Supplementary file for N Katayama *et al*., "Dynamic Neural Network Modulation Associated with Rumination in Major Depressive Disorder: A Prospective Observational Comparative Analysis of Cognitive Behavioral Therapy and Pharmacotherapy"

SUPPLEMENT FOR THE STUDY PROCEDURE

(Supplemental Text)

Materials and methods

Participants

During their usual consultations, psychiatrists provided information brochures to patients with major depressive disorder (MDD) who were invited to participate. Interested patients who provided contact details were scheduled with research staff. Each participant underwent a comprehensive assessment by a psychiatrist for eligibility. The inclusion criteria were as follows: (i) aged 20–69 years; (ii) had MDD (either single or recurrent episodes) based on a structured clinical interview for DSM-IV diagnosis (SCID) (1) conducted by psychologists who had received extensive training in the administration of semistructured interviews; (iii) met the operational criterion of a total score of 8 or greater on the 17-item GRID-Hamilton Depression Rating Scale (GRID-HAMD) (2); (iv) experienced at least clinical-level depression symptoms; (v) were scheduled to receive pharmacotherapy, cognitive behavioral therapy (CBT), electroconvulsive therapy (ECT), or repetitive transcranial magnetic stimulation (rTMS) treatment at the discretion of their psychiatrist; and (vi) were able to understand the purpose and

content of the study and express in writing their free and voluntary consent to participate. The exclusion criteria were as follows: (i) had a history of comorbid alcohol/substance use disorder or alcohol/substance use disorder within the past two years; (ii) currently experiencing a manic episode; (iii) had current significant suicidal ideation or frequent suicide attempts; (iv) had antisocial personality disorder; (v) planned to relocate before the end of the study so that they could not continue to visit the clinic; (vi) had clinically diagnosed life-threatening or unstable physical or cerebrovascular diseases; (vii) had a pacemaker, aneurysm clips, artificial valves, cochlear implants, or other magnetic or electrically conductive metals rendering them unsuitable for MRI; and (viii) were unable to tolerate MRI because of claustrophobia. Patients were assigned to a CBT group, a pharmacotherapy group, or other treatment groups (ECT or rTMS) depending on the treatment they received.

We recruited healthy participants (HCs) from the community who were matched for age, sex, and educational background through a staffing agency and university website. The exclusion criteria were (i) current or past psychiatric, neurological, or substance abuse disorders and (ii) taking psychotropic medications.

Each participant provided written informed consent before study initiation.

Treatment groups

CBT group

Participants underwent 16 weekly CBT sessions, each lasting 50 min, conducted in person by therapists who had appropriate specialized training, complemented by routine clinical management by the patients' psychiatrists. Therapists administering CBT adhered to a specifically designed treatment manual for MDD, which was developed based on the principles outlined in *Beck's Treatment Manual* (4). All CBT therapists were knowledgeable about rumination-focused CBT (5) and used this technique when necessary. CBT sessions were administered by ten therapists—four psychiatrists and six clinical psychologists—each holding either a master's degree or a doctoral degree. These therapists had an average of 9.7 years of experience in CBT, with a standard deviation (SD) of 4.5 years. Prior to participating, they had provided CBT to an average of 44.6 patients with MDD (SD, 55.8). All therapists had received comprehensive CBT training, which included a two-day intensive workshop. This was augmented by one-hour onsite group supervision sessions conducted by an expert CBT core supervisor following each therapy session. These supervised sessions entailed detailed case reviews and feedback to ensure strict adherence to CBT protocols and to maintain a high level of competence throughout the study. Thus, the competence of all the therapists was controlled. Participants assigned to the CBT group continued with their standard treatment regimen, which involved typical care for depression managed by a psychiatrist. While pharmacotherapy was not strictly regulated, the prescribed treatments adhered to established guidelines for depression care, such as those recommended by

the Japanese Society of Mood Disorders (6).

Pharmacotherapy group

Pharmacotherapy was consistently managed by psychiatrists. Baseline assessments were systematically conducted prior to the initiation or modification of antidepressants such as selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, noradrenergic antidepressants, and specific serotonergic antidepressants. Following these initial assessments, the treatment regimen was aligned with the established guidelines set forth by the Japanese Society of Mood Disorders (6). These psychiatrists usually conducted medication checkups approximately biweekly, with each session lasting between 10 and 15 min. These consultations typically included evaluations of symptoms and standard clinical management, encompassing brief psychoeducational interventions and pharmacotherapy, such as those in the CBT group.

Assessment

Neuroimaging and MRI acquisition

Resting-state functional magnetic resonance imaging (fMRI) was performed at baseline (0 weeks) and after treatment (16 weeks). During the 10-min scans, the participants were instructed to stay awake and remain motionless with their eyes open, focusing on a fixation cross. The procedure involved 240 acquisitions. Imaging was performed using a 3.0-T scanner (GE

Discovery MR750 MRI; GE Healthcare, Chicago, IL) equipped with a 32-channel receiver coil to ensure high-quality image acquisition. Resting-state fMRI data were captured using gradient-echo echo planar imaging sequences with the following optimized parameters: repetition time (TR), 2500 ms; echo time (TE), 30 ms; field of view (FOV), 212 mm × 212 mm; flip angle, 90°; voxel size, 3.3 × 3.3 × 4 mm; and acquisition matrix, 64 × 64, with 36 slices. In addition to these functional scans, high-resolution T1-weighted anatomical images were acquired using a three-dimensional fast-spoiled gradient-echo sequence. The parameters for these scans were as follows: inversion time, 650 ms; TR, 6770 ms; TE, 3.01 ms; FOV, 230 × 230 mm; flip angle, 8°; voxel size, 0.9 × 0.9 × 1 mm; and acquisition matrix, 256 × 256, with 200 slices.

Preprocessing

For quality assurance, we used SPM12 in MATLAB 2021a (MathWorks, Natick, MA). The process involved determining the slice acquisition order, converting DICOM files to the NIfTI format, correcting the slice timing, and correcting the head motion. We then evaluated body motion, computed framewise displacement (FD), and identified flagged volumes with a threshold set at 0.5. The established quality criteria mandated that the mean displacements across the x-axis, y-axis, z-axis, pitch, roll, yaw, and FD should not exceed 3 mm. Moreover, flagged volumes were required to constitute less than 10% of the total volume, translating to less than 24 of the 240

volumes. In instances where the data did not adhere to these standards, the subjects were offered the option of undergoing a repeat fMRI scan, followed by another quality assessment round. Upon reimaging, data that did not satisfy these criteria were excluded. For images acquired using the Japanese Strategic Research Program for the Promotion of Brain Science (SRPBS) protocol (7), preprocessing was performed using fMRI prep version 20.0.2 on Docker Desktop version 4.13.1 (8), a robust processing pipeline.

We employed a systematic preprocessing approach to parcel all brain voxels into 116 distinct regions of interest (ROIs), adhering to the automated anatomical labeling 3 (AAL3) framework (9) used by in-house code in the Nilearn (10). Subsequently, for each participant, we computed the mean time series for all voxels within each ROI to derive a consolidated representation of the network dynamics. Next, we normalized the 116 ROI time series for each participant by centering to zero mean and scaling to unit variance. This normalization facilitated data amalgamation across participants, culminating in a comprehensive data matrix with dimensions of 116 ROIs × 239 timepoints × 135 participants. This matrix served as the foundational dataset for subsequent hidden Markov model (HMM) analysis (**Figure 3A**).

When the HMM decomposes multivariate data into several dimensions, the high spatial dimensionality of the fMRI datasets causes stability problems during parameter estimation. To circumvent these issues, we first subjected the datasets to principal component analysis. This step

was critical for distilling the data into a more manageable form by focusing on the 68 principal components that retained approximately 90% of their original signal variance. This not only enhanced the robustness of our results by minimizing the number of parameters required for estimation but also significantly improved the signal-to-noise ratio (11) **(Figure 3B).**

Dynamic whole-brain state analysis using the HMM

HMM and fMRI analysis

To analyze time-series data, we used an HMM, which assumes that behind a complex, multivariate time series such as those obtained from fMRI and electroencephalography lies a sequence drawn from a finite set of hidden states (12, 13). Although these states adhere to a uniform probabilistic distribution framework, they are characterized by unique distribution parameters. Here, we applied an HMM with a multivariate Gaussian distribution to a concatenated dataset. This approach aims to accurately estimate brain activation patterns that are commonly shared across groups. HMM inference was conducted using the HMM-MAR toolbox (14).

Estimating the HMM parameters

This was achieved through variational Bayesian inference, a probabilistic method of model parameter estimation. A critical aspect of HMM inference involves determining the number of states and the configuration of the covariance matrix prior to parameter estimation. While various methodologies exist to assist in selecting the number of states, this choice primarily affects the

granularity of the captured brain dynamics rather than yielding a singular correct answer, representing a balance between timing detail and data interpretability. Here, we estimated 12 states based on previous studies (15). To decrease the dominance of a single state over time, we opted for a single full covariance matrix applicable across all states.

Time-varying functional connectivity (TVFC) estimates using HMM are known to exhibit instability, characterized by variability in solutions across different inference runs. To mitigate this issue and obtain stable results, our approach leverages the concept of free energy, which is rooted in Bayesian principles. In our methodology, we executed model inferences 150 times and subsequently identified the most accurate model as that with the lowest free energy (16).

Dynamics and HMM state transitions

Using the inferred HMM, we extracted the key properties of the HMM states and indices to investigate group differences and treatment effects. All HMM dynamic characteristics were derived from the posterior probability time course (14). We quantified the state fractional occupancies as the proportion of time during which a state was active. The lifetime of each state was calculated as the duration before the transition to another state. In addition, we determined the occurrence rate by measuring a state's activation frequency per time step (i.e., the TR). Critical analysis involved examining transition probabilities to ascertain the state-transition dynamics, particularly identifying the originating and subsequent states when transitions were frequent.

These measurements, coupled with the state durations, provided insight into the time-varying brain network dynamics.

Statistical analysis

We used R version 4.0.2 with the "ggplot2" package (version 3.4.4). For all analyses, $p < 0.05$ and the false discovery rate (FDR) correction were used to determine the significance level. Additionally, for all analyses using the HMM state dynamics, we performed nonparametric permutation testing to investigate statistical significance (17). By running 1000 permutations to estimate the statistical values, we created a null distribution. The iterations stopped when the estimated standard error of the mean became less than 0.01. Each statistical value, such as an F value in a generalized linear mixed model (GLMM), was thresholded at the corresponding critical probability threshold (corrected for multiple comparisons at $p < 0.05$), and statistical values exceeding this threshold were rejected. These procedures were conducted using the "lmPerm" package (version 2.1.0) for R.

HMM time courses: MDD vs. HC group

We employed a GLMM, incorporating age and sex as fixed effects and participant identifiers as random effects. We included age and sex, which are considered extraneous to the core investigation, to mitigate their confounding influence and ensure a more accurate analysis of the

variables of interest. Additionally, the clinical status (i.e., MDD patients or HCs) was factored into the model. The dependent variable was an index obtained from the HMM time course described above to test the effect of clinical status.

HMM time course vs. rumination severity

We explored the correlation between HMM-derived temporal metrics and rumination severity as measured by the RRS. To ensure robustness, we employed partial correlation analysis, controlling for potential confounding factors such as age and sex.

HMM time courses vs. treatment modality (CBT or pharmacotherapy)

We investigated the combined effects of treatment and temporal factors on the HMM index, particularly in relation to MDD pathophysiology and rumination severity. To elucidate the different mechanisms underlying pharmacotherapy and CBT, we intentionally omitted the alternative therapeutic approaches, ECT and rTMS, from the analysis. We employed a GLMM that encompassed both the interaction and main effects of treatment group and time as independent variables, with a post hoc analysis focusing on within-group comparisons of the HMM index before and after treatment. This additional analysis provides valuable insights into the specific changes attributable to treatment.

To minimize selection bias, we implemented propensity score matching using the “matchIt” package (version 4.5.5) for R. Scores were calculated using a logistic regression model, with the

choice between CBT and pharmacotherapy as the dependent variable. We incorporated the baseline characteristics shown in **Table 1** as independent variables in this model (18). This strategy was pivotal in ensuring equitable comparisons between the treatment groups and in effectively adjusting for baseline confounders. We employed nearest-neighbor matching with a stringent 0.1-caliper distance to identify appropriately matched cases. After establishing this controlled setting, we estimated the effects of the treatment modalities using comprehensive multivariable regression analysis.

Demographic and clinical data

Categorical data were analyzed using Fisher's exact test, and continuous data were analyzed using two-tailed *t* tests, comparing the groups for all demographic and clinical characteristics. Using a GLMM, clinical data, including HAMD and RRS, were also examined for time × treatment (CBT or pharmacotherapy) interactions to verify the effect of each treatment, and post hoc analysis was performed for pre- and posttreatment comparisons within groups. We also controlled for covariates using propensity scores.

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Table S1: Differences in the dynamics of each hidden Markov model (HMM) state between patients with major depressive disorder (MDD)and healthy controls (HCs)

	HC		MDD				
variable	mean	sd	mean	sd	beta_val	p_val	sig
ave_state1	0.066	0.036	0.068	0.038	0.002	1.000	
ave_state2	0.115	0.044	0.115	0.043	0.000	1.000	
ave_state3	0.109	0.055	0.106	0.052	-0.006	0.548	
ave_state4	0.085	0.037	0.100	0.042	0.015	0.045	*
ave_state5	0.081	0.035	0.092	0.039	0.011	0.145	
ave_state6	0.058	0.069	0.048	0.048	-0.010	1.000	
ave_state7	0.055	0.063	0.054	0.051	0.000	1.000	
ave_state8	0.074	0.034	0.074	0.036	0.001	0.909	
ave_state9	0.097	0.045	0.119	0.044	0.023	0.000	*
ave_state10	0.103	0.057	0.073	0.043	-0.030	0.000	*
ave_state11	0.077	0.056	0.047	0.042	-0.029	0.000	*
ave_state12	0.080	0.044	0.103	0.046	0.023	0.000	*
LT_state1	4.303	1.889	4.041	1.425	-0.266	1.000	
LT_state2	5.388	1.978	5.582	2.009	0.179	1.000	
LT_state3	7.442	3.164	7.402	3.550	-0.158	1.000	
LT_state4	5.224	1.943	5.110	1.512	-0.144	1.000	
LT_state5	4.832	1.791	5.231	2.108	0.353	1.000	
LT_state6	4.493	3.801	3.981	3.379	-0.489	1.000	
LT_state7	3.837	3.450	3.835	2.483	0.033	1.000	
LT_state8	4.423	1.601	4.740	1.934	0.310	1.000	
LT_state9	4.423	1.583	4.368	1.318	-0.057	1.000	
LT_state10	4.906	1.866	4.356	1.948	-0.653	1.000	
LT_state11	4.255	2.142	2.932	2.402	-1.340	0.017	*
LT_state12	4.827	1.752	4.899	1.789	0.015	1.000	
pop_state1	0.014	0.009	0.014	0.007	0.000	1.000	
pop_state2	0.021	0.009	0.021	0.008	0.001	1.000	
pop_state3	0.017	0.007	0.015	0.008	-0.001	0.387	
pop_state4	0.017	0.006	0.019	0.009	0.002	0.226	

pop_state5	0.016	0.007	0.018	0.008	0.001	1.000	
pop_state6	0.009	0.009	0.008	0.007	-0.001	0.891	
pop_state7	0.010	0.010	0.011	0.008	0.001	0.484	
pop_state8	0.015	0.008	0.016	0.008	0.001	1.000	
pop_state9	0.021	0.011	0.026	0.010	0.006	0.000	*
pop_state10	0.020	0.010	0.015	0.010	-0.004	0.025	*
pop_state11	0.015	0.012	0.010	0.010	-0.006	0.024	*
pop_state12	0.014	0.008	0.020	0.010	0.006	0.000	*
switch	0.228	0.026	0.232	0.023	0.005	0.372	
tp1to1	0.662	0.042	0.653	0.045	-0.010	0.435	
tp1to2	0.036	0.013	0.035	0.016	-0.001	1.000	
tp1to3	0.022	0.008	0.025	0.009	0.003	1.000	
tp1to4	0.019	0.006	0.019	0.005	0.000	1.000	
tp1to5	0.028	0.010	0.028	0.011	0.000	1.000	
tp1to6	0.028	0.008	0.028	0.009	-0.001	1.000	
tp1to7	0.030	0.010	0.029	0.010	-0.001	1.000	
tp1to8	0.040	0.015	0.042	0.016	0.002	1.000	
tp1to9	0.026	0.010	0.027	0.011	0.000	1.000	
tp1to10	0.024	0.008	0.027	0.009	0.003	0.435	
tp1to11	0.037	0.016	0.037	0.015	0.000	1.000	
tp1to12	0.024	0.009	0.025	0.008	0.002	0.758	
tp2to1	0.046	0.015	0.043	0.012	-0.003	0.711	
tp2to2	0.682	0.043	0.688	0.045	0.006	1.000	
tp2to3	0.022	0.007	0.023	0.006	0.000	1.000	
tp2to4	0.033	0.012	0.035	0.012	0.003	0.711	
tp2to5	0.030	0.009	0.031	0.009	0.000	1.000	
tp2to6	0.032	0.010	0.031	0.009	-0.001	0.711	
tp2to7	0.034	0.009	0.036	0.012	0.001	1.000	
tp2to8	0.036	0.010	0.037	0.011	0.001	1.000	
tp2to9	0.042	0.015	0.046	0.015	0.003	0.711	
tp2to10	0.032	0.013	0.031	0.011	-0.001	1.000	
tp2to11	0.051	0.018	0.054	0.014	0.003	1.000	

tp2to12	0.031	0.010	0.030	0.009	-0.001	1.000
tp3to1	0.031	0.010	0.035	0.011	0.004	0.299
tp3to2	0.029	0.010	0.029	0.009	0.000	0.941
tp3to3	0.718	0.065	0.711	0.052	-0.008	0.744
tp3to4	0.019	0.005	0.020	0.005	0.000	0.941
tp3to5	0.024	0.007	0.025	0.008	0.001	0.963
tp3to6	0.031	0.009	0.029	0.009	-0.002	0.627
tp3to7	0.030	0.010	0.032	0.011	0.001	1.000
tp3to8	0.034	0.015	0.032	0.011	-0.002	0.627
tp3to9	0.037	0.012	0.034	0.011	-0.003	0.588
tp3to10	0.032	0.014	0.031	0.010	-0.001	0.872
tp3to11	0.028	0.008	0.030	0.009	0.003	0.379
tp3to12	0.036	0.015	0.035	0.015	-0.001	0.872
tp4to1	0.026	0.007	0.028	0.009	0.002	0.732
tp4to2	0.035	0.012	0.035	0.012	0.000	1.000
tp4to3	0.021	0.007	0.022	0.008	0.001	1.000
tp4to4	0.685	0.052	0.682	0.045	-0.003	1.000
tp4to5	0.032	0.012	0.031	0.011	-0.001	1.000
tp4to6	0.034	0.009	0.034	0.011	0.000	1.000
tp4to7	0.029	0.007	0.030	0.009	0.000	1.000
tp4to8	0.032	0.011	0.031	0.011	-0.001	1.000
tp4to9	0.028	0.011	0.030	0.011	0.002	1.000
tp4to10	0.032	0.012	0.034	0.011	0.002	0.798
tp4to11	0.031	0.009	0.032	0.009	0.001	1.000
tp4to12	0.043	0.016	0.047	0.015	0.004	0.798
tp5to1	0.025	0.008	0.028	0.010	0.002	0.405
tp5to2	0.025	0.008	0.024	0.008	0.000	0.922
tp5to3	0.030	0.013	0.031	0.012	0.002	0.922
tp5to4	0.031	0.010	0.034	0.013	0.003	0.405
tp5to5	0.682	0.046	0.684	0.047	0.002	0.922
tp5to6	0.032	0.010	0.030	0.009	-0.002	0.758
tp5to7	0.032	0.009	0.031	0.009	-0.001	0.904

tp5to8	0.033	0.011	0.034	0.012	0.001	0.888	
tp5to9	0.034	0.011	0.035	0.011	0.001	0.904	
tp5to10	0.021	0.006	0.024	0.007	0.003	0.041	*
tp5to11	0.039	0.015	0.036	0.012	-0.003	0.922	
tp5to12	0.037	0.016	0.036	0.012	0.000	0.922	
tp6to1	0.028	0.013	0.029	0.014	0.001	0.941	
tp6to2	0.022	0.010	0.022	0.010	0.001	1.000	
tp6to3	0.019	0.008	0.020	0.009	0.001	0.884	
tp6to4	0.024	0.010	0.026	0.012	0.002	0.884	
tp6to5	0.023	0.011	0.024	0.012	0.001	0.884	
tp6to6	0.652	0.061	0.667	0.071	0.018	0.884	
tp6to7	0.025	0.006	0.025	0.007	-0.001	1.000	
tp6to8	0.024	0.008	0.025	0.010	0.001	0.884	
tp6to9	0.022	0.011	0.022	0.012	0.000	1.000	
tp6to10	0.023	0.010	0.024	0.009	0.001	0.941	
tp6to11	0.025	0.010	0.026	0.008	0.001	0.884	
tp6to12	0.021	0.007	0.023	0.009	0.002	0.884	
tp7to1	0.024	0.009	0.025	0.010	0.002	0.676	
tp7to2	0.020	0.008	0.022	0.011	0.002	0.676	
tp7to3	0.019	0.007	0.020	0.008	0.001	1.000	
tp7to4	0.028	0.013	0.028	0.015	0.000	1.000	
tp7to5	0.025	0.011	0.026	0.013	0.002	0.744	
tp7to6	0.027	0.006	0.026	0.010	-0.002	0.676	
tp7to7	0.656	0.057	0.655	0.070	0.001	1.000	
tp7to8	0.024	0.009	0.024	0.010	0.000	1.000	
tp7to9	0.022	0.008	0.025	0.013	0.004	0.568	
tp7to10	0.022	0.011	0.024	0.010	0.002	0.676	
tp7to11	0.034	0.015	0.033	0.013	-0.001	1.000	
tp7to12	0.023	0.009	0.023	0.009	0.000	1.000	
tp8to1	0.030	0.011	0.030	0.011	0.000	0.871	
tp8to2	0.022	0.007	0.022	0.007	0.000	0.871	
tp8to3	0.028	0.010	0.029	0.012	0.001	0.871	

tp8to4	0.029	0.009	0.029	0.010	0.000	0.922
tp8to5	0.027	0.010	0.028	0.011	0.001	0.871
tp8to6	0.031	0.009	0.030	0.009	-0.001	0.871
tp8to7	0.027	0.008	0.028	0.010	0.002	0.871
tp8to8	0.644	0.037	0.646	0.043	0.002	0.871
tp8to9	0.034	0.012	0.033	0.013	-0.001	0.871
tp8to10	0.045	0.016	0.045	0.015	0.000	0.898
tp8to11	0.023	0.007	0.024	0.007	0.000	0.871
tp8to12	0.027	0.008	0.025	0.010	-0.001	0.871
tp9to1	0.040	0.015	0.039	0.014	0.000	1.000
tp9to2	0.037	0.012	0.035	0.011	-0.002	0.825
tp9to3	0.028	0.010	0.031	0.012	0.003	0.825
tp9to4	0.043	0.016	0.041	0.014	-0.002	1.000
tp9to5	0.032	0.012	0.033	0.012	0.001	0.825
tp9to6	0.035	0.013	0.033	0.011	-0.003	0.825
tp9to7	0.042	0.013	0.046	0.017	0.003	0.825
tp9to8	0.038	0.013	0.038	0.015	0.001	1.000
tp9to9	0.667	0.046	0.665	0.053	-0.001	1.000
tp9to10	0.052	0.018	0.048	0.015	-0.004	0.825
tp9to11	0.033	0.011	0.032	0.011	0.000	1.000
tp9to12	0.026	0.009	0.027	0.008	0.001	0.825
tp10to1	0.042	0.017	0.039	0.016	-0.003	0.743
tp10to2	0.041	0.019	0.037	0.015	-0.004	0.425
tp10to3	0.018	0.006	0.018	0.005	0.000	1.000
tp10to4	0.036	0.015	0.034	0.014	-0.003	0.427
tp10to5	0.035	0.015	0.031	0.013	-0.004	0.366
tp10to6	0.035	0.011	0.033	0.012	-0.003	0.427
tp10to7	0.039	0.014	0.035	0.014	-0.004	0.425
tp10to8	0.029	0.009	0.028	0.009	-0.002	0.427
tp10to9	0.027	0.010	0.028	0.010	0.000	0.984
tp10to10	0.667	0.053	0.659	0.048	-0.011	0.425
tp10to11	0.022	0.007	0.023	0.007	0.001	0.663

tp10to12	0.035	0.016	0.034	0.014	-0.001	0.743
tp11to1	0.022	0.007	0.023	0.007	0.001	0.720
tp11to2	0.021	0.009	0.020	0.008	-0.001	0.671
tp11to3	0.030	0.015	0.029	0.012	-0.002	0.720
tp11to4	0.024	0.011	0.024	0.010	-0.001	0.720
tp11to5	0.026	0.012	0.025	0.010	-0.001	0.720
tp11to6	0.030	0.011	0.028	0.010	-0.002	0.671
tp11to7	0.026	0.009	0.025	0.008	-0.001	0.671
tp11to8	0.035	0.018	0.034	0.015	-0.001	0.980
tp11to9	0.035	0.026	0.030	0.013	-0.007	0.363
tp11to10	0.021	0.006	0.022	0.007	0.002	0.671
tp11to11	0.651	0.049	0.648	0.052	-0.005	0.834
tp11to12	0.023	0.008	0.022	0.009	0.000	0.834
tp12to1	0.025	0.007	0.029	0.012	0.004	0.263
tp12to2	0.031	0.013	0.031	0.012	0.000	1.000
tp12to3	0.044	0.019	0.042	0.014	-0.002	1.000
tp12to4	0.028	0.011	0.029	0.012	0.001	0.846
tp12to5	0.035	0.013	0.034	0.014	-0.001	1.000
tp12to6	0.033	0.010	0.031	0.010	-0.002	0.816
tp12to7	0.029	0.010	0.028	0.008	-0.001	0.846
tp12to8	0.031	0.011	0.029	0.010	-0.002	0.846
tp12to9	0.024	0.007	0.025	0.008	0.002	0.705
tp12to10	0.030	0.014	0.032	0.011	0.003	0.705
tp12to11	0.027	0.008	0.027	0.007	0.000	1.000
tp12to12	0.675	0.051	0.671	0.050	-0.004	0.816

Table S2: Impact of treatment modalities on hidden Markov model (HMM) time courses: Cognitive behavioral therapy (CBT) versus pharmacotherapy.

	ANOVA *p* value			Post hoc analysis	
	Between groups			Within group	
	(group-by-time)			(pre-post)	
values	group	time	interaction	CBT	Pharmacotherapy
ave_state1	0.288	0.272	0.922		
ave_state2	0.583	0.824	0.564		
ave_state3	0.240	1.000	0.863		
ave_state4	1.000	0.843	0.279		
ave_state5	0.922	0.474	[b]0.075		
ave_state6	0.094	0.902	0.706		
ave_state7	0.655	0.961	0.941		
ave_state8	0.533	0.342	0.163		
ave_state9	0.007	0.361	0.686		
ave_state10	0.144	0.941	0.784		
ave_state11	0.902	0.843	0.594		
ave_state12	0.026	0.961	0.312		
LT_state1	0.619	0.200	0.824		
LT_state2	0.168	0.606	0.863		
LT_state3	0.615	0.619	1.000		
LT_state4	0.655	0.615	[b]0.060		
LT_state5	0.961	0.619	1.000		
LT_state6	0.337	0.745	0.314		
LT_state7	0.564	0.804	0.296		
LT_state8	0.032	0.902	0.231		
LT_state9	0.922	0.178	0.121		
LT_state10	0.863	0.765	0.390		
LT_state11	0.236	0.121	0.638		
LT_state12	0.210	0.594	0.548		
pop_state1	0.660	0.765	0.902		
pop_state2	0.745	0.340	0.765		
pop_state3	0.377	0.125	0.961		

pop_state4	0.452	0.594	1.000		
pop_state5	0.961	1.000	0.706		
pop_state6	0.351	0.902	0.784		
pop_state7	0.922	1.000	0.540		
pop_state8	0.643	0.405	0.289		
pop_state9	0.003	0.902	0.138		
pop_state10	0.030	0.548	0.922		
pop_state11	0.804	0.510	0.633		
pop_state12	0.070	0.843	[a]0.046	[a]0.046	0.74
switch	0.961	0.138	[a]0.007	[a]0.008	0.68
tp1to1	0.342	0.660	0.159		
tp1to2	0.438	0.863	0.401		
tp1to3	1.000	0.070	0.643		
tp1to4	1.000	0.980	0.882		
tp1to5	0.643	0.438	0.606		
tp1to6	1.000	0.053	0.114		
tp1to7	0.481	0.368	0.442		
tp1to8	0.383	0.420	1.000		
tp1to9	0.533	0.351	0.606		
tp1to10	0.643	0.154	0.882		
tp1to11	0.189	0.533	0.902		
tp1to12	0.843	0.357	[a]0.031	[a]0.036	0.80
tp2to1	0.686	0.022	0.980		
tp2to2	0.037	1.000	[b]0.061		
tp2to3	0.157	1.000	0.804		
tp2to4	0.082	0.462	0.265		
tp2to5	0.462	1.000	1.000		
tp2to6	0.902	0.980	0.655		
tp2to7	0.922	0.980	[b]0.078		
tp2to8	0.922	0.902	0.660		
tp2to9	0.135	0.784	0.264		
tp2to10	0.521	0.362	0.120		

tp2to11	0.765	0.784	0.863
tp2to12	0.004	0.824	0.804
tp3to1	0.191	0.254	0.804
tp3to2	0.200	0.638	0.765
tp3to3	0.638	0.686	0.784
tp3to4	0.643	0.505	0.295
tp3to5	0.603	0.863	0.686
tp3to6	0.219	1.000	0.961
tp3to7	0.018	0.843	[b]0.081
tp3to8	0.337	0.302	1.000
tp3to9	0.725	0.114	0.298
tp3to10	0.541	0.556	0.500
tp3to11	0.236	0.121	[a]0.040
tp3to12	0.623	0.458	0.290
tp4to1	0.123	0.366	0.824
tp4to2	0.271	0.638	0.922
tp4to3	0.619	0.725	0.745
tp4to4	0.441	0.922	0.686
tp4to5	0.291	0.039	0.941
tp4to6	0.474	0.961	0.804
tp4to7	0.228	0.029	0.660
tp4to8	0.022	0.633	[b]0.084
tp4to9	1.000	0.571	0.643
tp4to10	0.442	1.000	0.843
tp4to11	1.000	0.366	0.804
tp4to12	0.089	0.980	0.177
tp5to1	0.210	0.745	1.000
tp5to2	0.149	0.353	0.534
tp5to3	0.745	0.725	0.660
tp5to4	0.033	1.000	0.426
tp5to5	0.882	0.594	0.655
tp5to6	0.706	0.229	0.103

tp5to7	0.286	0.686	0.433
tp5to8	0.594	0.843	0.725
tp5to9	0.554	0.882	0.158
tp5to10	0.522	0.961	[b]0.073
tp5to11	0.745	0.961	0.603
tp5to12	0.902	0.765	0.667
tp6to1	1.000	0.257	0.725
tp6to2	0.660	0.522	0.902
tp6to3	0.824	0.863	0.765
tp6to4	0.415	0.003	[a]0.034
tp6to5	1.000	0.784	0.941
tp6to6	0.540	0.660	0.686
tp6to7	0.603	0.100	0.980
tp6to8	0.902	0.117	0.451
tp6to9	0.296	0.516	0.606
tp6to10	0.765	0.182	[a]0.042
tp6to11	1.000	0.060	[b]0.086
tp6to12	0.706	0.452	0.199
tp7to1	0.516	0.184	0.144
tp7to2	0.173	0.941	0.784
tp7to3	0.035	0.026	0.686
tp7to4	0.594	0.882	0.594
tp7to5	0.089	0.025	0.902
tp7to6	1.000	0.045	0.296
tp7to7	0.980	0.563	1.000
tp7to8	0.804	0.592	0.784
tp7to9	0.725	0.366	0.260
tp7to10	0.804	0.824	1.000
tp7to11	0.474	0.583	0.745
tp7to12	0.346	1.000	0.745
tp8to1	0.725	0.667	0.288
tp8to2	0.643	0.941	0.843

tp8to3	0.062	0.882	0.281
tp8to4	0.638	0.259	0.481
tp8to5	0.490	0.103	0.221
tp8to6	0.332	0.390	1.000
tp8to7	0.922	0.573	0.303
tp8to8	0.643	0.619	0.482
tp8to9	0.408	0.804	1.000
tp8to10	0.081	0.941	0.444
tp8to11	0.902	0.824	0.432
tp8to12	0.462	0.490	0.843
tp9to1	1.000	1.000	0.594
tp9to2	0.462	0.922	0.667
tp9to3	0.293	0.522	0.264
tp9to4	0.606	0.473	0.980
tp9to5	0.941	0.458	0.843
tp9to6	0.902	0.633	0.961
tp9to7	0.122	0.293	1.000
tp9to8	0.655	1.000	0.615
tp9to9	0.370	0.804	0.405
tp9to10	0.500	0.882	0.961
tp9to11	0.167	0.941	0.863
tp9to12	0.357	0.606	[b]0.055
tp10to1	0.186	0.060	0.385
tp10to2	0.824	0.725	0.534
tp10to3	1.000	0.784	0.863
tp10to4	0.667	0.141	0.189
tp10to5	0.563	1.000	0.606
tp10to6	0.843	0.068	0.686
tp10to7	0.401	0.623	1.000
tp10to8	0.941	0.660	0.745
tp10to9	0.922	0.046	0.252
tp10to10	0.980	0.655	0.211

tp10to11	0.980	0.477	0.139		
tp10to12	0.922	0.922	0.686		
tp11to1	1.000	1.000	0.581		
tp11to2	0.396	0.318	[a]0.031		
tp11to3	0.556	0.016	[a]0.019		
tp11to4	0.078	0.980	0.824		
tp11to5	0.980	0.227	0.706		
tp11to6	0.067	0.165	0.843		
tp11to7	0.583	0.455	0.391		
tp11to8	0.725	0.706	0.363		
tp11to9	0.980	0.922	0.272		
tp11to10	0.262	0.922	0.902		
tp11to11	1.000	0.401	0.882		
tp11to12	0.079	0.225	0.533		
tp12to1	0.026	0.500	0.510		
tp12to2	0.015	0.784	[a]0.010	[a]0.021	0.57
tp12to3	0.233	0.096	0.745		
tp12to4	0.139	0.231	0.573		
tp12to5	0.150	0.002	[a]0.026	[a]0.033	0.059
tp12to6	0.961	0.470	1.000		
tp12to7	0.863	1.000	0.413		
tp12to8	0.455	0.510	1.000		
tp12to9	0.236	0.554	0.260		
tp12to10	0.505	0.182	0.725		
tp12to11	0.706	1.000	0.540		
tp12to12	0.024	0.196	0.226		

tp, transition probability; [a]FDR $p<0.05$; [b]FDR $p<0.1$

Table S3. Clinical response to CBT or pharmacotherapy

	CBT (n=28)		Drug (n=32)		Group difference (CBT > Drug)	p values		
	Mean	SD	Mean	SD		Arm	Time	Interaction
GRID-HAMD score						.804	<.001	.863
0 weeks (baseline)	16.82	3.02	16.81	5.83	$t(104) = 0.426$, $p = .671$			
16 weeks (postintervention)	7.36	6.11	6.21	6.11	$t(104) = 0.753$, $p = .453$			
Pre > post	$t(104) = 6.36$, p<.001[a]		$t(104) = 6.71$, p<.001[a]					
RRS total score						<.001	.003	.615
0 weeks	60.43	10.76	50.41	21.22	$t(103) = 2.963$, $p = .004$			
16 weeks	50.40	13.90	40.25	14.84	$t(103) = 2.341$, $p = .021$			
Pre > post	$t(103) = 2.31$, p=.022[a]		$t(103) = 1.84$, p=.068					
RRS brooding score						.0152	<.001	.804
0 weeks	15.00	3.24	13.12	5.54	$t(103) = 2.043$, $p = .043$			
16 weeks	12.16	4.49	10.64	4.09	$t(103) = 1.333$, $p = .185$			
Pre>post	$t(103) = 2.84$, p=.022[a]		$t(103) = 2.07$, p=.090					
RRS reflection score						<.001	.349	.706
0 weeks	10.89	3.14	8.94	4.18	$t(103) =$			

					2.543, p = .012
16 weeks	10.64	3.60	8.00	3.86	$t(103)$ = 3.016, p = .003
Pre>post	$t(103)$ = .25, p=.80		$t(103)$ = .863, p=.390		

The data are n (%) or means (SD).

CBT, cognitive behavioral therapy; Drug, pharmacotherapy; GRID-HAMD, 17-item GRID-Hamilton Depression Rating Scale; RRS, Rumination Response Scale

[a]FDR_corrected p value < 0.05