p < 0.05$) in the right hemisphere: Orbital_and_Polar_Frontal ($t = 2.49$, p_fdr < 0.05); Anterior_Cingulate_and_Medial_Prefrontal ($t = 2.54$, p_fdr < 0.05); Medial_Temporal ($t = 2.68$, p_fdr < 0.05); Inferior_Frontal ($t = 2.51$, p_fdr < 0.05); Inferior_Parietal ($t = 2.63$, p_fdr < 0.05); and Auditory_Association ($t = 3.03$, p_fdr < 0.05).

Having found statistically significantly higher temporal variability as just described in cortical divisions of particular relevance to emotion and depression, Orbital_and_Polar_Frontal, Anterior_Cingulate_and_Medial_Prefrontal, and Medial_Temporal (Rolls et al., 2020), we next investigated post hoc which cortical regions within these divisions had higher temporal variability, to narrow down some key regions.

First, some individual cortical regions had higher temporal variability of the functional connectivity in the right hemisphere in the MDD group. For the Orbital_and_Polar_Frontal, and Anterior_Cingulate_and_Medial_Prefrontal divisions, significantly higher temporal variability was found for: OFC ($t = 2.67, p = 0.008$); 10v ($t = 2.62$, df $= 403, p = 0.009$); 10r ($t = 2.05$, df $= 403$, $p = 0.04$); 47 l ($t = 3.41$, df $= 403, p = 0.0007$); 47 s ($t = 2.49$, df $= 403, p = 0.01$); and 47 m ($t = 2.42$, df $= 403$, $p = 0.02$). For the Medial Temporal Division (and related posterior cingulate cortex), the following cortical regions had higher temporal variability in the MDD group: EC ($t = 2.26$, df $= 403$, $p = 0.02$); 31 pv ($t = 2.19$, df $= 403$, $p = 0.03$).

Second, we planned post hoc comparisons for key sets of cortical regions within these divisions with known related functions. Significantly higher temporal variability in the MDD cohort was found for the group mean of a key group of cortical regions for emotion and depression (Rolls, 2023b; Rolls et al., 2026a; Rolls et al., 2022c): 10r, 10v, p32, OFC ($t = 2.97, p < 0.01$). Similar higher temporal variability in the MDD cohort was found for the group mean of cortical regions providing spatial inputs to the left hippocampal memory system (Rolls, 2026a, 2026b; Rolls et al., 2023b; Rolls et al., 2024c): VMV1, VMV2, VMV3, VVC, PHA1, PHA2, PHA3 ($t = 2.53$, $p = 0.01$). Similar higher temporal variability in the MDD cohort was found for the group mean of cortical regions implicated in episodic memory (Ma et al., 2022; Rolls et al., 2023g): Hipp, EC, 31pd, 31 pv, 7 m ($t = 2.84$, $p < 0.01$). An implication is that the functional connectivities of these vmPFC and medial temporal lobe memory-related cortical regions are less stable across time in first episode patients with major depressive disorder.

The temporal variability of the functional connectivity was found to be higher ($p = 0.009$) in the MDD group than the HC group for the Anterior Cingulate and Medial Prefrontal Division (which includes the ventromedial prefrontal cortex regions) using a phase-randomised surrogate-data comparison matched to each participant's static covariance, as shown in the Supplementary Material section 5. This indicates that the observed group difference in temporal variability exceeds what a stationary process with the same static FC produces. However, the temporal variability differences were generally reduced with this surrogate analysis, so that we do not argue that the higher temporal variability of the functional connectivity in the MDD group is independent of the static functional connectivity. However, as noted in the Introduction, a difference in the temporal variability of the functional connectivity as measured is of interest as it is a dynamic property of the brain even if it is related to some extent to the static functional connectivity.

To cast more light on the temporal variability of functional connectivity, Fig. 3 shows that there tends to be lower Temporal Variability of the functional connectivity as a function of higher mean functional

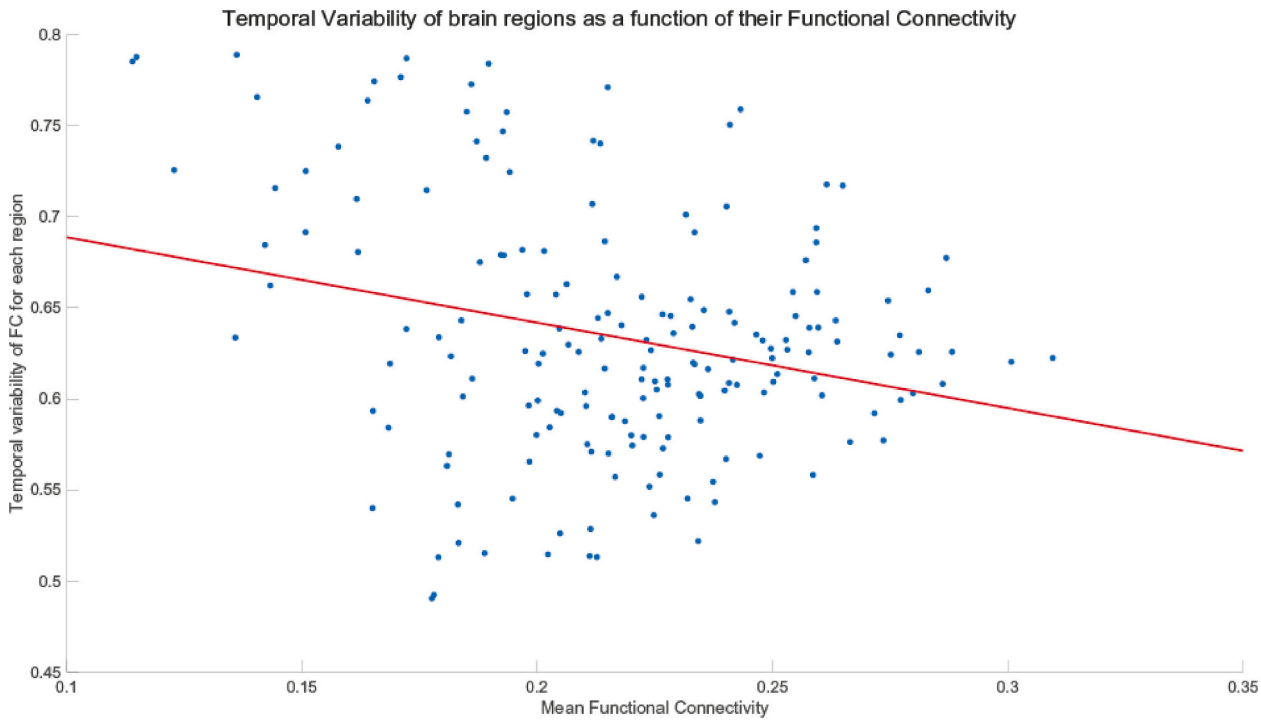

Fig. 3. Temporal variability of the BOLD signal as a function of the mean functional connectivity of each of the 180 cortical regions in the right hemisphere. The correlation was −0.26, $p = 0.0004$.

connectivity between each of the 180 cortical regions in the right hemisphere. The correlation was −0.26, $p = 0.0004$. An implication is that regions not locked to other cortical regions with strong functional connectivity tend to be free to wander more across time, that is, to be less stable.

To assess to what extent the higher temporal variabilities of the functional connectivities reported above for some cortical regions in MDD were independent of the static functional connectivity, the analyses described above were repeated with the static functional connectivity of each region regressed out as covariates of no interest. The directions of the MDD–HC differences in temporal variability were generally significant and consistent with the original findings, but the t values were lower. For example, for the Anterior Cingulate and Medial Prefrontal Division (which includes the ventromedial prefrontal cortex regions) $t = 2.32$ $p = 0.02$; for the Medial Temporal Division $t = 2.10$ $p < 0.04$; and for the Orbital and Frontal Polar Division $t = 2.14$ $p < 0.04$. The implication is that the differences in the temporal variability of the functional connectivity described here were partly but not completely related to the differences in static functional connectivity. Again, as noted above, a higher temporal variability of the functional connectivity as measured in MDD is of interest as it is a dynamic property of the brain even if it is related to some extent to the static functional connectivity.

When the SNR was regressed out of the analyses, the main effects of interest remained, with higher temporal variability of the functional connectivity in the MDD group found for the right Anterior Cingulate and Medial Prefrontal Division (which includes the ventromedial prefrontal cortex regions) $t = 2.51$ p_fdr = 0.05; for the Medial Temporal Division $t = 2.75$ p_fdr = 0.05; and for the Orbital and Frontal Polar Division $t = 2.48$ p_fdr = 0.05.

Given the somewhat lower educational attainment in the MDD group (Table 1) and the possibility that the educational difference may partly reflect consequences of illness in this young first-episode cohort, a sensitivity analysis was performed in which education was omitted from the covariate set. It is shown in Supplementary Material section S9 that the main findings on the higher temporal variability of the functional connectivity in the MDD group in key ventromedial prefrontal cortex and medial temporal lobe cortical areas were robust to exclusion of education as a covariate.

No significant correlations of the temporal variability of the functional connectivity with the symptoms were found, with the details in the Supplementary Material section S10. Correlations of the symptoms with the functional connectivity were found in this cohort, and are described elsewhere (Rolls et al., 2026a).

3.2. Volumetric analysis

Fig. 4 shows for all cortical regions the t value for the right hemisphere for volume differences as MDD – Controls. In contrast to the temporal variability of functional connectivity analysis, no significant differences between MDD and HC were found for any HCP-MMP division.

After FDR correction on the right 180 HCPex individual cortical regions, significantly smaller volume in MDD patients was found for R_VVC ($t = -4.09$, p_fdr < 0.05) and R_PSL ($t = -3.51$, p_fdr < 0.05). The VVC is a key region for object and for spatial inputs to reach the hippocampal memory system (Rolls et al., 2023b; Rolls et al., 2024b; Rolls and Turova, 2025). The PSL (Peri-Sylvian Language region) is a language-related region with effective connectivity with an auditory-dominated semantic network in the superior part of the anterior temporal lobe (Rolls et al., 2022a).

In addition the following left hemisphere vmPFC or hippocampal system regions showed smaller volumes, though not significant after fdr correction: PeEc ($t = -2.45$, df = 402, $p = 0.01$); 13l ($t = -2.40$, df = 409, $p = 0.02$. There was no significant difference in the volume of the hippocampus between MDD patients and HCs.

For the anterior cingulate cortical regions, we performed a group comparison for the averaged volume in the left and right hemispheres. This was not significant after FDR correction.

3.3. Diffusion tractography analysis

The numbers of streamlines between cortical regions were calculated

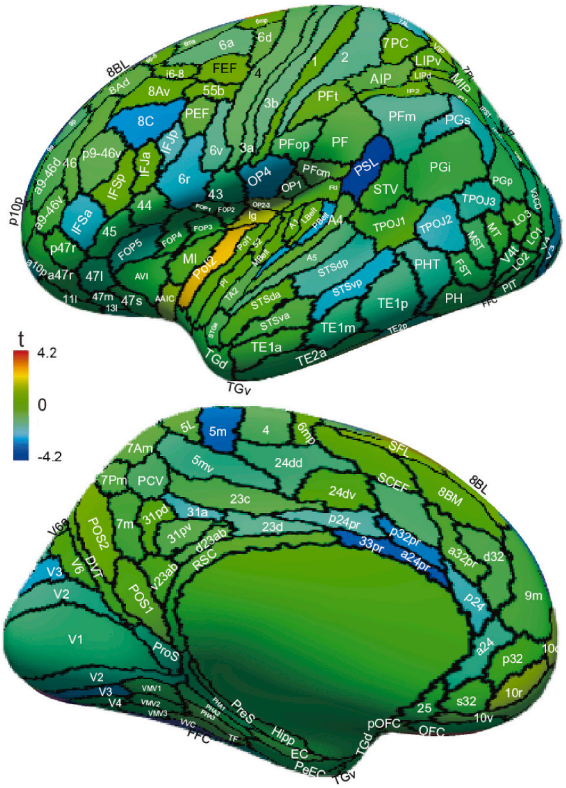

Fig. 4. Volumetric comparison of the volumes of each HCP-MMP cortical region in the right hemisphere with a t colorbar showing the difference MDD – Healthy Controls. The labels of the regions in the HCPex atlas are provided in Table S1.

separately for the 180 cortical regions in the right and left hemispheres for the reason provided in the Methods, with 175 MDD and 235 HC participants. To provide a validation that the analyses for this dataset were reasonable, the correlation between the streamline matrices in the Fudan healthy control streamline 180 × 180 matrix and the Human Connectome Project matrix (Rolls et al., 2026b) was found to be 0.98.

Fig. 5 shows for reference the numbers of streamlines in the MDD group for the right hemisphere.

Fig. 6 shows the t values of the differences in the number of streamlines in MDD – Controls for the right hemisphere. No cortical division or region or subcortical region showed a significant difference between MDD patients and controls in the *t*-test comparison of the numbers of streamlines in the MDD – the Healthy Control group, after applying FDR correction for the right or left hemisphere cortical regions, or for the 33 × 180 subcortical regions in each hemisphere. There were some differences that were significant without FDR correction, but these appeared to be randomly distributed across pairs of brain regions, and the sign of the difference also varied (see Fig. 6). (Of these uncorrected differences in the number of streamlines, 3031 were positive for MDD – HC, and 2270 were negative.)

The implication of what is shown in Fig. 6 (of no differences in the structural connectome after FDR correction) is that differences in the structural connectome, measured by the number of streamlines between cortical regions, are unlikely to contribute to the differences in the temporal variability of the functional connectivity described here between MDD patients and the controls. Further, the t values of the differences in the number of streamlines between MDD patients and controls (Fig. 6) were not correlated with the t values of the differences in the functional connectivity between MDD patients and controls ($r = -0.07$ across the 360 cortical regions). That provides more evidence that the non-significant structural differences between MDD and controls measured by the numbers of streamlines did not contribute to the functional neural differences between MDD and controls, whether measured by the temporal variability of the functional connectivity or by the functional connectivity itself. For comparison in the same cohort, the number of significant differences ($p < 0.05$ after FDR correction) for the functional connectivity for the same 180 × 180 cortical regions between the MDD and HC groups was 235 in the right hemisphere and 160 in the left hemisphere (Rolls et al., 2026a).

4. Discussion

In this large cohort of as yet untreated patients with first episode major depressive disorder with a mean age of 22 years, increased temporal variability of the functional connectivity was found in key cortical divisions (Orbital and Polar Frontal; Anterior Cingulate and Medial Prefrontal; and Medial Temporal, all significant after FDR correction for multiple comparisons), with key individual ventromedial prefrontal cortex / medial OFC regions: OFC, 10v, and 10r (Fig. 2). These results were more evident for the right hemisphere. Increased temporal variability of the functional connectivity was also found for the Medial Temporal cortex division, with key regions including the ventromedial visual (VMV1–3 and VVC) and medial parahippocampal (PHA1–3) regions that provide spatial scene inputs to the hippocampal memory system (Rolls, 2026b; Rolls et al., 2023b), and the hippocampus, entorhinal cortex and parts of the posterior cingulate cortex (31 pv and 31pd) involved in episodic memory (Rolls, 2023a; Rolls and Treves, 2024; Rolls et al., 2023g). The increased temporal variabilities of the functional connectivities of these vmPFC reward-related and hippocampal memory-related system can be interpreted as evidence for less stability of the functioning of these cortical regions in depression. A suggested implication is that happy memories, and happy prospective thinking, may be poorly maintained in depression given that these cortical regions are involved in reward value and memory including prospective memory (Rolls, 2022, 2023b). Consistent with this, there is reduced functional connectivity between these vmPFC regions and the hippocampal memory system in these first episode patients with major depressive disorder (Rolls et al., 2026a). Also consistent is the general relation of high temporal variability of the functional connectivity of a cortical region being somewhat associated with a lower mean functional connectivity of a cortical region with other cortical regions, as shown in Fig. 3. The divisions with significantly higher temporal variability of functional connectivity do include lateral orbitofrontal cortex regions, and indeed regions 47l, 47s, and 47m had higher temporal variability in depression in this first episode cohort, but in this cohort high functional connectivity of the lateral orbitofrontal cortex was not evident (Rolls et al., 2026a), so the result for the temporal variability of these lateral orbitofrontal cortex regions are not unexpected.

The higher temporal variability of the functional connectivity of reward-related vmPFC and hippocampus-related memory regions described here is a property of a cortical region, and is distinct from functional connectivity, which describes measures of correlations between pairs of cortical regions. The implication of these findings is therefore that these reward-related vmPFC and memory-related hippocampal system regions have less stability across time and are less related to other brain systems that fluctuate less, and so contribute to the lower stability of happy positive memories and prospective thinking about the future. An implication for treatment is that new treatments are needed that will in depression increase the stability of vmPFC and hippocampus-related memory regions. New treatments are needed in that typical antidepressant drugs such as selective serotonin reuptake inhibitors do not treat the reduced functional connectivity of medial orbitofrontal (and thereby related vmPFC) regions (Rolls et al., 2020). The research described here leads to the suggestion that reducing the temporal variability of these vmPFC and medial temporal regions may be another useful measure. These treatments might include pharmaceutical agents, or cognitive or behavior therapy, or electrical stimulation of the brain (Johnson et al., 2024; Rolls et al., 2020; Zhang et al., 2024a).

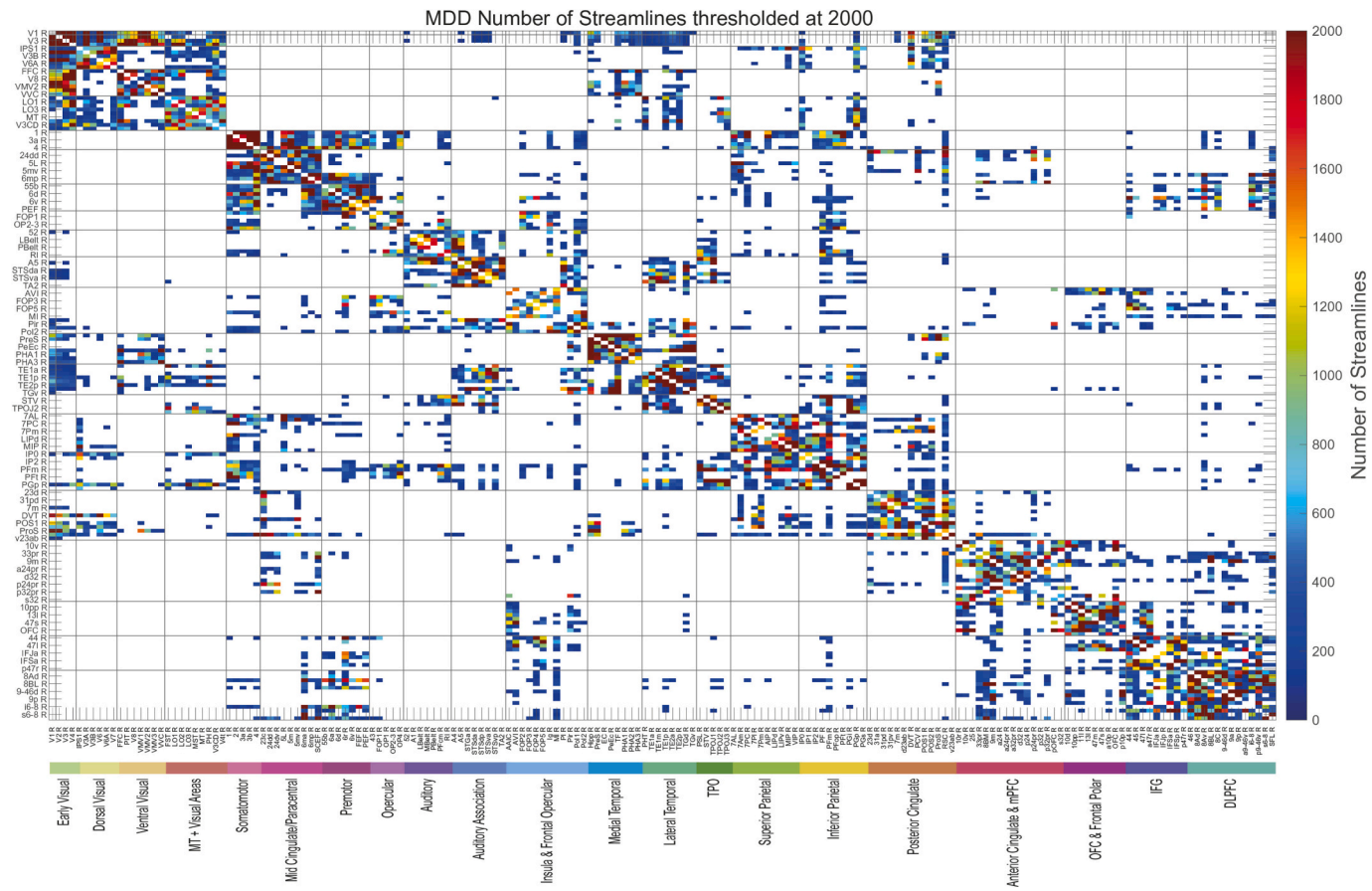

Fig. 5. The number of streamlines between all cortical regions in the right hemisphere for the Major Depressive Disorder (MDD, $n = 179$) group. The number of streamlines was thresholded at 100 to show the main connections. The maximum value was 11,100, found for early visual cortical regions, but the maximum value shown in the figure was limited at 2000 to show numbers or other regions more clearly. The labels of the regions in the HCPex atlas are provided in Table S1, and the cortical divisions in this atlas are named below.

The increased temporal variability of vmPFC and hippocampal memory systems described here, and the reduced functional connectivity between these systems (Rolls et al., 2026a), in this relatively young (age 22 years) first-episode group of people with major depressive disorders were found in the absence of major structural differences in the brain. (No differences between the depressed (MDD) and control (HC) groups were found in the structural connectome measured by the number of streamlines between cortical regions after FDR correction, whereas 395 differences in the functional connectivity combining the left and right hemispheres were found after FDR correction in the same cohort.) This is important, for although there are general relationships between structural measures and functional measures such as functional connectivity (Blanco et al., 2024; Fjell et al., 2017; Hermundstad et al., 2013), the differences in the temporal variability of FC described here and functional connectivity (Rolls et al., 2026a) between MDD and controls were not associated with structural differences. In fact, this is very reasonable, for functional connectivity and brain function can vary with task demands (e.g. visual tasks for faces, places, tools and body parts, and the resting state) in individuals in whom the structural connectivity is constant (Rolls et al., 2024b). For example, the volumetric analysis revealed little that was statistically significant, apart from a reduced volume of VVC and PSL. The VVC is a key region for object and for spatial inputs to reach the hippocampal memory system (Rolls et al., 2023b; Rolls et al., 2024b; Rolls and Turova, 2025), and its reduced volume in this cohort is consistent with some differences in the medial temporal lobe memory system that are indicated by increased temporal variability described here. Consistent with the rather few differences in volumetric measures in depression found in our first-episode untreated cohort, reduced hippocampal volume has been reported in recurrent, but not first episode, major depressive disorder, in the ENIGMA consortium (Schmaal et al., 2020), and in addition the low replicability in brain structural-magnetic-resonance-imaging maps for five psychiatric diagnoses has been noted (Alexander-Bloch and Raznahan, 2026). An implication of the results described here is that functional measures of the brain are more informative than structural measures about brain changes or differences that relate to first-episode depression, with use of the untreated state as described here important so that the differences found are not related to the treatment, but instead to the depression. The concept we propose is that functional changes, such as differences in functional connectivity, and the variability of functional connectivity described here, provide more useful information about the brain changes related to depression, because the functional changes are found in first episode MDD patients, but the volume differences as described here are less evident, and indeed volume differences of the hippocampus were not found by the ENIGMA consortium in ($N = 583$) first-episode patients (Schmaal et al., 2020). Further, we show here that there are no differences in the number of streamlines between cortical regions in untreated first episodic depression, providing further evidence that functional differences such as for example functional connectivity and its temporal variability may provide better evidence about the key brain systems related to depression itself. The structural differences that are found in patients with multi-episode longer term and pharmacologically treated depression (which includes the ENIGMA cohort (Schmaal et al., 2020) and other cohorts (Chen et al., 2023)) may reflect therefore not what is found in first-episode depression in this investigation, but could be related at least in part to the effects of many years of being depressed,

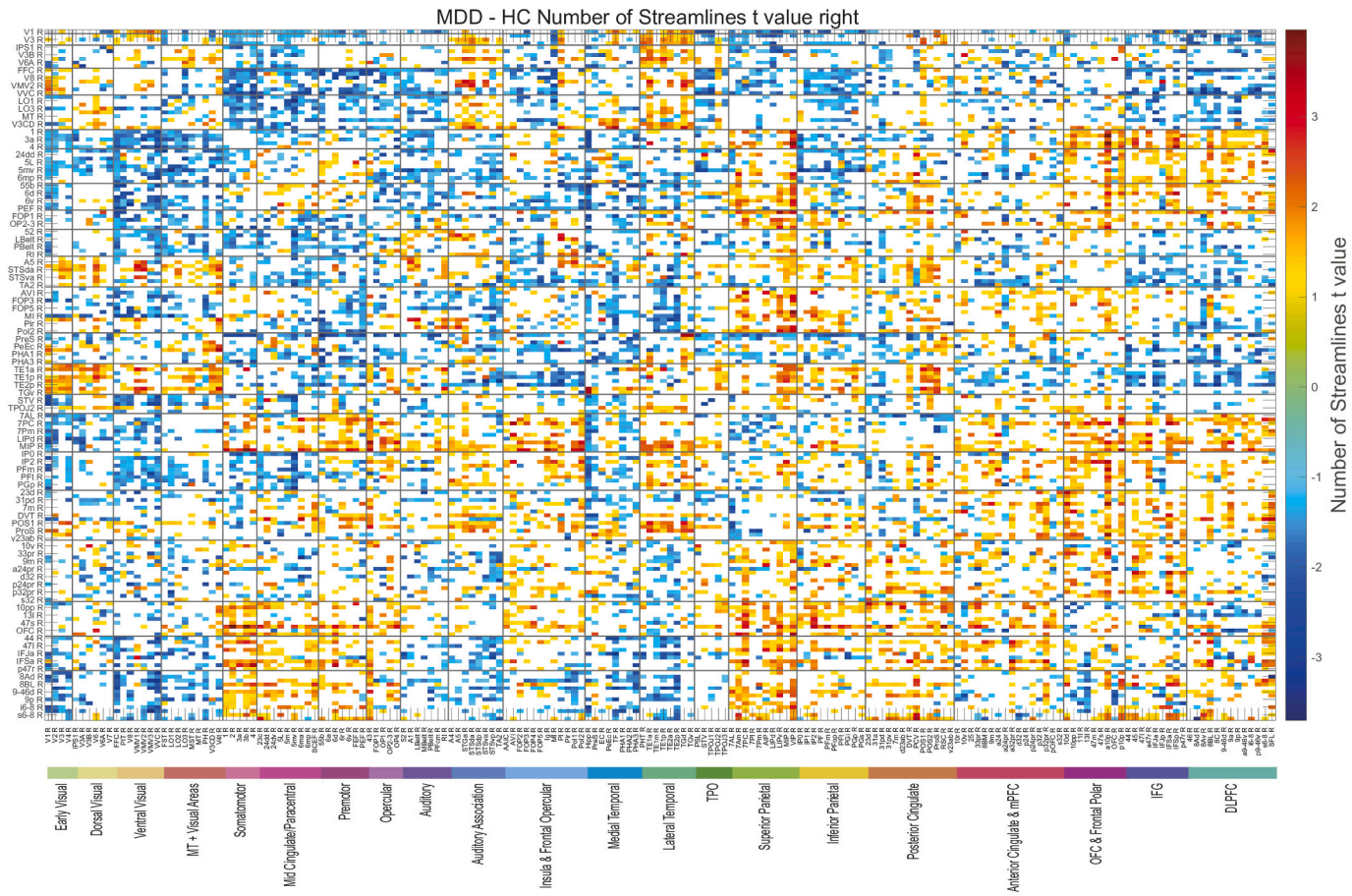

Fig. 6. The t-values for the difference in the number of streamlines between all cortical regions in the right hemisphere for the Major Depressive Disorder (MDD, $n = 179$) group minus the Healthy Control ($n = 235$) group. The threshold for a difference to be colored was set at $t = 1.0$.

or effects of treatment. This has very important implications for future research.

In conclusion, we have shown that the temporal variability of the Functional Connectivity of the reward-related vmPFC and the memory-related hippocampal memory system is higher in patients with MDD than controls. The vmPFC involvement is an important extension of earlier research (Rolls et al., 2020; Zhang et al., 2024a), and fits with this being close to a treatment site using deep brain stimulation (Johnson et al., 2024). The findings are very important we believe for understanding depression, for these reward and memory systems regions are implicated in depression by reduced functional connectivity between them (Rolls et al., 2026a; Rolls et al., 2020), and were obtained in this cohort not yet receiving treatment so are not due to drug effects, and were obtained in this young first episode group (age 22 years) so are not due to years of the effects of multiple episodes of being depressed. Moreover, the cortical regions involved were delineated well with the HCP-MMP atlas (Glasser et al., 2016). Another key and potentially very important conclusion is that these functional differences were found in the absence of structural connectivity differences between MDD and controls, emphasizing the importance of measures such as functional connectivity and its variability in characterizing brain systems with differences related to depression itself (rather than its long-term effects) when seeking to understand and treat depression.

Ethical permission

The present dataset forms part of a multicenter cohort, the Zhangjiang International Brain Bank (ZIB)-MDD cohort.

(https://zib.fudan.edu.cn/detail?categoryId&queueId=35&categoryName&queueIndexId=3001).

The data collection was approved by its corresponding ethics committee (ClinicalTrials.gov identifier: The ZIB-MDD cohort (ChiCTR2000031931)). All participants provided written informed consent after information on the research procedures had been provided by the study team, as provided for in the Declaration of Helsinki.

Author contribution

ETR designed and led the research, performed many of the analyses, produced most of the Figures, and wrote the paper. YC performed the preprocessing of the data, performed the statistical analyses, and contributed to writing the paper. YY and C-CH prepared the protocol for the diffusion tractography analyses, and its description. QL and JF provided funding. TZ is a member of the ZIB consortium, the other members of which are JF, QL and Xiang Wang, and which designed the data collection. Xiang Wang was responsible for the data collection. WC and QL provided statistical advice. All authors provided comments on the paper, and all authors approved submission.

Studies in Human

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place.

This study was approved by the ClinicalTrials.gov identifier: The ZIB-MDD cohort.

(Approval No. ChiCTR2000031931)

CRediT authorship contribution statement

Yinhan Chen: Writing – review & editing, Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Edmund T. Rolls:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yanlin Yu:** Methodology. **Chu-Chung Huang:** Writing – review & editing, Visualization, Supervision, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Qiang Luo:** Writing – review & editing, Methodology, Data curation. **Wei Cheng:** Formal analysis. **Xiang Wang:** Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Tianhong Zhang:** Methodology. **Jianfeng Feng:** Resources, Funding acquisition, Conceptualization.

Informed consent and patient details

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

Code availability

Data preprocessing was performed using an in-house MATLAB-based package that integrates FSL, AFNI, and the BrainWavelet toolbox that is available (https://github.com/weikanggong/Resting-state-fMRI-preprocessing). The iDIO toolbox is available at https://github.com/iDIO4dMRI/iDIO.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

2025 Yangtze River Delta Science and Technology Innovation Community Joint Research (Basic Research) Project (NO. 2025CSJZN01700 to QL). Shanghai Municipal Science and Technology Major Project (No. 2018SHZDZX01 to JF). 111 Project of the Ministry of Education of the People's Republic of China (No. B18015 to JF). QL is partially supported by grants from the National Natural Science Foundation of China (32441107 and 82272079), and the Program of Shanghai Academic Research Leader (23XD1423400). The funders took no part in the design of the research or in publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2026.104073.

Data availability

Data will be made available on request.

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