Altered Dynamic Functional Connectivity of the Frontoparietal Network in Major Depressive Disorder: Evidence for Hypoconnectivity and Reduced State Transitions

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Abstract

Major depressive disorder (MDD) is associated with cognitive inflexibility and impaired executive function, yet the underlying network-level dynamics related to connectivity patterns remain poorly characterized. Prior research on the frontoparietal control network (FPN), a hub of cognitive regulation, has yielded inconsistent findings, often relying on static connectivity models that overlook the brain's temporally evolving architecture. Here, we leverage resting-state fMRI (rs-fMRI) data from a large, harmonized multisite dataset (n = 887; 442 MDD, 445 controls) to examine the dynamic functional connectivity (dFC) of the FPN. Using a sliding-window approach and k-means clustering, we identified three recurring FPN connectivity states. Compared to controls, patients with MDD spent significantly more time in a hypoconnected state, exhibited prolonged dwell within this configuration, and showed a global reduction in the number of transitions between network states, reflecting diminished neural flexibility. Critically, transitions between hypoconnected and hyperconnected states were selectively impaired, suggesting disrupted efficient access to functionally distinct network modes. These results demonstrate that MDD is characterized not only by altered connectivity strength but by a constricted repertoire of dynamic brain states. This temporal dysregulation of the FPN may constitute a network-level mechanism underlying cognitive inflexibility in depression, highlighting dFC as a promising modality for mechanistic insight and translational applications.

Keywords: Major Depressive Disorder (MDD), Dynamic Functional Connectivity (dFC), Frontoparietal Network (FPN), Resting-State fMRI (rs-fMRI), Neural Flexibility, Cognitive Control

1 Introduction

Major depressive disorder (MDD) is a prevalent and disabling psychiatric condition, affecting over 270 million people worldwide and representing the leading cause of non-fatal health loss, with more than 37 million years lived with disability (YLDs) in 2019 (Yan et al., 2024). Clinically, MDD combines affective symptoms such as persistent sadness and anhedonia with cognitive deficits in executive function, attention, inhibitory control, and emotion regulation. These disturbances contribute to relapse risk, chronic impairment, and poor functional outcomes (Buckner et al., 2008; Joormann & Vanderlind, 2014; Tian et al., 2016; Lundberg et al., 2022; Li et al., 2022). Diagnosis, however, still relies on symptom-based classifications such as the DSM, which lack biological specificity, underscoring the need for neurobiological markers that provide objective, quantifiable indices of illness status, severity, and trajectory (Young et al., 2016).

Given the need for objective biomarkers, resting-state functional magnetic resonance imaging (rs-fMRI) has emerged as an approach for investigating the neural substrates of MDD. Analyses of intrinsic functional connectivity within rs-fMRI have revealed that MDD reflects disrupted communication across large-scale brain networks, notably the default mode network (DMN), salience network (SN), and frontoparietal control network (FPN) that may underlie the disorder's cognitive and affective disturbances (Fu-Cai, 2024; Dichter et al., 2015; Ma et al., 2024; Zhang et al., 2016; Demirtaş et al., 2016; Wei et al., 2013; Kaiser et al., 2015; Chen et al., 2019; Balzekas et al., 2018; Zhang et al., 2018).

The frontoparietal control network (FPN) is a large-scale system anchored in the lateral prefrontal and posterior parietal cortices, serving as a flexible hub for coordinating distributed brain activity (Kaiser et al., 2015; Cao et al., 2021). Through its central role in top-down cognitive control, attentional allocation, and emotion regulation, the FPN integrates cognitive and affective processes essential for adaptive behavior (Wu et al., 2024; Lee, 2024; Buchanan et al., 2014). In MDD, altered FPN connectivity has been consistently associated with impairments in executive functioning, inhibitory control, and attentional regulation (Yu et al., 2019; Schultz et al., 2017; Kaiser et al., 2015).

Empirical evidence further highlights the behavioral relevance of FPN dysfunction in depression. Aberrant connectivity within the network has been linked to maladaptive self-referential processing and rumination, reinforcing negative affect and cognitive rigidity (Mısır et al., 2023; Wagner et al., 2016). These findings position the FPN as a key substrate through which large-scale network dysfunction contributes to the cognitive and affective disturbances of depression (Tan et al., 2020; Yang et al., 2024). Collectively, these observations converge to establish the FPN as a central neural substrate of the cognitive-affective phenotype of MDD and a promising target for biomarker development.

Despite converging evidence for FPN dysfunction in MDD, the precise directionality of within-network alterations remains inconsistent. Several influential reports have documented hypoconnectivity within the FPN, suggesting impaired cognitive control capacity. There are both meta-analytic and empirical studies that have demonstrated robust reductions in intra-FPN connectivity across rs-fMRI investigations (Kaiser et al., 2015; Liu et al., 2019; Machaj et al., 2024).

In contrast, some large-scale investigations have reported no significant differences in FPN connectivity between depressed and healthy individuals, or failed to detect robust within-FPN alterations (Javaheripour et al., 2021; Whitton et al., 2018). More recently, evidence has emerged for the opposite pattern. Comprehensive meta-analyses based on rs-fMRI and electrophysiological studies have identified increased intra-FPN coupling in depression, with some work linking FPN hyper-connections to severe symptoms of depression like suicide risk (Zhang et al., 2025; Ren et al., 2025; Chu et al., 2025). Collectively, these inconsistencies complicate efforts to clarify how FPN dysfunction contributes to cognitive and executive deficits in depression and limit its utility as a reliable neural marker.

One of the reasons for this inconsistency in results is the use of the statistic functional connectivity (sFC) approach in previous studies, which treats connectivity as stable across the entire scan. This assumption neglects the inherently dynamic nature of brain network interactions. A growing body of research shows that functional connectivity fluctuates over time, even during rest, and that these temporal dynamics are relevant to cognition and psychiatric symptoms (Demirtas et al., 2016; Marchitelli et al., 2021).

dFC studies have shown that MDD is associated with reduced variability, fewer transitions, and longer dwell time in hypoconnected states, suggesting impaired neural flexibility (Hu et al., 2024; Li et al., 2019). To date, no study has explicitly examined the temporal dynamics of FPN connectivity in individuals with MDD compared to healthy controls, which might be the potential explanation for the inconsistency in previous studies. Another potential explanation for these inconsistencies is the substantial heterogeneity across samples, ranging from clinical and genetic differences to environmental exposures, as well as variability in analytic strategies. Using large-scale, multisite datasets with harmonized processing can help overcome these issues by reducing site-related biases and increasing statistical power, thereby supporting more reliable and generalizable findings (Yu et al, 2018; Xie et al, 2022).

Given the limitations of static connectivity approaches and the inconsistencies in prior findings, we hypothesize that dynamic features of FPN connectivity may offer a more sensitive and functionally relevant characterization of network dysfunction in MDD. In particular, temporal properties of dFC, such as the stability and flexibility of network states, may reflect core aspects of the disorder, including cognitive inflexibility and impaired executive regulation. By focusing on these time-varying patterns, this study seeks to clarify previous discrepancies in the literature and assess the utility of dynamic connectivity as a potential neural marker of depression.

To address this, we examined time-resolved FPN connectivity using data from the REST-meta-MDD consortium, a large, harmonized, multisite dataset comprising 887 participants. Dynamic connectivity was estimated using a sliding-window approach, followed by k-means clustering to identify recurring FPN connectivity states. From these state sequences, we derived three key temporal metrics: fractional occupancy (the proportion of time spent in each state), mean dwell time (the average duration within a state before transitioning), and the number of transitions (a proxy for network flexibility). These measures provide a granular view of FPN dynamics and allow for direct comparison of neural state properties and temporal connectivity patterns between individuals with depression and healthy controls. This study represents the first large-scale, FPN-focused dFC analysis in MDD and

aims to identify network-level signatures that differentiate diagnostic groups and advance the development of dynamic biomarkers in psychiatric research.

2 Methods

2.1 Participants and Dataset

Data for this study were obtained from the REST-meta-MDD project, the largest coordinated effort to collect rs-fMRI data in MDD to date (Yan et al., 2019). The full consortium dataset The study includes 2,428 participants (1,300 patients with MDD and 1,128 healthy controls, HCs) recruited by 17 research groups across 25 hospitals in China.

For the present analysis, we focused on participants who met standardized inclusion criteria to ensure both clinical validity and data quality. Eligible individuals were between 18 and 65 years of age and had at least 5 years of formal education. Patients were diagnosed with MDD according to DSM-IV criteria (First et al., 1997), confirmed through structured clinical interviews conducted by trained psychiatrists, and were required to have a score of at least 8 on the 17-item Hamilton Depression Rating Scale (HAMD-17; Williams, 1988) at the time of scanning. To ensure robust estimation of dFC, only sites with resting-state scans lasting at least 8 minutes (TR = 2 seconds, $\geq$240 volumes) were included, consistent with prior work showing that longer scan lengths yield more reliable estimates of time-resolved connectivity (Birn et al., 2013). Functional data were parcellated using the Dosenbach 160-region atlas (Dosenbach et al., 2010), a well-validated set of regions of interest optimized for connectivity analyses.

Participants were excluded if their behavioral or imaging data were incomplete or if their functional scans showed missing signal across multiple brain regions. After applying these criteria, the final dataset comprised 442 patients with MDD and 445 HCs collected across seven sites. Demographic and clinical characteristics of the included participants are summarized in Table 2, with site-specific distributions presented in Table 1. Group differences in demographic measures, including age, sex distribution, HAMD scores, and illness duration, were examined using Welch's two-sample t-tests for age and χ^2 tests for sex. No significant differences were observed between the age and sex. All study protocols were approved by the institutional review boards of the participating sites, and written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

2.2 Data Preprocessing

rs-fMRI data were preprocessed using the Data Processing Assistant for rs-fMRI (DPARSF; Yan & Zang, 2010) following the standardized protocol of Yan et al. (2019). The first 10 volumes were removed, after which slice-timing correction, realignment, and co-registration of each participant's T1-weighted image to the mean functional image were performed. Structural images were segmented into gray matter, white matter, and cerebrospinal fluid, and functional data were normalized to Montreal Neurological Institute (MNI) space and resampled to 3 mm isotropic voxels.

Site	Variable	HC	MDD
15	Number of subjects	42	35
	Age (years)	39.19 ± 14.46	46.80 ± 12.84
	Sex (M/F)	17 / 19	11 / 24
	HAMD	–	26.43 ± 5.11
	Illness duration (months)	–	34.47 ± 53.81
17	Number of subjects	42	31
	Age (years)	21.57 ± 6.32	21.84 ± 3.16
	Sex (M/F)	13 / 29	7 / 24
	HAMD	–	19.52 ± 5.30
	Illness duration (months)	–	–
19	Number of subjects	30	24
	Age (years)	35.63 ± 10.09	39.33 ± 11.43
	Sex (M/F)	14 / 16	4 / 20
	HAMD	–	21.62 ± 6.62
	Illness duration (months)	–	90.75 ± 99.35
20	Number of subjects	229	235
	Age (years)	39.57 ± 15.74	38.46 ± 11.93
	Sex (M/F)	73 / 156	81 / 154
	HAMD	–	21.43 ± 5.05
	Illness duration (months)	–	50.09 ± 65.53
21	Number of subjects	65	64
	Age (years)	36.51 ± 12.52	34.47 ± 13.15
	Sex (M/F)	28 / 37	32 / 32
	HAMD	–	17.58 ± 6.41
	Illness duration (months)	–	90.46 ± 99.47
22	Number of subjects	20	29
	Age (years)	24.35 ± 7.07	34.14 ± 9.95
	Sex (M/F)	12 / 8	14 / 15
	HAMD	–	22.79 ± 5.02
	Illness duration (months)	–	38.90 ± 43.63
23	Number of subjects	23	24
	Age (years)	33.00 ± 12.05	26.00 ± 7.96
	Sex (M/F)	8 / 15	14 / 10
	HAMD	–	21.58 ± 5.36
	Illness duration (months)	–	25.21 ± 29.12

Table 1. Site-specific demographic and clinical characteristics of healthy controls (HCs) and patients with major depressive disorder (MDD). Data are presented as mean ± standard deviation where applicable. HAMD = Hamilton Depression Rating Scale.

Nuisance signals, including the Friston 24 head-motion parameters, white matter, and cerebrospinal fluid, were regressed out, and a linear trend term was included to control for scanner drifts. Participants with mean framewise displacement greater than 0.2 mm were excluded. Finally, temporal band-pass filtering (0.01–0.1 Hz) was applied to the time series to retain frequencies relevant to resting-state activity.

Variable	**HC**	**MDD**	**df**	**t**	χ^2	**p**
Number of subjects	445	442	–	–	–	–
Age	36.11 ± 14.82	36.47 ± 12.77	867.7	0.38	–	0.698
Sex (M/F)	165 / 280	163 / 279	1.0	–	0.00	1.000
HAMD	–	21.24 ± 5.76	–	–	–	–
Illness duration (months)	–	55.65 ± 73.49	–	–	–	–

Table 2. Overall demographic and clinical characteristics of patients with major depressive disorder (MDD) and healthy controls (HCs). Data are presented as mean ± standard deviation where applicable. Group differences were assessed using Welch's t-tests (for age) or χ^2 tests (for sex). HAMD = Hamilton Depression Rating Scale.

2.3 Dynamic Functional Connectivity Analysis

dFC was estimated using the Dynamic Brain Connectome toolbox (DynamicBC, version 2.2; Liao et al., 2014) implemented in MATLAB 2022 (The MathWorks, 2022). Regional BOLD time series were extracted from the 21 nodes of the FPN defined by the Dosenbach 160 atlas (Dosenbach et al., 2010). To capture time-varying changes in connectivity, we employed a sliding-window correlation approach (Allen et al., 2014). Each participant's time series was segmented into windows of 22 TRs (44 s) with a step size of 1 TR (2 s), yielding 209 overlapping windows across the full resting-state scan. Within each window, Pearson correlation coefficients were computed between all pairs of FPN nodes, resulting in a 21 × 21 connectivity matrix. The correlation values were then Fisher z-transformed to improve the normality of the distribution.

Following the construction of windowed matrices, additional preprocessing was performed in Python 3.10 (Python Software Foundation, 2022) to prepare the data for subsequent analyses. Correlation values were numerically stabilized to avoid extreme values at ±1, Fisher's r-to-z transformation was applied, and the upper-triangular elements of each matrix (excluding the diagonal) were extracted to form feature vectors that compactly represented the connectivity patterns within each time window. Matrices containing invalid values (e.g., NaNs or infinities) were excluded to ensure data quality. This procedure yielded a set of time-resolved connectivity vectors for each participant, characterizing the evolving temporal organization of FPN connectivity across the scan. These dynamic connectivity vectors were concatenated and used as input for the subsequent clustering analysis.

An overview of the FPN dFC pipeline is shown in Figure 1: we extracted BOLD time series from 21 FPN nodes, applied a sliding-window correlation (22 TR, step 1 TR) to obtain windowed 21×21 matrices, and then clustered the vectorized windows; the resulting state sequence per subject yielded fractional occupancy, mean dwell time, and transition counts.

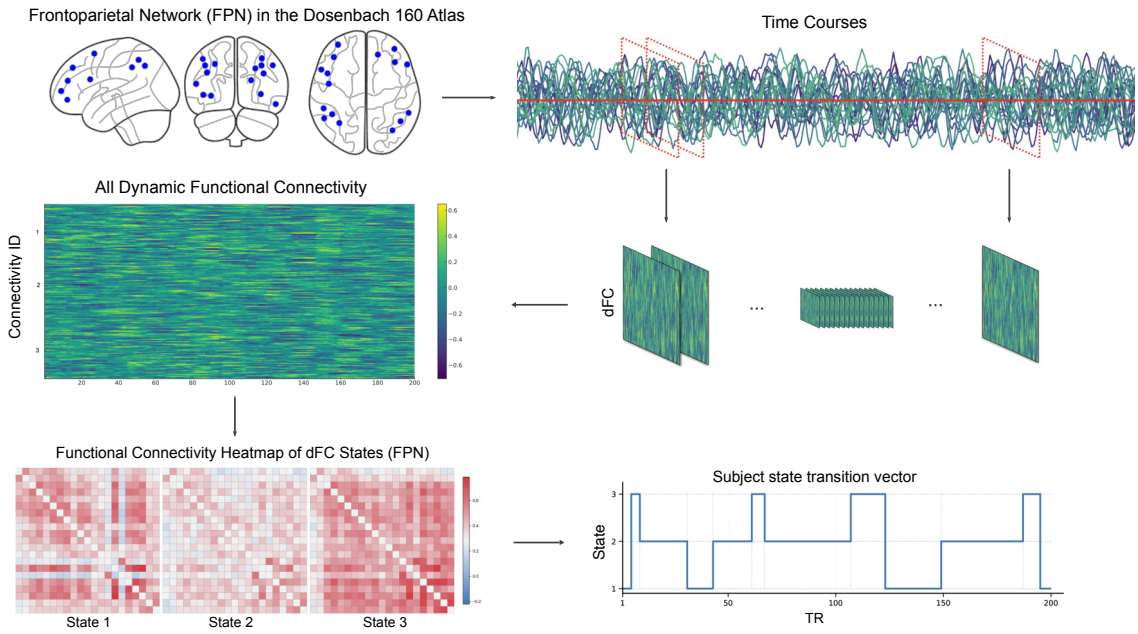

Figure 1. Analysis pipeline for dynamic frontoparietal network (FPN) connectivity. BOLD time series were extracted from 21 FPN nodes defined by the Dosenbach 160 atlas (top left). A sliding window (22 TR; step = 1 TR) was applied to each subject's time courses (top right), and Fisher z–transformed Pearson correlations were computed within each window to yield a sequence of 21×21 dynamic functional connectivity (dFC) matrices (middle). All windowed matrices across participants were concatenated and clustered with k-means ($k = 3$) to identify recurring FPN states (bottom left; state centroids shown as connectivity heatmaps). For each participant, the resulting state sequence (bottom right) was used to compute temporal features: fractional occupancy, mean dwell time, and total number of state transitions.

2.4 Clustering Analysis

To identify recurring patterns of dFC within the FPN, we applied k-means clustering to the windowed connectivity vectors derived from the 21 FPN nodes of the Dosenbach 160 atlas (Dosenbach et al., 2010). Clustering was performed with the Euclidean (L2) distance metric, a standard approach in dFC research (Allen et al., 2014), which produced the same results as the Manhattan (L1) distance in our high-dimensional setting while being more computationally efficient.

To enhance stability, we first identified exemplar windows, defined as local maxima in the temporal variance of connectivity across ROI pairs (Allen et al., 2014). Exemplar windows from all participants were pooled and clustered with k-means using 500 random initializations (replicates) and allowing up to 500 iterations per run. These group-level centroids were then used to initialize a second round of k-means clustering applied to the full set of FPN dFC windows across all subjects, minimizing sensitivity to random starting conditions. The optimal number of clusters was determined using the elbow criterion (Tibshirani et al., 2001), which showed an inflection at $k = 3$ (Figure 2).

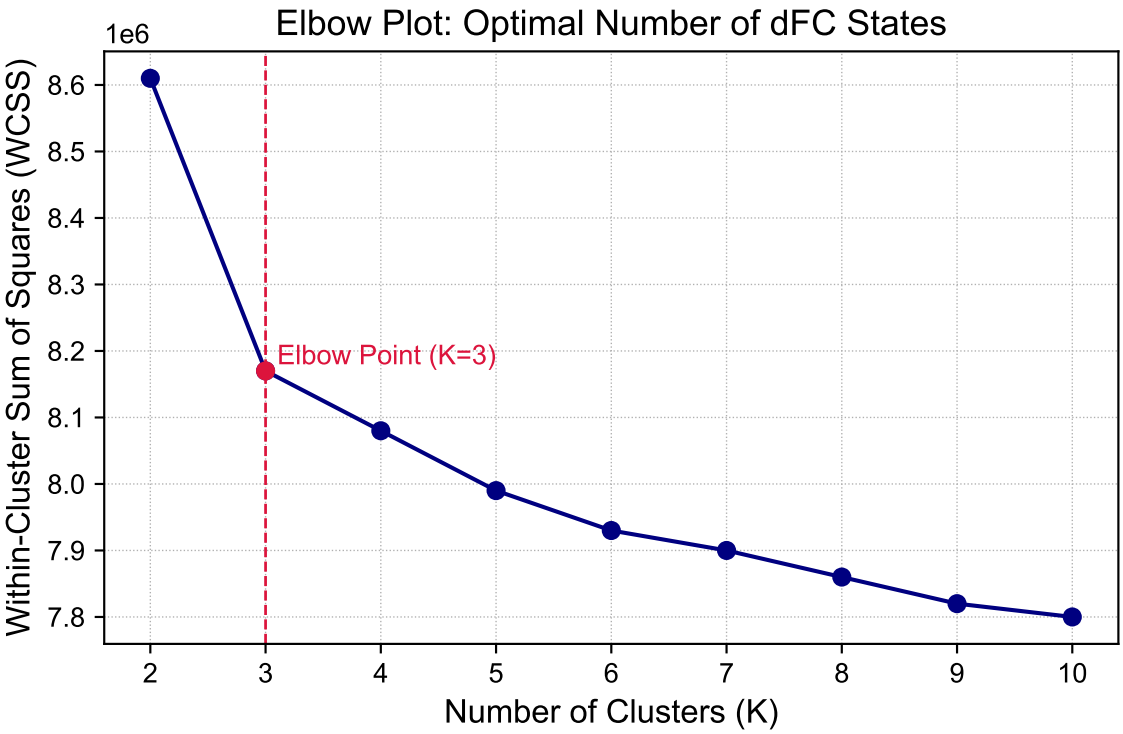

Figure 2. Elbow plot for determining the optimal number of clusters (k) in the k-means clustering of dynamic functional connectivity (dFC) states within the frontoparietal network (FPN). The plot shows within-cluster sum of squares (WCSS) as a function of k. The inflection point at $k = 3$ indicates the optimal balance between model complexity and within-cluster homogeneity.

As shown in Figure 2, the elbow at three clusters indicated a balance between parsimony and within-cluster homogeneity. Accordingly, each dFC window was assigned to a connectivity state based on the minimum Euclidean distance between its vectorized connectivity pattern and the final cluster centroids. From these state sequences, we derived three temporal features to characterize individual dFC dynamics. Fractional occupancy was defined as the proportion of windows assigned to a given state, indexing the predominance of that connectivity configuration. Mean dwell time measures the average number of consecutive windows spent in a state before switching, reflecting temporal stability.

The number of transitions captured the total frequency of state changes across the scan, providing an index of network flexibility.

2.5 Statistical Analysis

2.5.1 Within-subject comparison of state-wise FC strength

To examine whether mean FC strength differed across the three connectivity states within individuals, we applied a repeated-measures ANOVA. When the assumption of sphericity was violated, the Greenhouse–Geisser correction was applied to adjust the degrees of freedom. Significant effects were further explored with paired post-hoc t-tests, and p-values were corrected for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) procedure ($\alpha = 0.05$). This analysis was used to determine whether the connectivity states identified through clustering represented meaningfully distinct patterns of functional coupling, rather than trivial variations of the same underlying configuration.

2.5.2 Between-group statistical comparisons

To test whether dynamic connectivity metrics differed between healthy controls and depressed patients, we conducted independent two-sample Welch's t-tests for each measure. Group comparisons were performed for fractional occupancy and mean dwell time of each connectivity state, as well as for the total number of state transitions per subject. The Welch's t-test was chosen, given the heterogeneity of variance between groups. Resulting p-values were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) procedure ($\alpha = 0.05$).

In a complementary analysis, we further examined differences in the frequency of specific state-to-state transitions between groups. For each subject, we extracted the number of transitions between all pairs of distinct states (self-transitions excluded). These transition counts were compared between groups using Welch's t-tests, with FDR correction applied across all transitions. This analysis allowed us to identify which particular reconfiguration pathways differentiated patients from controls, beyond overall transition frequency.

3 Results

3.1 Demographic and clinical characteristics

Demographic and clinical data for the included participants are summarized in Table 2. Site-wise distributions are provided in Table 1. The final sample comprised 445 healthy controls (HCs) and 442 patients with MDD. Groups did not differ significantly in age (HC: 36.11 ± 14.82 years; MDD: 36.47 ± 12.77 years; $t(867.7) = 0.38$, $p = 0.698$) or sex distribution (HC: 165 males / 280 females; MDD: 163 males / 279 females; $\chi^2(1) < 0.001$, $p = 1.000$). Clinical data in the MDD group indicated a mean HAMD-17 score of 21.24 ± 5.76 and a mean illness duration of 55.65 ± 73.49 months.

3.2 Identification of Dynamic Connectivity States

Using k-means clustering applied to windowed FPN connectivity matrices, we identified three recurring dFC states. The optimal number of clusters ($k = 3$) was determined via

the elbow criterion, which indicated diminishing returns beyond three states (Figure 2). The three states exhibited distinct patterns of functional coupling (Figure 4). State 1 was characterized by moderate connectivity across FPN regions, State 2 by globally reduced connectivity (hypoconnectivity), and State 3 by strongly positive connections, particularly among lateral prefrontal and parietal nodes. These configurations are broadly consistent with prior reports of recurring large-scale brain network states during rest (Allen et al., 2014; Damaraju et al., 2014).

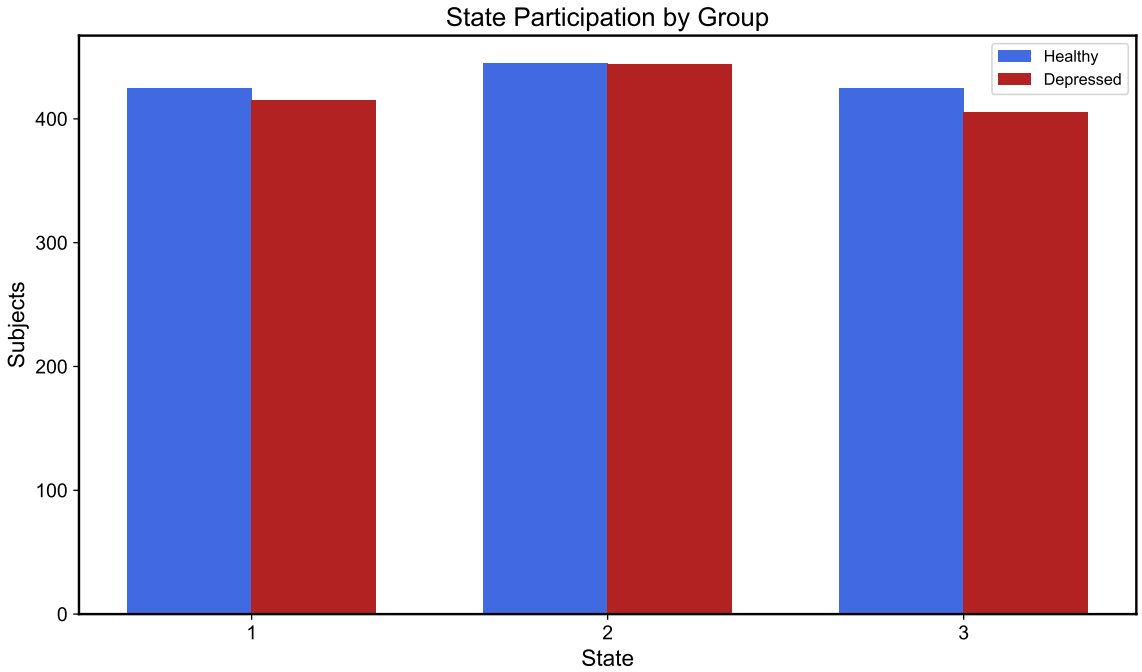

Figure 3. Participant-level engagement with dynamic frontoparietal network (FPN) states across groups. Bars represent the number of participants in each group (patients with major depressive disorder [MDD] vs. healthy controls [HCs]) who occupied each state at least once during the resting-state fMRI scan. The similar distributions support the validity of group comparisons in subsequent temporal dFC analyses.

3.3 Within-Subject Differences in State-wise FC Strength

To establish whether the identified states represented distinct functional configurations rather than trivial fluctuations, we compared mean FC strength across states within individuals. A repeated-measures ANOVA revealed a highly significant main effect of state, *F*(1.80, 1597.20) = 5179.65, *p* < .001 (Greenhouse–Geisser corrected). Greenhouse–Geisser $\epsilon = 0.90$). Post-hoc paired comparisons showed that all three states differed significantly from each other after FDR correction (all $q < 0.001$; Figure 5; Table 3).

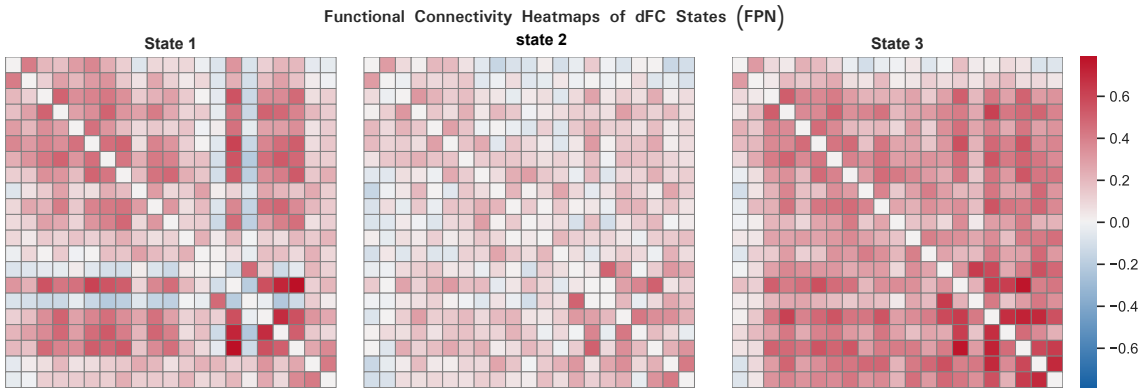

Figure 4. Connectivity matrices for the three dynamic frontoparietal network (FPN) states identified via k-means clustering of resting-state fMRI data. State 1 shows moderate functional coupling, State 2 exhibits widespread hypoconnectivity, and State 3 displays strong positive connectivity, especially among lateral prefrontal and parietal regions. Values represent Fisher z-transformed Pearson correlation coefficients across 21 FPN nodes from the Dosenbach atlas.

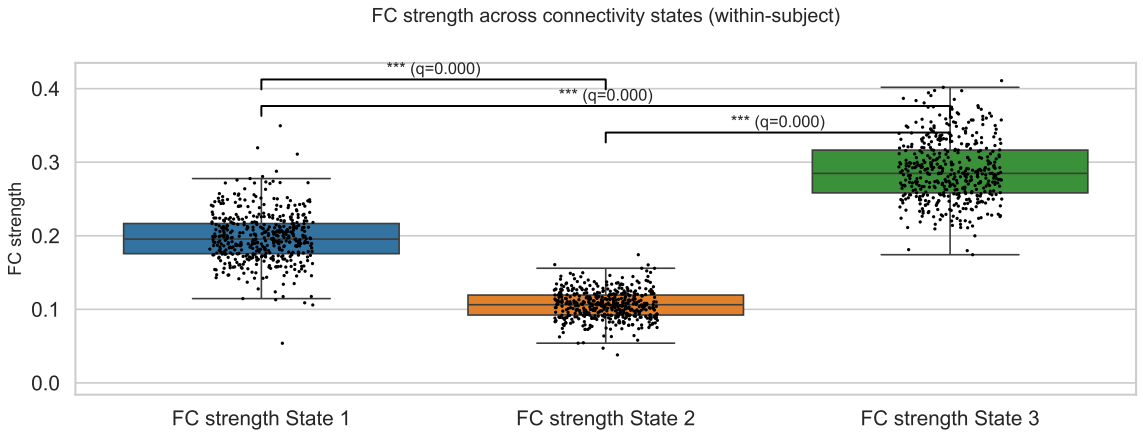

Figure 5. Within-subject comparisons of mean functional connectivity (FC) strength across the three dynamic frontoparietal network (FPN) states. Boxplots show the distribution of Fisher z-transformed average pairwise correlations among 21 FPN nodes. State 2 exhibits significantly lower FC (hypoconnectivity), State 3 shows the highest FC, and State 1 is intermediate. Error bars represent the standard error of the mean. Differences were assessed via repeated-measures ANOVA with post-hoc t-tests (Benjamini-Hochberg FDR-corrected).

Specifically, State 2 demonstrated the lowest mean FC strength, consistent with a hypoconnected profile, whereas State 3 exhibited the strongest connectivity, and State 1 showed intermediate values. These findings confirm that the clustering procedure successfully captured meaningfully distinct dFC states.

(a) Descriptive Statistics

State	n	Mean	SD
FC strength State 1	836	0.198	0.043
FC strength State 2	886	0.106	0.025
FC strength State 3	826	0.288	0.056

(b) Repeated-Measures ANOVA

Effect	F	p	ϵ
State	5179.650	0.000	0.902

(c) Post-hoc Comparisons (FDR-Corrected)

Contrast	n	t	df	p	dz	Sig
State 1 vs State 2	1605	80.25	1604	0.000	2.003	***
State 1 vs State 3	1504	-57.46	1503	0.000	-1.482	***
State 2 vs State 3	1589	-124.48	1588	0.000	-3.123	***

Table 3. Within-subject comparison of mean functional connectivity (FC) strength across the three dynamic frontoparietal network (FPN) states. (a) Descriptive statistics (mean ± standard deviation). (b) Repeated-measures ANOVA results (Greenhouse-Geisser corrected where applicable). (c) Post-hoc paired t-test comparisons (Benjamini-Hochberg FDR-corrected). ***$q < 0.001$. FC values are Fisher z-transformed Pearson correlations.

3.4 Between-Group Comparisons of dFC Temporal Features

We next examined whether the temporal properties of these states differed between groups. Welch's t-tests revealed significant group effects for several metrics (Figure 6 for all metrics; Figure 7 for transitions focus; Table 4). Patients with MDD showed greater fractional occupancy of State 2 (depressed: $M = 0.553$, $SD = 0.240$; healthy: $M = 0.513$, $SD = 0.219$; $t(876.6) = -2.59$, $p = 0.010$, $q = 0.023$, $g = 0.18$), indicating that they spent a greater proportion of time in the hypoconnected state. Patients also exhibited longer mean dwell time in State 2 ($M = 18.44$, $SD = 27.11$) relative to controls ($M = 13.43$, $SD = 18.15$; $t(769.6) = -3.23$, $p = 0.001$, $q = 0.004$, $g = 0.22$), suggesting reduced flexibility in exiting this configuration. Additionally, the total number of transitions between states was lower in the depressed group ($M = 22.63$, $SD = 9.33$) compared with controls ($M = 24.84$, $SD = 8.45$; $t(875.3) = 3.69$, $p < 0.001$, $q = 0.002$, $g = 0.25$). No significant between-group differences emerged for State 1 or State 3 in either occupancy or dwell time (all $q > 0.05$).

Variable	Mean (Healthy)	Mean (Depressed)	t	df	p	p_FDR	Signif
Transitions	24.84 ± 8.45 (n=445)	22.63 ± 9.33 (n=442)	3.69	875.3	0.000	0.002	**
Occupancy State 1	0.23 ± 0.19 (n=445)	0.22 ± 0.17 (n=442)	1.18	881.7	0.239	0.279	ns
Occupancy State 2	0.51 ± 0.22 (n=445)	0.55 ± 0.24 (n=442)	-2.59	876.6	0.010	0.023	*
Occupancy State 3	0.25 ± 0.18 (n=445)	0.23 ± 0.19 (n=442)	2.04	884.3	0.042	0.073	ns
Mean dwell time State 1	5.71 ± 3.45 (n=445)	5.74 ± 3.54 (n=442)	-0.10	884.2	0.922	0.922	ns
Mean dwell time State 2	13.43 ± 18.15 (n=445)	18.44 ± 27.11 (n=442)	-3.23	769.6	0.001	0.004	**
Mean dwell time State 3	6.75 ± 4.76 (n=445)	6.29 ± 4.28 (n=442)	1.54	876.1	0.124	0.174	ns

Table 4. Between-group comparisons of dynamic functional connectivity (dFC) metrics in patients with major depressive disorder (MDD) and healthy controls (HCs). Data are presented as mean ± standard deviation (with sample size in parentheses). Group differences were assessed using Welch's t-tests, with Benjamini-Hochberg FDR correction applied across comparisons. $^{**}q < 0.01$, $^{*}q < 0.05$, ns = not significant.

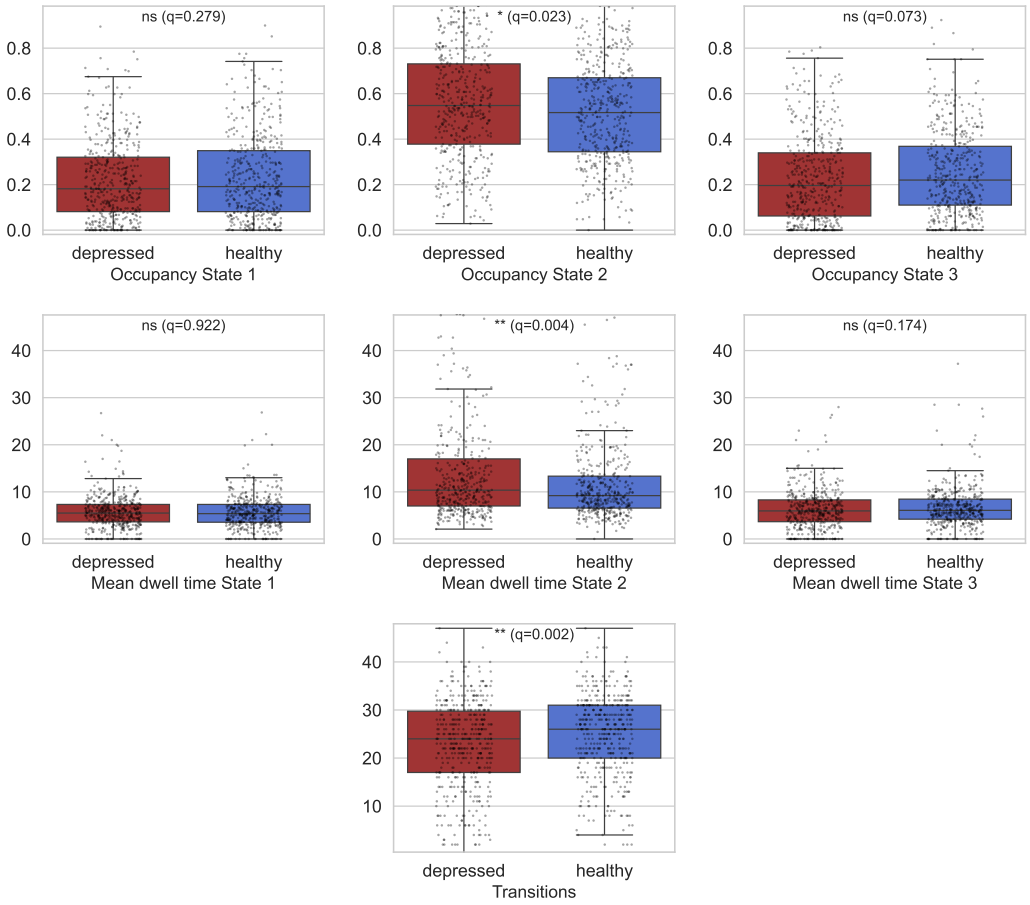

Figure 6. Detailed group comparisons of dynamic functional connectivity (dFC) metrics in the frontoparietal network (FPN). Boxplots display fractional occupancy (top row), mean dwell time (middle row), and total number of state transitions (bottom row) for each of the three states, stratified by group (patients with major depressive disorder [MDD] vs. healthy controls [HCs]). Asterisks denote significant differences (Welch's t-tests with Benjamini-Hochberg FDR correction).

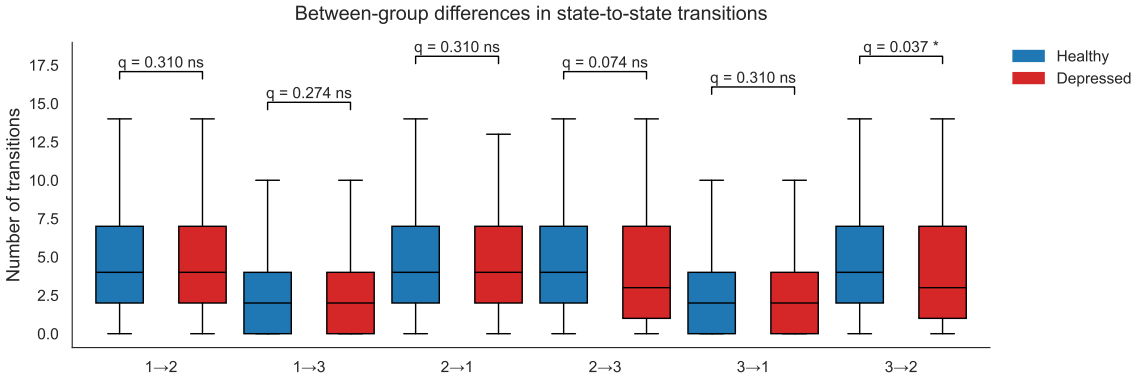

Figure 7. Between-group comparisons of dynamic functional connectivity (dFC) metrics in the frontoparietal network (FPN). Boxplots illustrate differences between patients with major depressive disorder (MDD) and healthy controls (HCs) in fractional occupancy, mean dwell time, and total number of state transitions across the three FPN states. Asterisks indicate significant differences (Welch's *t*-tests with Benjamini-Hochberg FDR correction).

3.5 State-to-State Transition Profiles

To further evaluate the dynamics of switching between states, we compared the frequency of specific state-to-state transitions across groups (Table 5). Welch's t-tests with FDR correction revealed that patients exhibited significantly fewer transitions from State 3 to State 2 compared with controls (t(885) = 2.75, p = 0.006, q = 0.037). The transition from State 2 to State 3 also showed a nominal group difference before correction (t(877) = 2.25, p = 0.025), although this effect did not remain significant after FDR adjustment (q = 0.074). No other transition pathways approached significance (all q > 0.05). Together, these results suggest a selective disruption in reconfigurations involving State 2, particularly in the ability to shift between the strongly connected state (State 3) and the hypoconnected configuration (State 2), indicating altered flexibility in transitioning between distinct network modes.

Transition	Mean (HC)	SD (HC)	Mean (MDD)	SD (MDD)	t	p	q	Signif
$1 \to 2$	4.98	3.67	4.73	3.56	1.02	0.310	0.310	ns
$1 \to 3$	2.64	2.70	2.37	2.73	1.49	0.137	0.274	ns
$2 \to 1$	4.99	3.64	4.69	3.59	1.22	0.223	0.310	ns
$2 \to 3$	4.81	3.69	4.27	3.48	2.25	0.025	0.074	ns
$3 \to 1$	2.64	2.71	2.45	2.79	1.03	0.304	0.310	ns
$3 \to 2$	4.78	3.70	4.12	3.45	2.75	0.006	0.037	*

Table 5. Between-group differences in state-to-state transition frequencies in patients with major depressive disorder (MDD) and healthy controls (HCs). Data are presented as mean ± standard deviation. Group differences were assessed using Welch's *t*-tests, with Benjamini-Hochberg FDR correction applied across comparisons. $^*q < 0.05$, ns = not significant.

4 Discussion

This study presents large-scale evidence indicating that MDD is associated with disruptions in the temporal dynamics of FPN connectivity. While previous research has primarily focused on static functional connectivity (sFC) changes in MDD, our findings extend this line of inquiry and demonstrate that these disorders are also observable in the dynamic organization of brain networks. Using harmonized rs-fMRI data from the REST-meta-MDD consortium (Yan et al., 2019), we identified three recurring FPN connectivity states. It was found that individuals with MDD spend significantly more time in a hypoconnected state, have a longer duration in this configuration, and show an overall reduction in the number of transitions between states. Specifically, a distinct defect was observed in the direct transition between hypoconnected and hyperconnected states. These results indicate that MDD is not only characterized by abnormal connectivity strength but is also associated with reduced temporal flexibility in FPN engagement. This decrease in dynamic adaptability may reflect underlying neural rigidity, which could be a mechanical basis for the cognitive inflexibility commonly observed in depression (Zheng et al., 2024; Menon, 2011). Overall, these findings highlight the importance of dFC analyzes in elucidating the temporal network disruption architecture in psychiatric disorders.

A preliminary observation from this study is greater time spent in a relatively weakly connected FPN state among individuals with MDD. This state, marked by globally reduced coherence among prefrontal and parietal regions, likely impairs the FPN's core functions, including cognitive control, attentional regulation, and emotion modulation (Cole et al., 2014; Harding et al., 2015). The sustained presence of this hypoconnected configuration may therefore reflect a neural mechanism underpinning core cognitive symptoms of depression, impaired attentional disengagement, reduced inhibitory control, and diminished cognitive flexibility (Schultz et al., 2018; Rhee et al., 2024; Huang et al., 2022).

Our findings of reduced intra-FPN coupling are consistent with prior reports of hypoconnectivity in MDD (Kaiser et al., 2015; Liu et al., 2019; Machaj et al., 2024). However, there are studies that have observed no significant alterations (Javaheripour et al., 2021; Whitton et al., 2018) or even hyperconnectivity, sometimes linked to severe symptoms such as suicidality (Zhang et al., 2025; Ren et al., 2025; Chu et al., 2025). Such inconsistencies likely arise from the reliance on static functional connectivity, which collapses temporal variability into an average strength measure. In this framework, brief but strong episodes of coupling can disproportionately inflate mean connectivity, masking the more enduring hypoconnected state (Hutchison et al., 2013; Calhoun et al., 2014). By using a dynamic connectivity approach, we demonstrate that depressed individuals predominantly remain in a hypoconnected FPN configuration, with only infrequent transitions into more integrated states. This temporal perspective reconciles prior divergent findings and highlights the value of dynamic methods for capturing the prevailing neural dysfunction in MDD.

In addition to increased occupancy, individuals with MDD exhibited significantly longer dwell times within the hypoconnected FPN state, indicating sustained engagement with a maladaptive neural configuration. From a dynamical systems perspective, this suggests that the hypoconnected state functions as a deep attractor basin in the neural landscape of depression, one that resists perturbation and constrains transitions into more adaptive configurations (Rolls, 2016; Deco et al., 2017; Hayes et al., 2015). Such entrenchment

reflects neurodynamic rigidity, consistent with behavioral findings that depression is marked by perseveration, impaired task-switching, and set-shifting deficits (Snyder, 2013; Gibb et al., 2013).

Prolonged residence in this state may provide a neural substrate for repetitive negative thinking and maladaptive rumination, processes known to maintain depressive episodes by limiting access to regulatory and executive resources, consistent with evidence that reduced global connectivity of the fronto-parietal control network relates to depression symptoms (Hamilton et al., 2015; Kaiser et al., 2015; Schultz et al., 2018). Prior dFC studies have similarly reported that patients spend longer periods "stuck" in specific connectivity states, with longer dwell times correlating with symptom severity (Marusak et al., 2016; Demirtas et al., 2016). Our findings extend this work by implicating the FPN specifically, suggesting that depression involves not only reduced network connectivity but also a pathological stabilization of hypoconnected states, which may explain the cognitive and affective inflexibility characteristic of the disorder.

Complementary to the abnormalities seen in occupancy and dwell time, patients also showed a significant decrease in the overall number of transitions between brain states. In contrast, healthy individuals displayed a more dynamic range of activity, frequently shifting between weak, moderate, and strong connections within the frontoparietal network, while people with depression showed a more limited pattern of transitions. These results are in line with prior findings showing that depressed individuals demonstrate a reduction in their brains' functional flexibility and demonstrated a reduced number of transitions in the whole brain (An et al., 2024; Cole et al., 2013; Han et al., 2020; Wang et al., 2024).

These transitions between states are increasingly considered markers of the brain's adaptability, its ability to reconfigure itself in response to changing environmental demands or internal goals (Bassett et al., 2011; Shine et al., 2016). Subsequently, a reduction in these transitions suggests a more profound problem with the brain's flexibility in adjusting its network states to fit the task or context, a capacity that's critical for things like executive function and emotion regulation (Cole et al., 2013; Buhle et al., 2014).

Importantly, this reduction in flexibility wasn't just seen in the low-connectivity state: even when depressed individuals entered states with stronger connectivity, they still showed fewer transitions overall. This points to a broader rigidity in how brain states are organised over time, not just something tied to one particular state (An et al., 2024; Demirtaş et al., 2016). This finding lines up with behavioural research showing that people with depression often struggle to flexibly shift their thinking when the situation changes, highlighting the real-world significance of these neural inflexibilities (Snyder, 2013; Rock et al., 2014).

Another important aspect of this study is the identification of specific disruptions in the dynamic transitions between different functional states (Shine et al., 2016; Wang et al., 2021). In particular, we observed that the transition from a hyperconnected state to a hypoconnected state in the frontoparietal network (FPN) was significantly reduced in individuals with MDD. A similar pattern was also observed in the reverse direction, aligning with previous findings on disrupted state-switching and functional imbalance in depression (Han et al., 2020; Schultz & Cole, 2018).

These large-scale reconfigurations reflect direct shifts between highly integrated and highly disconnected network states, a phenomenon linked to rare but intense co-fluctuation "events" that have a major impact on network dynamics (Esfahlani et al., 2020; Pope et

al., 2021). The reduction of these transitions in depression suggests a decreased ability to flexibly shift between different functional patterns of the FPN.

Functionally, this impairment may appear as slowed thinking, reduced attentional flexibility, and difficulty quickly redirecting cognitive resources—symptoms that are commonly reported in depression (Rock et al., 2014; Snyder, 2013; Semkovska et al., 2019). The transitions were maintained through the intermediate state, suggesting that patients may still have the ability to shift between configurations, but they rely on slower and less efficient paths. This interpretation aligns with network control and energy-landscape models, which suggest that moving between distant states usually involves passing through intermediate steps that come with a higher control cost (Gu et al., 2017; Ramirez-Mahaluf et al., 2020).

By relying on these indirect routes, this provides a compelling neural explanation for the slow and effortful cognitive processes seen in depression, offering a clear reason for the real-world difficulties patients experience when quick cognitive flexibility is needed.

In sum, this study highlights that major depressive disorder is not only associated with altered connectivity strength but also with disruptions in the temporal dynamics of the frontoparietal control network. Individuals with depression tend to remain longer in hypoconnected states, show reduced flexibility in shifting between configurations, and exhibit selective impairments in direct transitions between distinct states. These temporal alterations provide a mechanistic account of the cognitive rigidity and perseverative tendencies often observed in depression and help to reconcile inconsistencies in prior static connectivity studies. By emphasizing the dynamic nature of frontoparietal dysfunction, our findings underscore the importance of moving beyond static approaches to capture the temporal features of brain network organization in psychiatric disorders.

5 Conclusion

This study provides large-scale evidence that major depressive disorder is characterized by disruptions in the temporal dynamics of the frontoparietal control network. We identified three recurring connectivity states and found that individuals with depression spend more time in a hypoconnected configuration, remain in this state for longer durations, and transition less frequently overall. Crucially, we observed that not all transitions were equally affected: direct shifts between the most distinct states, the hypoconnected and hyperconnected configurations, were selectively reduced. This pattern indicates that the depressed brain is not only biased toward weakly connected states but also limited in its ability to reconfigure efficiently across the full range of network dynamics.

These alterations point to a narrowing of the network's temporal repertoire and provide a mechanistic explanation for the neural rigidity and cognitive inflexibility often observed in depression. By adopting a dynamic perspective, our findings reconcile inconsistencies in static connectivity research, showing that while hyperconnected states are present, they are accessed less frequently, and the predominant feature of depression is a reduced capacity to flexibly switch between states. Taken together, this work underscores the importance of temporal dynamics in understanding frontoparietal dysfunction and highlights dynamic connectivity measures as promising candidates for biomarker development in major depressive disorder.

This study has several limitations. First, although multisite harmonization was employed, residual variability across scanners and acquisition protocols cannot be fully excluded. Second, dynamic functional connectivity measures depend on methodological choices, including window length, parcellation, and clustering approach, which may shape the precise state configurations identified. Finally, we did not examine clinical subgroups of major depressive disorder, such as first-episode versus recurrent cases or medicated versus drug-naïve patients, which could help determine whether temporal abnormalities represent trait markers, state effects, or treatment-related changes.

Future work should extend these findings in several important directions. Stratified analyses of MDD subtypes will be necessary to clarify heterogeneity in temporal dynamics and to test whether specific patterns distinguish clinical profiles. Linking neural state features with behavioral and cognitive measures will provide insight into how temporal rigidity translates into real-world impairments. Applying machine learning approaches may further reveal the value of these temporal markers for automated classification, prediction, and stratification of patients. Beyond the frontoparietal control network, future studies should also analyze both within-network dynamics and their relationship to between-network connectivity, which may uncover how altered temporal patterns in the FPN interact with broader brain systems. Together, these steps will help refine the mechanistic understanding of depression and advance the translational potential of dynamic connectivity features as biomarkers.

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Declaration of competing interest

The authors declare no conflicts of interest.

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