A Data-Driven Closed-Loop Control Approach to Drive Neural State Transitions for Mechanistic Insight

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Abstract

Repetitive negative thinking (RNT) is a transdiagnostic risk factor for mood disorders, consistently associated with altered biological substrates, including functional connectivity in key brain networks. As a stable cognitive feature linked to vulnerability across disorders, RNT presents a compelling target for intervention. However, leveraging RNT as a modifiable mechanism requires a deeper understanding of its causal neural dynamics and how targeted modulation can induce adaptive change. This study introduces a data-driven framework combining dynamical system reconstruction (DSR) with model predictive control (MPC) to infer optimal control policies for transitioning between resting and sad mood brain states, based on functional magnetic resonance imaging (fMRI) data. Using generative DSR models trained on fMRI data from participants with a remitted major depressive disorder (rMDD) and matched healthy controls from a resting state period and a sad mood induction task, we reconstruct nonlinear brain dynamics and derive region-specific control strategies for transitioning from resting to sad mood states. Our results demonstrate that small brain regions, such as the subgenual anterior cingulate cortex (sgACC), exhibit higher controllability, requiring less energy to drive state transitions. Notably, rMDD group shows reduced control energy demands and stronger neural connectivity, particularly relating to dorsolateral prefrontal cortex (DLPFC)-hippocampal pathways, suggesting heightened susceptibility to relapse into negative mood states. These findings highlight the potential of closed-loop control approaches to uncover mechanistic insights into RNT and inform targeted interventions for mood disorders in the future.

Introduction

Repetitive negative thinking (RNT)—a pattern of persistent, repetitive negative thoughts from which it is difficult to disengage—is a core transdiagnostic feature of mood and anxiety disorders (Bell et al., 2023; Moulds and McEvoy, 2025). It encompasses cognitive phenomena such as rumination and worry, and is characterized by its abstract, self-focused content and perceived uncontrollability (Gustavson et al., 2018). Importantly, RNT often persists beyond symptomatic remission and has been robustly

linked to the onset, maintenance, and severity of psychopathology (Spinhoven et al., 2018; Timm et al., 2017). Intervening on RNT thus remains a pressing goal for prevention and treatment. However, effective intervention requires mechanistic insight into how neural systems shift into RNT-associated states.

Previous studies have associated RNT with altered functional connectivity across large-scale brain networks, particularly increased coupling between default mode and fronto-parietal regions and decreased coupling with the salience network (Lydon-Staley et al., 2019; Zamoscik et al., 2018; Zhu et al., 2012). Elevated levels of connectivity involving the parahippocampal gyrus, anterior cingulate cortex, and posterior cingulate cortex have been especially prominent in remitted depression (Zamoscik et al., 2014). Yet these descriptive findings fall short of revealing the causal mechanisms that govern transitions between healthy and maladaptive cognitive states.

To uncover such mechanisms, generative models that simulate brain dynamics—and allow for controlled perturbation—have emerged as a powerful framework (Durstewitz et al., 2021, 2023; Luo et al., 2025). Within this framework, optimal control theory enables formal inference of the minimal interventions required to shift brain states under physiological constraints (Brunton and Kutz, 2019). Prior work has applied linear control models to empirical connectivity data to study cognitive transitions, predict symptom severity, or evaluate controllability in neurological conditions (Betzel et al., 2016; Deng et al., 2022; Lynn and Bassett, 2019; Medaglia et al., 2017; Parkes et al., 2024; Yao et al., 2025). Others have introduced biophysical or neural field models to simulate state transitions in conditions such as epilepsy (Salfenmoser and Obermayer, 2022; Taylor et al., 2015). In mental disorder treatments, interventions have been conceptualized within a model predictive control problem (Brar et al., 2018; Chang et al., 2020; Santaniello et al., 2011; Steffen et al., 2024). While valuable, many of these approaches rely on simplified, often linear dynamics, which limit mechanistic interpretability and fail to capture the nonlinear behaviors—such as multistability or chaos—that characterize real neural systems (Breakspear, 2017; Driscoll et al., 2024; Strogatz, 2015; Volkmann et al., 2024). Biologically more detailed models often rely on handcrafted equations (Martínez et al., 2023; Taylor et al., 2015), which are typically not learned from data and are thus difficult to adapt or generalize across individuals and datasets.

Recent advances in dynamical systems reconstruction (DSR) offer a promising alternative. Data-driven methods learn expressive, nonlinear models directly from time series data and can act as computational surrogates of neural systems (Brenner et al., 2025; Brunton and Kutz, 2019; Durstewitz et al., 2023; Hess et al., 2023; Pathak et al., 2018). Here, we build on these advances by combining nonlinear DSR with optimal control to investigate the mechanisms underlying RNT. Using fMRI data from participants with a remitted major depressive disorder (rMDD) and matched healthy controls (HC) during a negative mood induction task, a paradigm eliciting RNT, we train DSR models that capture individual neural dynamics (Brenner et al., 2025; Volkmann et al., 2024). By deriving and analyzing optimal control policies within these models, we aim to identify the causal structure that enables transitions between healthy and pathological states.

Our contributions are fourfold: We present a novel data-driven framework for inferring closed-loop optimal control policies based on nonlinear DSR models. We perform in silico experiments to examine control trajectories between RNT-associated and baseline brain states. We show that inferred control policies differ between rMDD and HC individuals, reflecting altered neural dynamics. We identify key brain regions with elevated controllability and link these findings to underlying connectivity. Together, these results offer a mechanistic, model-based perspective on RNT and establish a foundation for future causal interventions targeting pathological brain states.

2 Results

This study seeks to derive optimal control policies from fMRI recordings collected from rMDD and HC individuals to gain mechanistic insights into the neural processes underlying transitions between resting and sad mood induction states. Figure 1 depicts the general procedure.

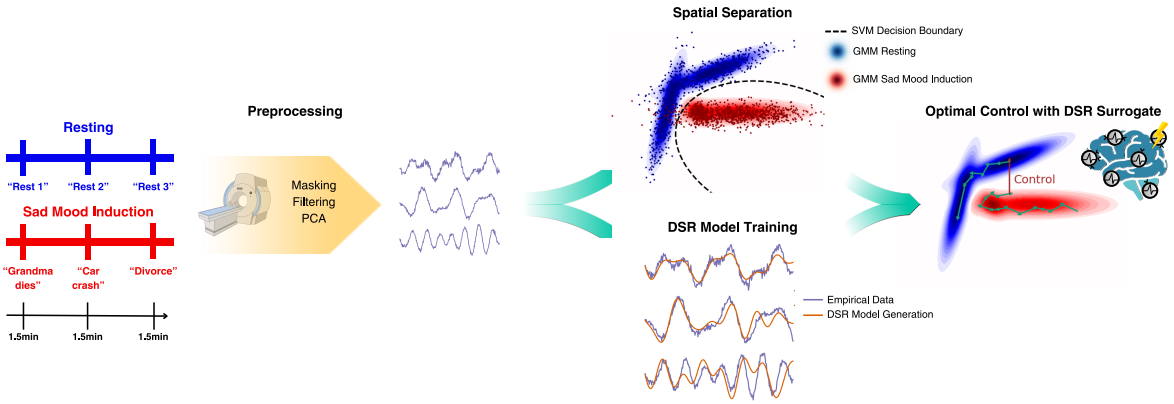

Figure 1: Neural activity was measured during two cognitive states, a resting state, and a sad mood induction state (Zamoscik et al., 2014). After preprocessing, fMRI recordings are used to train a classifier that separates rest from sad mood (top), and to train DSR models that serve as brain surrogates (bottom). The trained classifiers serve to identify the control target. After verifying the reconstruction quality, we train optimal control strategies on the inferred DSR models that drive neural states from resting to sad mood induction states.

Spatial Separation Between Resting and Sad Mood Induction To characterize differences in the representation and distribution of the two cognitive states—needed for downstream control analyses—we first trained separate Gaussian Mixture Models (GMMs) for the resting state and sad mood induction conditions (see Figure 2a for details on the preselected regions of interest; ROIs). Consistent with both groups reporting increased negative affect after sad mood induction (Zamoscik et al., 2014), the two states were well separable, with the GMMs achieving high classification accuracy on 25% held-out test sets using 5-fold cross-validation ($94\% \pm 3\%$), by assigning each test sample to the condition with higher likelihood (Figure 2b). Comparable classification performance was achieved using support vector machines (SVMs) with a nonlinear kernel ($93\% \pm 3\%$); in contrast, linear classifiers such as linear discriminant analysis (LDA) and linear-kernel SVMs performed poorly, highlighting the nonlinear nature of the boundary separating the two cognitive states. No significant group differences in classification performance were observed between HC and rMDD participants. GMMs were used in downstream analyses to define target for optimal control and to decode neural activity, inferring cognitive states from both empirical and generated trajectories. Neural state separation was still retained when sampling from the GMMs (Figure A2a).

DSR Models Learn the Underlying Dynamics Next, we inferred subject-level generative models from the neural data using piecewise linear recurrent neural networks (PLRNNs) trained with a state-of-the-art DSR protocol (Hess et al., 2023). These state-space type models—also referred to as *world models* in reinforcement learning (Ha and Schmidhuber, 2018; Hafner et al., 2025)—consist of a latent PLRNN model coupled with a linear decoder and enable the reconstruction of high-dimensional neural trajectories (see Section 5.3 for details). Representative reconstructions from the inferred models are shown in Figure 2d.

The inferred dynamics were found to be chaotic, characterized by positive maximum Lyapunov exponents ($\lambda_{\max} = 0.1 \pm 0.02$), in line with previous findings for resting states (Volkmann et al., 2024). This chaotic nature makes it inherently difficult to achieve a point-by-point match between predicted and empirical trajectories over time (Koppe et al., 2019; Mikhaeil et al., 2022; Schmidt et al., 2021). Despite this, the models successfully capture the data's underlying temporal structure, as evidenced by strong alignment in the recovered frequencies, measured in terms of the Hellinger distance D_H between power spectra ($D_H = 0.22 \pm 0.04$, Figure 2e). Moreover, the cross-correlation between different brain regions—commonly referred to as functional connectivity—exhibits highly similar patterns in both the empirical data and the model-generated test set trajectories (Figure 2c). These results underscore that, although exact trajectory matching is not expected, the inferred models nonetheless reproduce the essential statistical and spectral properties of the observed neural activity, indicating successful system identification under the DSR framework (Durstewitz et al., 2023).

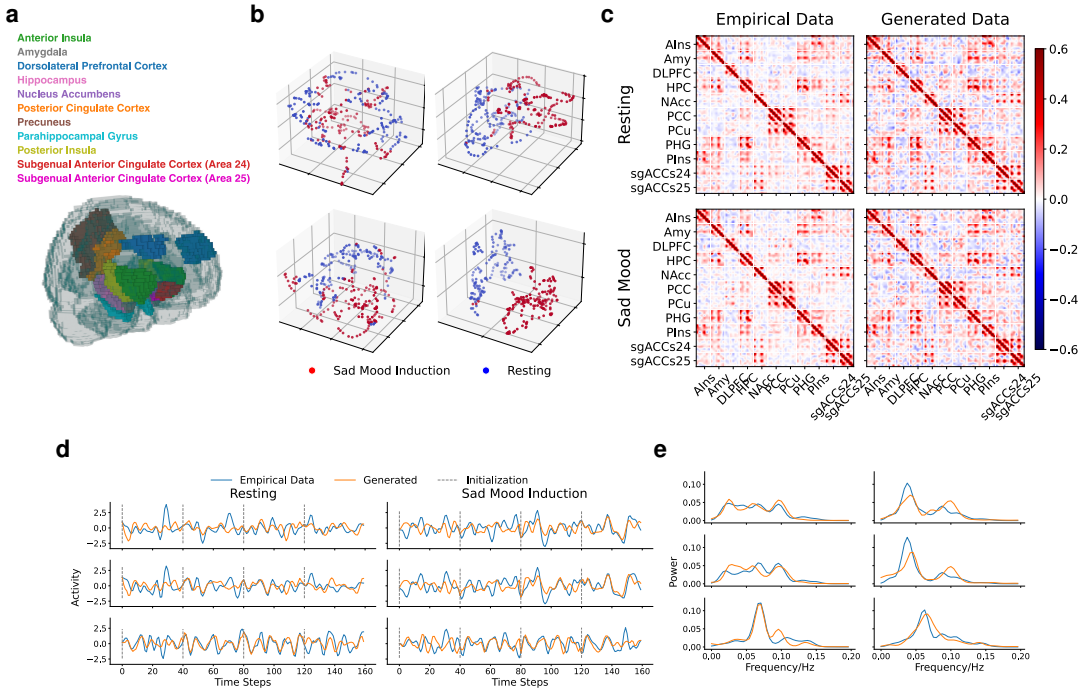

Figure 2: Neural state classifier and DSR model performance. **a**: Eleven bilateral regions of interest (ROIs) implicated in depression, as visualized here, were selected for analysis. **b**: Neural state representations projected via UMAP (McInnes et al., 2018), color coded by condition (resting: blue; sad mood induction: red) for selected participants. **c**: Median cross-correlation matrices between selected ROIs for empirical test data (left), and simulated test data from the DSR models (right). The observed connectivity patterns are consistent across empirical and simulated data. **d**: Example time series of empirical neural activity (blue) and model reconstructions (orange) for a few representative time series. Grey dashed lines indicate the initialization period for the model-generated trajectories. The final 40 time steps (test set) were not used during training. **e**: Normalized power spectra of the time series shown in **d**.

Learning Successful Control Policies Having established our DSR models, we next inferred optimal control policies by augmenting the models with an additive nonlinear control term (see Section 5.3). To derive these policies, we fixed the DSR model parameters and optimized only the control input. The objective of this optimization was to steer the inferred systems toward a desired target in a state-dependent manner. In other words, the resulting policies specify how specific brain regions should be stimulated depending on the current state, in order to reach a given target (e.g., how the amygdala must be modulated in order for the dynamical system to transition from rest to sad mood in a given time). Notably, our framework allows control to be restricted to specific output dimensions, such as, in this case, individual brain regions.

We considered a *soft target* strategy, which assigns probabilities across states based on the above mentioned GMMs and aims to steer the system toward probabilistically representative states (see Section 5.3 for details). To assess the effectiveness of the control policies, we evaluated the negative log-likelihood ($\mathrm{NLL}_{\mathrm{Ind}}$ and $\mathrm{NLL}_{\mathrm{Rest}}$ for the sad mood induction and resting state, respectively) under the GMM. The inferred control policies are governed by two hyperparameters: the control energy regularization parameter λ_{E}, which penalizes the magnitude of the control input, and the temporal horizon D, which defines the number of time steps allowed for the system to reach the target (cf. eqn. (4)).

To determine appropriate parameter values for the control energy regularization term λ_{E}, we first investigated the effect of λ_{E} on the trade-off between control energy and distance to the target, for models trained using the soft target approach on the bilateral amygdala (Figure 3a) and transitions from rest to sad mood. The resulting curve shows that for sufficiently large (or small) values of λ_{E}, the optimization favors minimizing either energy or target proximity, respectively. Importantly, the curve exhibits an elbow around $\lambda_{\mathrm{E}} = 0.1$, beyond which further reductions in target distance yield only marginal increases in energy efficiency—suggesting an optimal balance point in the trade-off. Based on this observation, we fixed λ_{E} at 0.1 for all subsequent analyses. The temporal horizon D was set to 10 to give the network some time to move toward the target using its own dynamics, while still requiring it to reach the target within a reasonable time frame for fMRI. We report results for alternative λ_{E} and D in the Supplement (Figure A3), demonstrating that our main conclusions are insensitive to moderate hyperparameter changes.

Figure 3b-3e illustrates the efficacy of our control protocol, and Figure A4 visualizes control policies across regions for a selected individual. Upon control activation, neural activity converges to the target, reverting to its intrinsic chaotic dynamics once control is deactivated. While state separation became more pronounced when control was applied across multiple brain regions (Figure A5), we observed a significant reduction in distance to the target even when controlling single regions. This improvement is driven by the indirect modulation of non-controlled regions through network-level interactions. The control policies also demonstrated the ability to generalize to previously unseen states: although the system may encounter novel configurations during deployment, the policies consistently guided the dynamics back toward the target. In principle the same procedure can be applied using a hard target approach (Figure A5).

Small Brain Regions Exhibit Great Controllability For subsequent analyses, we focused on two key questions: (1) Can we identify brain regions that are more effective than others in driving state transitions? and (2) How do these effects differ between individuals with rMDD and HC? Using the soft target approach, we derived separate control policies for each bilateral ROI.

While control policies across all regions achieved similar distances to the target (Figure 3e), the amount of energy required to achieve this convergence varied between regions (Figure 3f). Smaller regions, such as the subgenual anterior cingulate cortex (sgACC) and nucleus accumbens (NAcc), exhibited enhanced controllability, reaching the target more efficiently. Less controllability in larger brain areas might arise because they exhibit more spatial variability ($r(11) = 0.97$, $p < 0.001$), causing the first principal components to have greater variance as confirmed by a strong correlation between brain region size and control energy ($r(11) = 0.93$, $p < 0.001$). This increased dynamic range may require greater control energy to steer the distributed activity toward the target. On the other hand, sgACC and NAcc play a central role in negative mood control and are established targets for deep brain stimulation (Figee et al., 2022), such that increased controllability may also be attributed to an emphasized functional role.

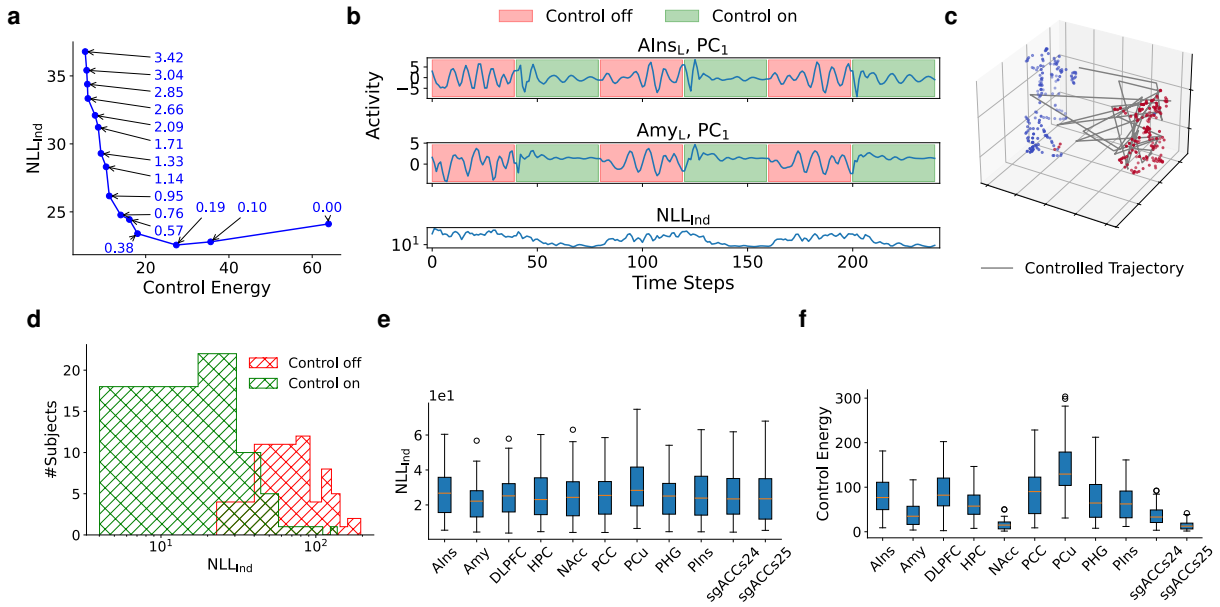

Figure 3: **a**: Pareto front illustrating the trade-off between $\mathrm{NLL_{Ind}}$ and control energy in a multiobjective optimization, using the amygdala as an example. Corresponding values of λ_{E} are indicated in the diagram. Saturation of the control occurs at approximately $\lambda_{\mathrm{E}} = 10^{-1}$, beyond which less regularization no longer improves $\mathrm{NLL_{Ind}}$. **b**: Example trajectories from a controlled region (left amygdala; Amy; middle) and an uncontrolled region (left anterior insula; AIns; top), both move toward the sad mood induction state, as confirmed by decoding with a Gaussian Mixture Model (bottom). **c**: UMAP projection reveals that generated trajectories align closely with the empirical sad mood induction state distribution (red), while diverging from resting state distributions (blue). **d**: Across all 60 subjects, control significantly reduces the negative log-likelihood of the trajectory over time steps under the GMM. **e**: Steering accuracy, quantified as the $\mathrm{NLL_{Ind}}$ distance to the target, is comparable across all stimulation sites, indicating that each region can drive the system equally close to the desired state. **f**: In contrast, the control energy required to achieve that steering differs significantly between regions.

Enhanced Neural Controllability to Sad Mood States in rMDD Patients Next, we examined differences in control policies between rMDD and HCs during the transition from resting to sad mood induction states. Overall, we observed a consistent pattern of lower control energy requirements in the rMDD group, suggesting that state transitions—and the maintenance of targets—were more easily achieved in this population (Figure 4a and Figure A6). During transitions from resting state to sad mood, individuals with rMDD exhibited reduced control energy requirements compared to HCs with statistically significant group differences observed across nearly all tested regions, with the exception of the NAcc and posterior cingulate cortex (PCC) (Figure 4b). This effect was robust across a broad range of regularization parameters and could not be attributed to a generally greater distance between the two states in the rMDD group, nor to a reduced separability between resting and sad mood states (Figure A2c). A significant difference in the proximity to the target, as measured by $\mathrm{NLL_{Ind}}$, was not observed (Figure 4c).

Connectivity Predicts Controllability Finally, we sought to identify mechanistic differences between groups that may underlie the altered controllability patterns observed in rMDD. To this end, we leveraged the piecewise linear architecture of our data-driven DSR model to estimate *coupling matrices* C, that is, transition dynamics expressed in observation space (see Section 5.3.5 for details).
The spectral norm of these coupling matrices, given by the largest singular value, was significantly higher in the rMDD group ($p < 0.001$, Figure 4d), indicating stronger global dynamical coupling relative to HCs.
To localize these effects, we examined the (6×6) submatrices of the full coupling matrices that quantify how activity in one region influences transitions in another. This revealed elevated directed coupling in

rMDD, particularly toward—but not away from—the dorsolateral prefrontal cortex (DLPFC) (Figure 4e), a region frequently implicated in cognitive control and the top-down regulation of affect.
Finally, we asked whether regional coupling strength predicts controllability. Specifically, we computed the spectral norm of the 66×6 submatrices representing directed coupling from each region to all others, and correlated these values with the control energy required to reach the target (Figure 4f, 4g). Across most regions, stronger outward coupling was associated with lower control energy, suggesting that regions with greater influence over the network facilitate more efficient control. This effect was particularly pronounced in the anterior insula (AIns), hippocampus (HPC), PCC, and parahippocampal gyrus (PHG) — all of which showed increased coupling in rMDD, and many of which directly or indirectly modulate DLPFC dynamics (Figure 4e). These findings may indicate that regions exerting strong outbound influence, especially those interfacing with prefrontal control circuits, play a central role in steering brain state transitions in depression.

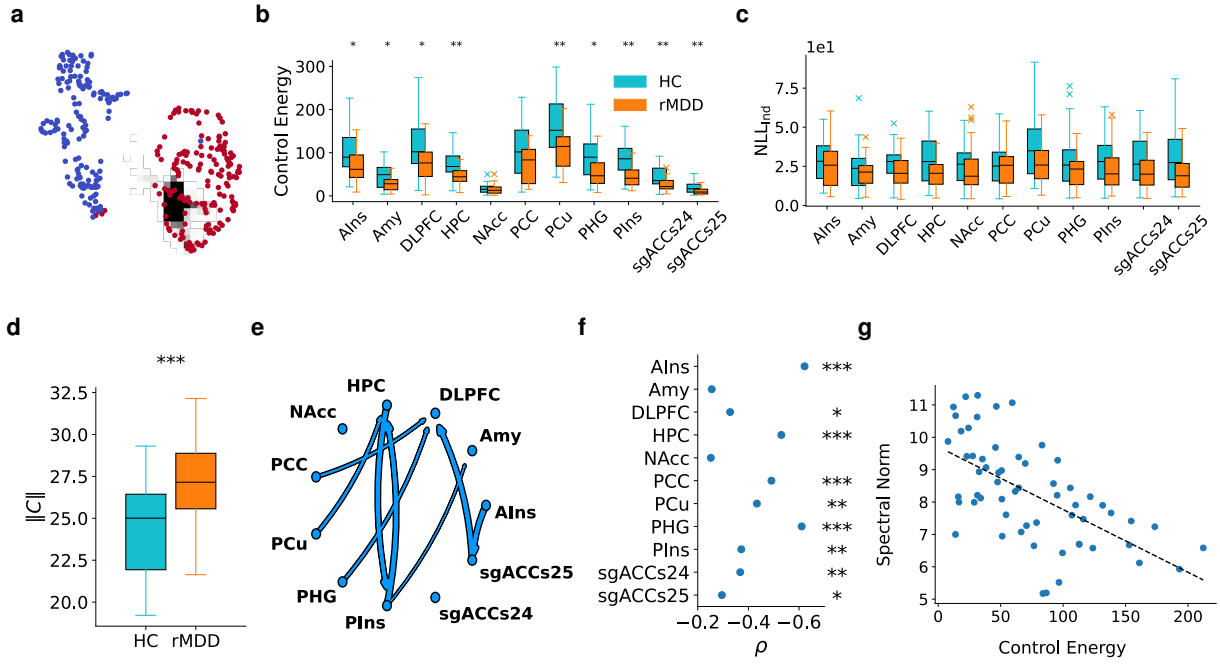

Figure 4: Control analyses and relationship to brain region coupling. **a**: UMAP visualization of empirical states (blue and red). Different initializations of controlled trajectories yield the heat map (black) of the controlled activity which shows that the activity remains in the sad mood induction region due to the control. **b**: Control energy required to drive the brain toward the target by stimulating individual brain regions. rMDD participants consistently require less energy than HC. **c**: Despite the different amounts of energy expended, the groups do not show significant differences in proximity to the target. **d**: Global coupling strength, measured as the spectral norm of the full coupling matrix C, is significantly higher in rMDD. **e**: Pairwise coupling strength between brain regions is computed as the spectral norm of 6×6 submatrices. Significant differences between groups in directed coupling ($p_{\text{FDR}} < 0.05$), depicted as arrows indicating the direction and strength of influence from one region to another. **f**: Correlation between regional coupling strength and control energy. Significant negative correlations indicate that regions with stronger outward influence require less control effort to reach the target, suggesting a mechanistic link between connectivity and controllability in rMDD. **g**: Parahippocampal gyrus (PHG) coupling strength (as measured via spectral norm) versus required control energy per subject. **b, d, f**: p values reflect FDR-corrected significance thresholds at thresholds $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

3 Discussion

In this study, we introduce a novel data-driven framework that integrates nonlinear DSR with model predictive control (MPC) to uncover the mechanistic underpinnings of brain state transitions in rMDD.

Our approach leverages expressive generative models, trained solely on empirical fMRI time series, to reconstruct neural dynamics and enable in silico causal intervention analyses. By treating these models as computational surrogates of the brain, we extend prior control-theoretic work — often limited to linear (Deng et al., 2022; Gu et al., 2015; Parkes et al., 2024; Yao et al., 2025) or biophysically constrained (Martínez et al., 2023; Taylor et al., 2015) models — into a generalizable and expressive framework capable of simulating and controlling neural trajectories at the level of individual subjects. Unlike traditional correlational analyses, our framework yields a causal, mechanistic account of how the brain transitions between functional states when a given area is activated (or deactivated). By learning optimal control policies on reconstructed latent dynamics, we can directly interrogate how specific neural perturbations shape the trajectory of brain activity. We demonstrate this utility in the context of a clinically salient question: identifying the mechanisms by which individuals with rMDD more readily enter and sustain states of negative affect. These results establish our method as a tool for probing the intervention targets that modulate transitions into—and potentially out of—pathological states.

Validity of the Generative Models Central to our approach is the training of DSR models that accurately reconstruct empirical neural dynamics. Beyond capturing the complex temporal evolution of the data, the models replicated key statistical and connectivity-based properties out-of-sample. In particular, functional connectivity patterns in the model-generated trajectories closely mirrored those observed in the empirical recordings. Notably, the models revealed elevated directed coupling in rMDD participants, consistent with previous findings of altered network interactions in depression (Lydon-Staley et al., 2019; Zhu et al., 2012), and elevated connectivity observed specifically in this dataset (Zamoscik et al., 2014), though our results were derived entirely from data-driven generative models. This cross-methodological convergence underscores the robustness of both our modeling framework and its capacity to extract clinically relevant neural signatures.

rMDD and the Control of Sad Mood States Our control-theoretic analysis yielded compelling evidence that individuals with rMDD require significantly less control energy to transition into, and maintain, sad mood states compared to healthy controls. This aligns with prior reports of heightened negative and diminished positive affect in response to sad mood induction in this group (Zamoscik et al., 2014). The finding was robust across nearly all examined brain regions, which were selected based on their prior implication in RNT and affective regulation. Importantly, participants whose regions exhibited stronger network coupling consistently required less energy to reach the target. This is consistent with the observation that networks with higher mean degree not only need fewer driver nodes but also incur lower control energy, because the extra connections provide multiple, "low-resistance" pathways for steering the system (Liu et al., 2011). To pinpoint which pathways drive this effect, we isolated each region's outgoing connections and observed that the association with lower control energy was particularly notable when coupling was directed toward the DLPFC. In other words, there was a tendency for regions that project more strongly into prefrontal control circuits to require less energy to steer the brain into a sad mood state.

These findings have at least two implications. First, they offer a mechanistic explanation for the increased vulnerability to negative affect in (remitted) depression: stronger dynamical outward coupling in key regions may render pathological states more accessible. Second, they suggest putative causal targets for intervention. Our analyses revealed strong negative correlations between control energy and coupling strength in multiple brain regions examined, but particularly the HPC, the PHG and the AIns—regions already implicated in affective control and neuromodulation therapies (Arulchelvan and Vanneste, 2023; Liu et al., 2021; Roet et al., 2020). Moreover, sgACC and NAcc emerged as particularly efficient hubs facilitating transitions between resting and sad mood states, potentially also serving as efficient control points for modulating maladaptive dynamics in depressive disorders.

Toward Personalized Closed-Loop Neurostimulation Beyond theoretical insight, our framework offers immediate translational opportunities. Because control is learned separately for each individual brain region, the method provides a principled way to assess regional controllability – an insight that can be used for personalized intervention planning. In particular, the framework allows for in silico perturbation analyses of potential stimulation targets, identifying regions that can steer the system with minimal energy or maximal precision (see also Fechtelpeter et al., 2024; Luo et al.,

2025; Muldoon et al., 2016).
Coupled with non-invasive brain stimulation technologies—such as transcranial magnetic stimulation or transcranial direct current stimulation—our framework could serve as the computational core of closed-loop neurostimulation systems. By dynamically adjusting stimulation parameters (e.g., target location, intensity, frequency) based on real-time neural state estimates, the system could optimize transitions toward desired cognitive or affective states. This vision aligns with recent efforts to move beyond static stimulation protocols and toward adaptive, personalized, and feedback-driven neuromodulation strategies (Santaniello et al., 2011; Steffen et al., 2024).
A key strength of our approach lies in its modularity and flexibility. While we focused here on transitions between resting and sad mood states, the same framework can be applied to other cognitive or clinical states, and extended to new objective functions. For example, by replacing the probabilistic GMM targets with objectives that prioritize signal stability, information content (e.g. signal-to-noise ratio), or spectral properties, future studies can investigate neural mechanisms underlying attention, memory, or executive control.
Moreover, the method opens avenues for systematically exploring neural variability (Garrett et al., 2013). In this study, we constrained control to individual regions, yielding relatively consistent solutions. However, when more regions are jointly engaged, it is likely that multiple near-optimal solutions will emerge. This multiplicity could underlie naturally occurring inter-individual differences in strategy, flexibility, or susceptibility to perturbation — dimensions that can now be quantitatively explored using our framework.

Limitations Despite the robustness of the modeling framework and the mechanistic insights it yields, the control approach remains to be validated. Specifically, we did not observe a significant association between control energy and mood ratings obtained during scanning, leaving open the question of whether the model-derived dynamics reflect subjectively experienced affective states. Furthermore, our inferences are based on full in silico simulations, which may not translate directly to practical neuromodulation: real-world stimulation protocols could impose additional physiological and technological constraints, and thus would likely require the inference of new, protocol-specific control strategies rather than a direct mapping of the simulated control energies. Future work should address these gaps by relating control metrics to behavioral or clinical measures and apply the proposed approach to infer stimulation strategies that account for the constraints of actual neuromodulatory interventions.

4 Conclusion

In summary, our study bridges the gap between dynamical systems theory and clinical neuroscience by providing a data-driven framework to investigate neural state transitions and how they could be manipulated. The altered controllability and connectivity patterns in rMDD highlight the potential of this approach to uncover novel neural dynamics and therapeutic targets for mood disorders. By advancing our understanding of the neural mechanisms underlying RNT, this work paves the way for more effective interventions tailored to the dynamic nature of psychiatric illnesses.

5 Methods

5.1 Sample

We reanalyzed a data set first reported in Zamoscik et al. (2014) (see also Huffziger et al., 2013; Lydon-Staley et al., 2019; Timm et al., 2017; Zamoscik et al., 2018; Zhang et al., 2023 for elaborate details). In brief, the study included 30 individuals with rMDD — defined as having experienced at least two episodes of MDD — and 30 HC matched for age, sex, and education, with no history or current diagnosis of MDD. The rMDD group had to be in partial or full remission for a minimum of two months. Exclusion criteria for all participants included clinical diagnoses of bipolar disorder, psychotic disorders, substance dependence, current substance abuse, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, eating disorders (all as per DSM-IV), and contraindications for MRI. A trained clinical psychologist conducted the diagnostic assessments using the Structured Clinical Interview for DSM-IV Axis I. The study received approval from the local ethics committee of

Heidelberg University and conformed to the Declaration of Helsinki. All participants provided written informed consent.

5.2 Experimental Data

Based on the study by Zamoscik et al. (2014), we selected two 4.5-minute fMRI sessions for analysis: the first resting state session and the first sad mood induction session from their more complex experiment. Sad mood induction was achieved using three personally significant negative life events, identified immediately prior to the fMRI session (e.g., a breakup, the death of a loved one, or a traumatic experience). These events were presented sequentially as keywords (each displayed for 1.5 minutes) accompanied by instrumental background music (excerpts from Albinoni's Adagio in G minor). Mood assessments were conducted using the Positive and Negative Affect Scale (PANAS; Watson et al., 1988) before and after the sad mood induction. Both groups reported sadder mood after mood induction where rMDD reported a significantly more increased negative affect and a similarly decreased positive affect compared with HC (Zamoscik et al., 2014). During the resting state session, participants also viewed emotionally neutral words (namely, "rest 1", "rest 2", "rest 3").

5.2.1 Preprocessing

The study used a 3T Trio Tim Scanner with a 12-channel head coil (Siemens Healthineers, Erlangen, Germany), acquiring functional images at a rate of 1.5s (TR). For additional details on data acquisition, data processing, and artifact correction, see Section A.1.
To obtain time-series data for modeling, anatomical masks were used to extract 11 brain regions from both hemispheres (Figure 2a), which were selected based on their known involvement in depression. Time series were standardized and subsequently bandpass filtered using cutoff frequencies of 0.0083 Hz and 0.15 Hz. For each subject, data was projected onto the top three principal components (PCs), which explained an average of 76% of the variance, with a minimum of 50% across all subjects. This yielded a 66-dimensional time series (2 hemispheres x 11 regions x 3 PCs), comprising 320 time points per subject, with 160 time points for each of the resting state and mood induction conditions. Finally, the time series — denoted as x_t in the following — was standardized for PLRNN, SVM, and GMM training. This scaling was reversed during control optimization, restoring each dimension to its original variance.

5.3 DSR Model and Control

5.3.1 DSR Model Architecture

To model the dynamics within the selected ROIs, we employ a state-space framework comprising a latent dynamical model coupled with an observation model. The latent dynamics are governed by the shallow PLRNN (shPLRNN; Hess et al., 2023), defined as

$$z_{t+1} = Az_t + W_1(\sigma(W_2 z_t + h_2) - \sigma(W_2 z_t)) + h_1 \tag{1}$$

with latent states $z_t \in \mathbb{R}^M$, diagonal matrix $A \in \mathbb{R}^{M \times M}$, connectivity matrices $W_1 \in \mathbb{R}^{M \times L}$ and $W_2 \in \mathbb{R}^{L \times M}$, and biases $h_2 \in \mathbb{R}^L$ and $h_1 \in \mathbb{R}^M$, where L is the dimension of the hidden layer, and $\sigma(\cdot)$ is a piecewise linear activation function (the Rectified Linear Unit; ReLU).
The observation model is linear and defined as $x_t = Bz_t$, where $B \in \mathbb{R}^{O \times M}$ and $O = 66$ is the observation dimension.
Each model is trained jointly on both the resting state and sad mood induction data from a single subject, without access to condition labels during training.

5.3.2 Model Training

Models were trained using backpropagation through time (BPTT) combined with generalized teacher forcing (GTF; Hess et al., 2023), a technique in which model-generated latent states are partially realigned with encoded states after gradient computation using linear interpolation with the interpolation parameter decaying from α_0 to α_1 during training. This alignment helps mitigate exploding and vanishing gradients during training. Encoded latent states z^{enc} were obtained by projecting observations into the latent space via the Moore-Penrose pseudoinverse B^{-1}.

Training was performed by minimizing a regularized mean squared error loss, which penalizes discrepancies between model-generated and empirical observations, as well as between model-generated and encoded latent states,

$$\mathcal{L}_{\text{DSR}} = \frac{1}{TO}\sum_{t=1}^{T}\|x_t^{\text{emp}} - x_t^{\text{gen}}\|^2 + \frac{1}{TM}\sum_{t=1}^{T}\|z_t^{\text{enc}} - z_t^{\text{gen}}\|^2 + \lambda_1\left(1-\kappa(B)\right)^2 + \lambda_2\|I-A\|_F^2 + \lambda_3\|W_1\|_F^2 + \lambda_4\|W_2\|_F^2, \quad (2)$$

where x_t^{gen} and z_t^{gen} refer to model generated observations and latent states generated according to eqn. (1) and the observation model, and $\kappa(B)$ denotes the condition number of the observation matrix B that is regularized towards 1 to promote numerical stability of the pseudoinverse via λ_1. λ_2 regularizes the diagonal entries of A toward 1 and λ_3 and λ_4 regulate L_2 penalties on W_1 and W_2, while $\|\cdot\|_F$ denotes the Frobenius norm.
We use the RAdam optimizer (Liu et al., 2020), with an exponentially decaying learning rate from η_0 to η_1, and momentum parameters $\beta_1 = 0.9$ and $\beta_2 = 0.999$.
The models are trained on the first 120 time steps of each session (75%; training set) and evaluated on the remaining 40 time steps (test set). During each training epoch, a full batch of 162 sequences of length $T = 40$ is sampled—comprising 81 sequences from the 120 training time steps of both the resting state and sad mood induction sessions. The hyperparameters including the matrix dimensions used in training were selected via grid search on the test set for a subset of five subjects, with the final values summarized in Table 1. For each participant, we trained five models with Xavier initialization (Glorot and Bengio, 2010) for up to 200,000 epochs and selected the model with the lowest test loss for subsequent experiments.

Physiological Confounds Since elevated connectivity levels were observed in the rMDD group—and such effects can potentially arise from physiological artifacts (e.g., cardiac and respiratory signals, Wilding et al., 2024; Zamoscik et al., 2018) — we re-estimated all shPLRNN models after removing these artifacts from the data. Using the TAPAS PhysIO toolbox (Kasper et al., 2017), we extracted subject-specific cardiac and respiratory regressors from the recorded physiology time series. We then applied ridge regression (ℓ_2 regularization) to model and subtract these nuisance signals, optimizing the regularization weight via cross-validation and assessing fit on a held-out test set. Importantly, the elevated connectivity patterns not only persisted but in some instances became even more pronounced (Figure A7). To remain conservative and retain the original neural signal structure, all subsequent analyses therefore used the models fitted to the uncorrected data.

5.3.3 DSR Model Evaluation

To quantify how well the DSR model reproduces the temporal structure of the data, we compare the power spectrum of each latent dimension between the measured trajectory and the model's reconstruction along the entire time series. Concretely, for each dimension $i \in \{1, \ldots, O\}$ we compute the Fast Fourier transform (Cooley and Tukey, 1965) of the time series, smooth the resulting power spectrum with a Gaussian kernel, and renormalize it to obtain two spectral densities, $S_i(\omega)$ (measured) and $P_i(\omega)$ (reconstructed). We then summarize their discrepancy by the mean Hellinger distance, $D_H\big(S,P\big) = \frac{1}{O}\sum_{i=1}^{O}\sqrt{1 \;-\; \int_{-\infty}^{\infty}\sqrt{S_i(\omega)\,P_i(\omega)}\;d\omega}$. This metric ranges from 0 (identical spectra) to 1 (maximally dissimilar), and thus provides a dimension-averaged measure of how faithfully the PLRNN captures the frequency content of the original signals.
To further assess model performance on unseen data, we also compared the functional connectivity patterns in the empirical and reconstructed test-set trajectories. Specifically, we computed the Pearson correlation matrix across all observed regions for both the empirical data and the held-out PLRNN reconstructions. This connectivity comparison ensures that the PLRNNs not only reproduce spectral properties but also preserve the inter-regional coupling structure present in the test data.

5.3.4 Model Predictive Control

Model Predictive Control (MPC) is a strategy that leverages a model of the system to predict future dynamics and optimize control actions over a finite time horizon. At each time step, it solves an optimization problem to minimize a cost functional — applying only the first control step before re-optimizing — and thereby enabling real-time adaptation. We integrate MPC with DSR to determine

the stimulus required to steer the brain into desired states (Figure 1). Using shPLRNNs (eqn. 1) trained on empirical fMRI data, we define an additive, state-dependent control term $u(z_t)$ that modifies the latent dynamics as follows

$$z_{t+1} = \text{shPLRNN}(z_t) + u(z_t), \quad u(z_t) := K_2\sigma(K_1 z_t + b), \tag{3}$$

where $\sigma(\cdot) = \text{ReLU}$, $K_1 \in \mathbb{R}^{Q\times M}$, $K_2 \in \mathbb{R}^{M\times Q}$ and $b \in \mathbb{R}^Q$. The shPLRNN parameters are fixed post-training; only the control parameters (K_1, K_2, b) are optimized (Figure A1).

Soft Target Objective To allow flexible control, we define a soft target using a GMM trained on empirical resting state or sad mood induction data (see Section 5.3.6). Instead of reaching a fixed state, the controlled trajectory is guided into high-likelihood regions under the GMM.
The loss function thus consists of a negative log-likelihood term and a regularization term penalizing control energy:

$$\mathcal{L}_{\text{cont}} = -c \sum_{t=D+2}^{T} \log p_{\text{GMM},s}\left(x_t^{\text{gen}}\right) + \lambda_{\text{E}} E_{\text{cont}} \tag{4}$$

where $c = \frac{10^{-4}}{T-D-1}$ ensures loss terms are comparable in magnitude, and control energy is defined as

$$E_{\text{cont}} = \sum_{t=1}^{T} \|s \odot Bu(z_t)\|^2, \tag{5}$$

where s are the pre-standardization standard deviations, restoring the original scale of each PC.

Control Optimization Control parameters K_1, K_2, b are optimized using the RAdam optimizer over up to 30,000 epochs with a constant learning rate η. Each trajectory starts from an empirical state and runs for $T = D + 11$ steps (1 for initialization, D before loss evaluation, and 10 to maintain the target). We use 240 empirical states for training and 80 for testing. Hyperparameters were set to $\lambda_{\text{E}} = 0.1$, $Q = 17$, and $\eta = 0.01$. Among five independently trained models, the one with lowest test loss is selected for analysis. The optimization was robust to initialization (Figure A8).

Restricting Control to Specific Brain Regions To assess controllability and region-specific influence, we constrain the control to act only on selected brain regions. While latent space constraints are trivial (e.g., via L1-regularization to promote sparsity), enforcing constraints in observation space is more complex due to the linear observation model, where latent dimensions are mixed and do not map directly onto individual brain regions.
We overcome this by projecting $u(z_t)$ onto the null space of the decoder rows corresponding to regions where control should be inactive. Let $B_{\text{red}} \in \mathbb{R}^{M_{\text{red}}\times M}$ denote the submatrix of B corresponding to these regions. We compute an orthonormal basis $N \in \mathbb{R}^{M\times \dim(\ker B_{\text{red}})}$ of $\ker(B_{\text{red}})$ via singular value decomposition and construct the projection matrix $P = NN^\top$ (see also Fechtelpeter et al., 2024). The constrained dynamics then become

$$z_{t+1} = \text{shPLRNN}(z_t) + Pu(z_t). \tag{6}$$

This ensures that $Bu(z_t)$ has no component in the restricted observation dimensions. The projection matrix P is computed once before training and remains fixed throughout optimization.

5.3.5 Coupling Matrix and Lyapunov Spectra

The shPLRNNs (eqn. (1)) permit efficient computation of coupling matrices and Lyapunov spectra along individual trajectories by exploiting the model's Jacobians J_{z_t}. At latent state z_t, the Jacobian of the update map $z_t \mapsto z_{t+1}$ is

$$J_{z_t} = \left.\frac{dz_{t+1}}{dz_t}\right|_{z_t} = A + W_1\left(D_{W_2 z_t + h_2} - D_{W_2 z_t}\right) W_2 \equiv A + W_{z_t} \tag{7}$$

where

$$D_x = \mathrm{diag}(\nu_1, \ldots, \nu_M), \qquad \nu_i = \begin{cases} 1, & (x_i \geq 0), \\ 0, & (\text{else}), \end{cases} \quad i = 1, \ldots, M.$$

Here W_{z_t} captures how different latent dimensions interact at time t, and is often called the cross-connection matrix.
Since our observations x_t are related to z_t by the linear map $x_t = B\, z_t$, the corresponding Jacobian in observation space is

$$\frac{\partial x_{t+1}}{\partial x_t} \;=\; B\,(A + W_{z_t})\,B^{-1} \;=\; C.$$

In other words, C is the coupling matrix of the observable dynamics. We thus interpret $\|C\|$ (its spectral norm) as quantifying how strongly activity in one region influences activity in another. We also evaluate $\|C\|$ at every z_t visited by the shPLRNN when driven by empirical resting state and sad mood-induction data, yielding a time-resolved measure of inter-regional coupling.
To compute Lyapunov exponents, we apply the algorithm of Vogt et al. (2022), which orthogonally projects $A + W_{z_t}$ onto tangent subspaces along each trajectory.

5.3.6 Statistical Analysis

State Separation To estimate the empirical distribution of brain states during resting state and sad mood induction, we trained separate GMMs of the respective datasets per subject. GMMs provide a probabilistic description of the state-space, capturing regions of high empirical density while allowing generalization to nearby states. Model selection based on the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) indicated that six mixture components best described the data (Figure A2b).
To quantify group-level differences in brain state distributions, we computed three distances between resting and sad mood GMMs: (i) maximum mean discrepancy (MMD), (ii) the L^2 norm in the space of square-integrable functions (both computed in closed form), and (iii) the sliced Wasserstein distance (estimated via sampling).

Control Evaluation and Group Statistics For model evaluation under control, trajectories were initialized from each of the 160 empirical brain states (resting or sad mood induction). After an initial warm-up period of D steps, we computed both the negative log-likelihood (NLL) under the target GMM and the cumulative control energy.
To assess regional specifity, the control experiment was repeated 11 times — each time with control restricted to one bilateral region. Across all 30 subjects per group and 160 initializations per condition, the resulting trajectories span $T = 80$ time steps, yielding NLL and energy tensors of shape $(30, 160, T)$. For statistical analysis, the first D steps were excluded to limit analyses to time points where target distance was penalized during training; the median was then computed across time and trials to yield a single value per subject.
Outliers were excluded based on the $1.5\times$ interquartile range criterion. Group differences were assessed using the Mann-Whitney U test (two-sided). All p-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the false discovery rate (FDR).

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A Supplementary Methods

A.1 fMRI Preprocessing

Imaging Parameters Functional imaging was conducted with T2*-weighted EPI scans (TR = 1.5 s, flip angle $\alpha = 80°$, TE = 28 ms, 24 slices, voxel size $3 \times 3 \times 4$ mm$^{\mathbf{3}}$, 180 volumes per phase), while high-resolution anatomical images were captured using T1-weighted MPRAGE sequences (TR = 2.3 s, TE = 3.03 ms, voxel size $1 \times 1 \times 1$ mm^3). Physiological data, namely pulse and respiration, were recorded at 50 Hz. The first 20 of the 180 images per phase were discarded and preprocessing was conducted with SPM12 (v7738).

Data Preprocessing and Artifact Correction Preprocessing for the anatomical images included segmentation of the anatomical images and normalization to the ICBM 2009b Nonlinear Asymmetric template, and for the functional images slice timing correction, realignment, coregistration to the anatomical data, normalization to standard space, and spatial smoothing with a FWHM=8x8x8 mm^3 Gaussian kernel.
Onset effects for the key words were modeled by convolving their onset stick function with the canonical hemodynamic response function and included in a regression model further containing the six standard motion parameters, their derivatives, the squared values of them, white matter, cerebrospinal fluid, and global signals (Parkes et al., 2018) as well as dummy regressors for volumes affected by small movements (framewise displacement $>$ 0.5mm, global intensity change z $>$4). We removed these confounds via ridge regression, then extracted the residual time series from each target region and applied the preprocessing pipeline described in 5.2.1.

A.2 DSR Hyperparameters

M	L	α_0	α_1	β_1	β_2	λ_1	λ_2	λ_3	λ_4	η_0	η_1
66	15	10^{-1}	10^{-3}	0.9	0.999	10^{-1}	0	10^{-4}	10^{-4}	10^{-3}	10^{-4}

Table 1: Hyperparameters used for DSR model training.

B Supplementary Figures

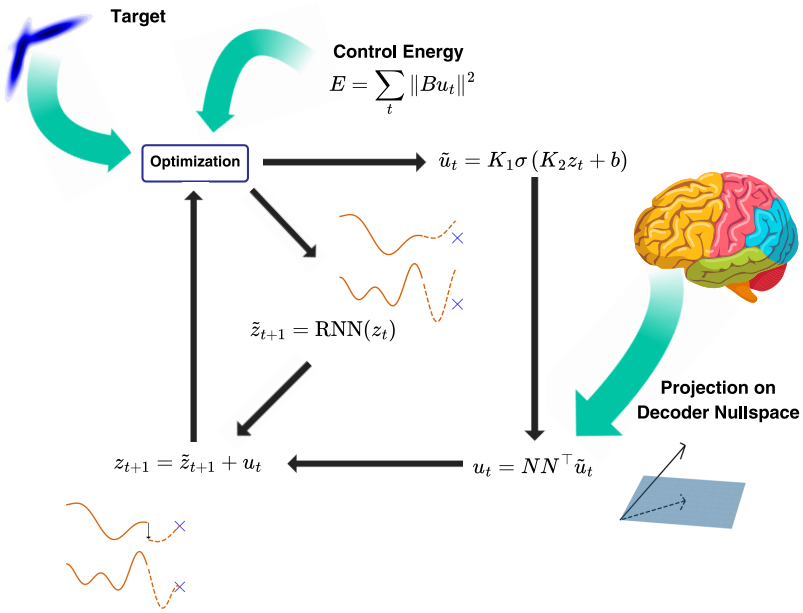

Figure A1: Closed-loop MPC framework. shPLRNNs inferred on the data model the uncontrolled brain dynamics (center). Control is applied via an additive term $u_t = u(z_t)$ (bottom left), optimized to drive the system toward a target state while minimizing control effort (top left). To restrict control to specific brain regions, $\tilde{u}_t$ is projected onto the null space of corresponding rows of the decoder B, using the projection matrix $NN^\top$ (bottom right).

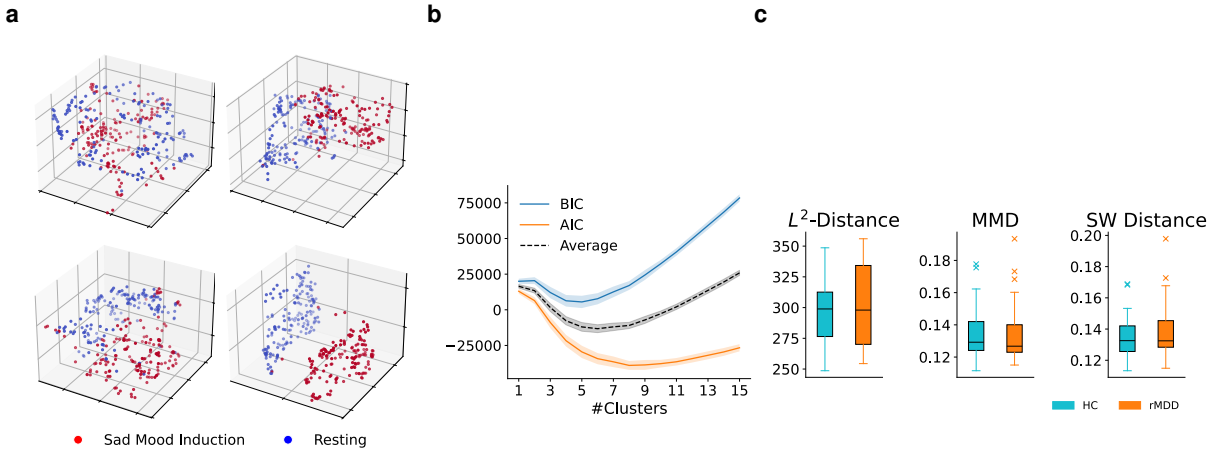

Figure A2: a: UMAP dimensionality reduction applied to states sampled from the Gaussian Mixture Models (GMMs) confirm that the empirical separation is well preserved (cf. Figure 2b). **b:** Model selection using AIC and BIC across subjects suggests optimal cluster number of 6. **c:** Group comparisons of the distance between GMMs fitted to the resting and sad mood induction states. No significant differences were observed across metrics: L^2 Distance ($p = 0.81$), Maximum Mean Discrepancy (MMD, $p = 0.92$), and Sliced Wasserstein Distance (SW, $p = 0.74$).

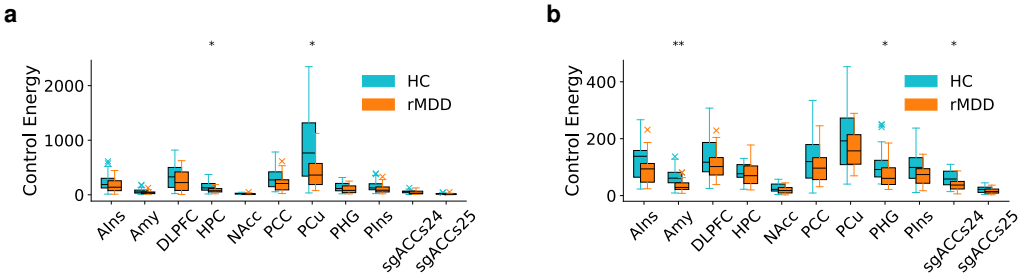

Figure A3: Measured effects are robust to variations in λ_E and D. a: When control energy is not penalized during training ($\lambda_E = 0$), overall energy levels increase, yet the rMDD group consistently requires less control. **b**: With a shorter temporal horizon $D = 5$, the model has fewer time steps before penalties on control energy and target distance are applied. **a, b** $^*p_{\text{FDR}} < 0.05$.

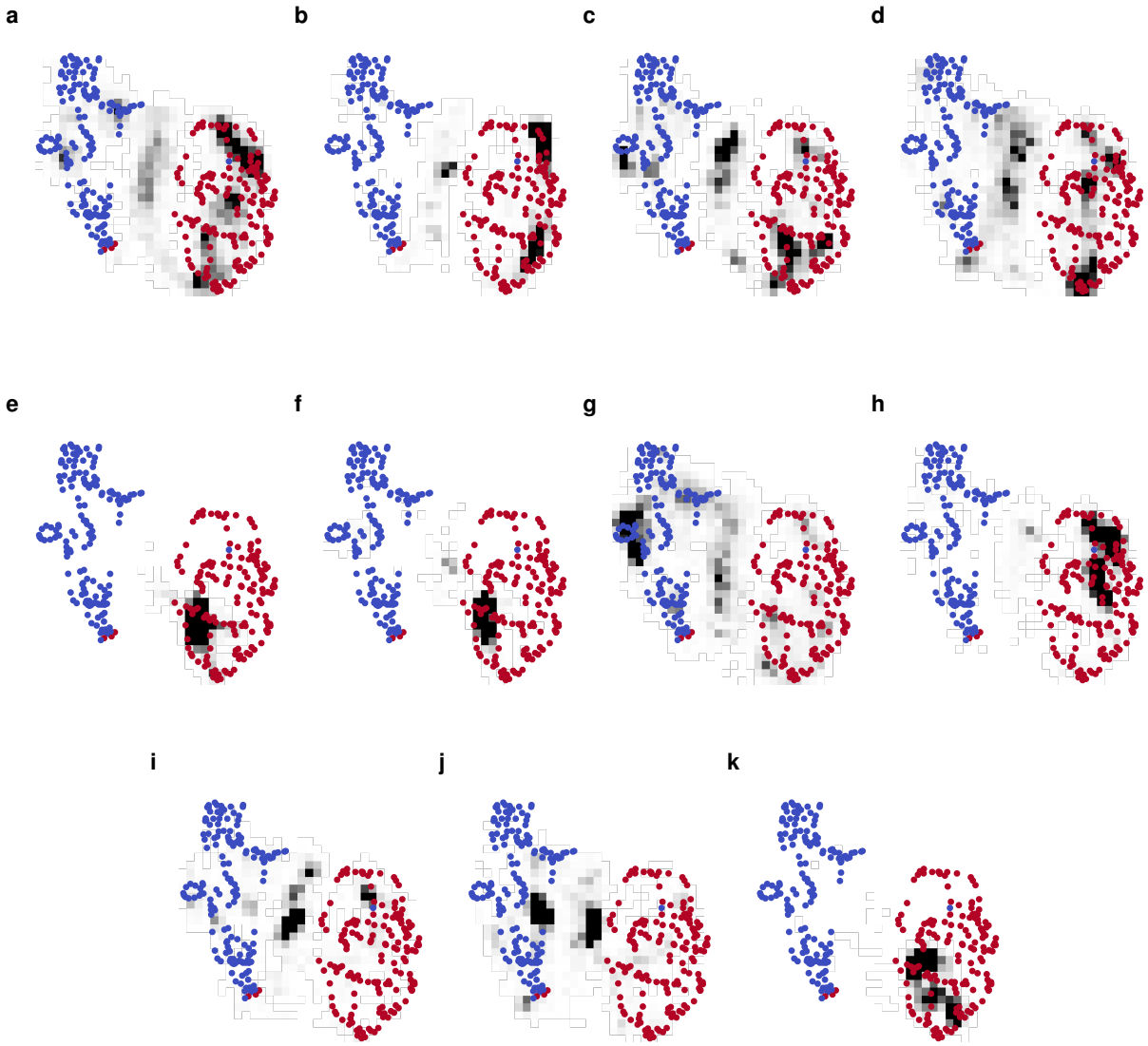

Figure A4: a-k: Two-dimensional UMAP visualizations of empirical states (sad mood induction in red, resting in blue) and controlled trajectories (black) for different targeted brain regions in a fixed subject. The control successfully maintains activity within the sad mood induction state-space region. Trajectories from multiple initializations are aggregated by spatial binning, and relative frequencies per bin are displayed as a heatmap. Time steps smaller than $D = 10$ were discarded.

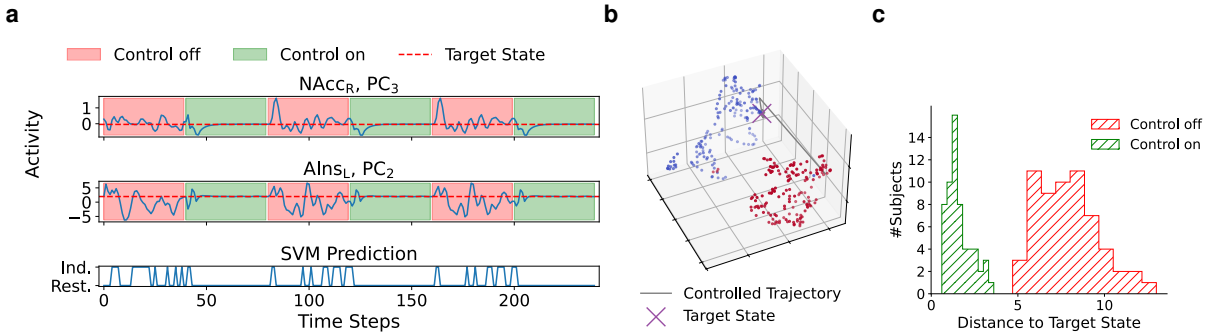

Figure A5: Hard target control: A specific empirical state (red dashed line) was designated as the target, and control was optimized using mean squared error (MSE) loss. Control was applied to all cortical regions. **a**: When control is activated, trajectories reliably converge toward the target state (red dashed line); when deactivated, dynamics revert to chaotic behavior. This effect is visible in both controlled (right anterior insula; AIns) and uncontrolled (left nucleus accumbens; NAcc) dimensions. The SVM decoder confirms convergence into the resting state region. **b**: UMAP visualization of a trajectory initialized at sad mood induction (red) converging to the target resting state (blue). **c:** Control significantly reduces the Euclidean distance to the target state (median across time), consistently across all subjects.

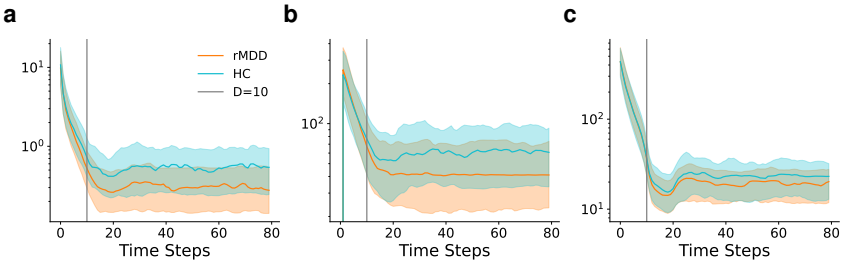

Figure A6: Temporal evolution of the evaluation measures. Control energy (**a**), $\mathrm{NLL}_{\mathrm{Rest}}$ (**b**), and $\mathrm{NLL}_{\mathrm{Ind}}$ (**c**) for the case of amygdala-targeted control. Curves show the median across subjects and initializations; shaded areas denote the inter-quartile range. While rMDD subjects consistently require less control energy, no significant differences are observed in the likelihoods that quantify the distance to initial and target states.

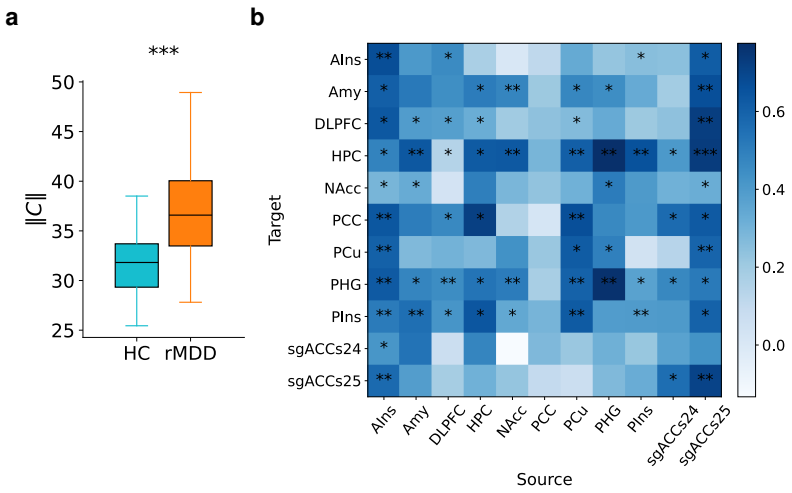

Figure A7: Connectivity differences are preserved when training on data corrected for physiological artifacts. When correcting the data for physiological effects (i.e. cardiac and respiratory noise) before training the shPLRNNs, the significant difference in connectivity between the groups remains evident. Both the global coupling (**a**) and the pairwise connectivity between brain regions (**b**, difference in median, rMDD-HC) is significantly stronger in rMDD. Here, $^{*}p_{\text{FDR}} < 0.05$,$^{**}p_{\text{FDR}} < 0.01$,$^{***}p_{\text{FDR}} < 0.001$.

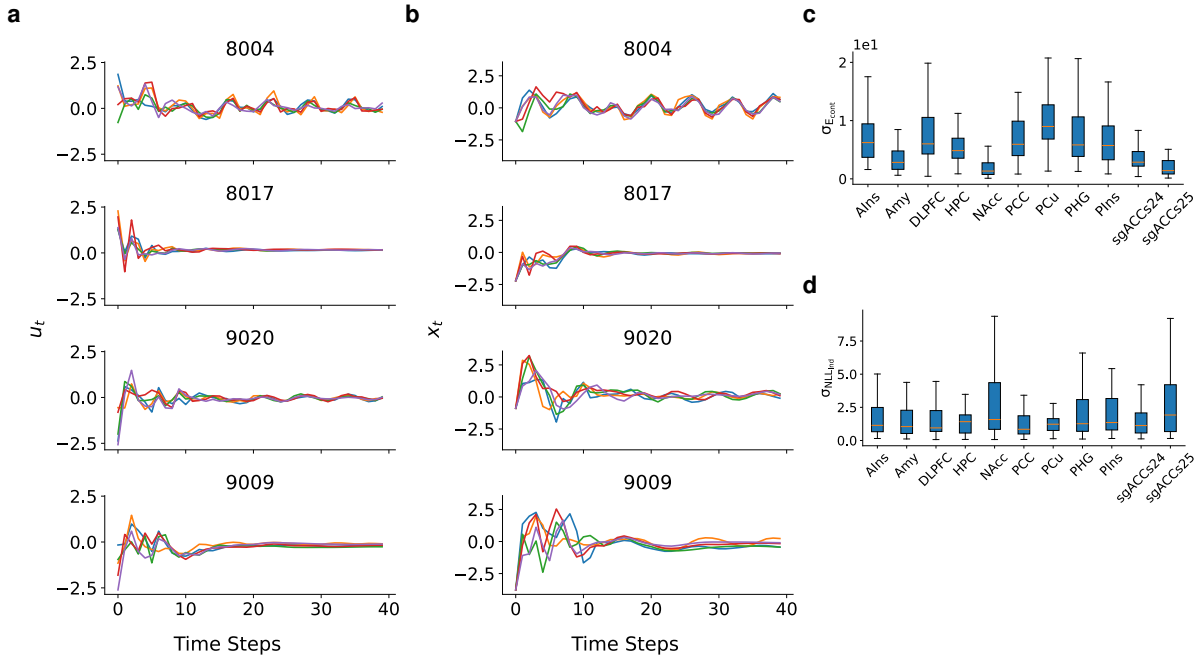

Figure A8: Control parameter optimization is robust to different initializations. For each experiment and subject, five models were independently optimized. Controlled trajectories show consistent control inputs u_t (**a**) and corresponding activity x_t (**b**) across runs, each represented by a separate curve, displayed for a selected number of subjects. While the chaotic dynamics amplify small deviations over time, variance across runs of control energy (**c**) and NLL_{Ind} (d) remains substantially smaller than inter-subject variance (cf. Figure 3e, 3f). The models with the lowest loss were used for analyses.