Connectome-Based Attractor Dynamics Underlie Brain Activity in Rest, Task, and Disease

Robert Englert [1,2], Balint Kincses[1,3], Raviteja Kotikalapudi[1,3], Giuseppe Gallitto[1,3], Jialin Li[1,3,4], Kevin Hoffschlag[1,3], Choong-Wan Woo[5,6], Tor D. Wager[7], Dagmar Timmann[1,3], Ulrike Bingel[1,3], Tamas Spisak[1,2]*

1 Center for Translational Neuro- and Behavioral Sciences (C-TNBS), University Medicine Essen, Germany
2 Department of Diagnostic and Interventional Radiology and Neuroradiology, University Medicine Essen, Germany
3 Department of Neurology, University Medicine Essen, Germany
4 Max Planck School of Cognition, Leipzig, Germany
5 Center for Neuroscience Imaging Research, Institute for Basic Science, Suwon, South Korea
6 Department of Biomedical Engineering, Sungkyunkwan University, Suwon, South Korea
7 Department of Psychological and Brain Sciences, Dartmouth College, Hanover, NH, USA
** corresponding author: tamas.spisak@uk-essen.de*

Key Points:

- We present a simple yet powerful computational model for large-scale brain dynamics
- The model uses a functional connectome-based Hopfield artificial neural network (*fcHNN*) architecture to compute recurrent "activity flow" through the functional brain connectome
- *FcHNN* attractor dynamics provide a mechanistic account for gradient- and state-dynamics in the brain in resting conditions
- *FcHNN*s conceptualize both task-induced and pathological changes in brain activity as a non-linear shift in these dynamics
- Our approach is validated using large-scale neuroimaging data from seven studies
- *FcHNN*s offers a simple and interpretable computational alternative to conventional descriptive analyses of brain function

Project website (with interactive manuscript): https://pni-lab.github.io/connattractor

Abstract

Understanding large-scale brain dynamics is a grand challenge in neuroscience. We propose functional connectome-based Hopfield Neural Networks (*fcHNN*s) as a model of macro-scale brain dynamics, arising from recurrent activity flow among brain regions. An *fcHNN* is neither optimized to mimic certain brain characteristics, nor trained to solve specific tasks; its weights are simply initialized with empirical functional connectivity values. In the *fcHNN* framework, brain dynamics are understood in relation to so-called attractor states, i.e. neurobiologically meaningful low-energy activity configurations. Analyses of 7 distinct datasets demonstrate that *fcHNN*s can accurately reconstruct and predict brain dynamics under a wide range of conditions, including resting and task states and brain disorders. By establishing a mechanistic link between connectivity and activity, *fcHNN*s offers a simple and interpretable computational alternative to conventional descriptive analyses of brain function. Being a generative framework, *fcHNN*s can yield mechanistic insights and hold potential to uncover novel treatment targets.

Introduction

Brain function is characterized by the continuous activation and deactivation of anatomically distributed neuronal populations (Buzsaki, 2006). Irrespective of the presence or absence of explicit stimuli, brain regions appear to work in concert, giving rise to a rich and spatiotemporally complex fluctuation (Bassett & Sporns, 2017). This fluctuation is neither random nor stationary over time (Liu & Duyn, 2013; Zalesky et al., 2014). It is organized around large-scale gradients (Margulies et al., 2016; Huntenburg et al., 2018) and exhibits quasi-periodic properties, with a limited number of recurring patterns known as "brain states" (Greene et al., 2023; Vidaurre et al., 2017; Liu & Duyn, 2013).

A wide variety of descriptive techniques have been previously employed to characterize whole-brain dynamics (Smith et al., 2012; Vidaurre et al., 2017; Liu & Duyn, 2013; Chen et al., 2018). These efforts have provided accumulating evidence not only for the existence of dynamic brain states but also for their clinical significance (Hutchison et al., 2013; Barttfeld et al., 2015; Meer et al., 2020). However, the underlying driving forces remain elusive due to the descriptive nature of such studies.

Conventional computational approaches attempt to solve this puzzle by going all the way down to the biophysical properties of single neurons, and aim to construct a model of larger neural populations, or even the entire brain (Breakspear, 2017). These approaches have shown numerous successful applications (Murray *et al.*, 2018; Kriegeskorte & Douglas, 2018; Heinz *et al.*, 2019). However, the need to estimate a vast number of free parameters in such models hampers their ability to effectively bridge the gap between explanations at the level of single neurons and the complexity of behavior (Breakspear, 2017). Recent efforts using coarse-grained brain network models (Schirner *et al.*, 2022; Schiff *et al.*, 1994; Papadopoulos *et al.*, 2017; Seguin et al., 2023) and linear network control theory (Chiêm *et al.*, 2021; Scheid *et al.*, 2021; Gu *et al.*, 2015) opted to trade biophysical fidelity to phenomenological validity. The challenge for such models lies in modelling the relation between the structural wiring of the brain and functional connectivity. The "neuroconnectionist" approach, on the other hand, (Doerig *et al.*, 2023) aims at "cognitive/behavioral fidelity" (Kriegeskorte & Douglas, 2018), by using artificial neural networks (ANNs) that are trained to perform various tasks, as brain models. However, the need to train ANNs for specific tasks inherently limits their ability to explain task-independent, spontaneous neural dynamics (Richards *et al.*, 2019).

Here we propose a novel approach that combines the advantages of large-scale network models and neuroconnectionism, to investigate brain dynamics. Similar to neuroconnectionism, we utilize an ANN as a high-level computational model of the brain. However, our model is not explicitly trained for a specific task. Instead, we set its weights empirically, with data based on the "activity flow" (Cole *et al.*, 2016; Ito *et al.*, 2017) across regions within the functional brain connectome, as measured with functional magnetic resonance imaging (fMRI, Figure 1B). Specifically, we employ a continuous-space Hopfield Neural Network (HNN) (Hopfield, 1982; Krotov, 2023), with its nodes representing large-scale brain areas, and its weights initialized with the functional connectivity values between these areas. Based on the topology of the functional connectome, this architecture establishes an energy level for any arbitrary activation patterns and determines a "trajectory of least action" towards one of the finite number of stable patterns, known as *attractor states*, that minimize this energy. In this simple yet powerful framework, brain dynamics can be conceptualized as an intricate, high-dimensional path on the energy landscape (Figure 1C), arising from the activity flow (Cole *et al.*, 2016) within the functional connectome and constrained by the "gravitational pull" of the attractor states of the system. Given its generative nature, the proposed model offers testable predictions for the effect of various perturbations and alterations of these dynamics, from task-induced activity to changes related to brain disorders.

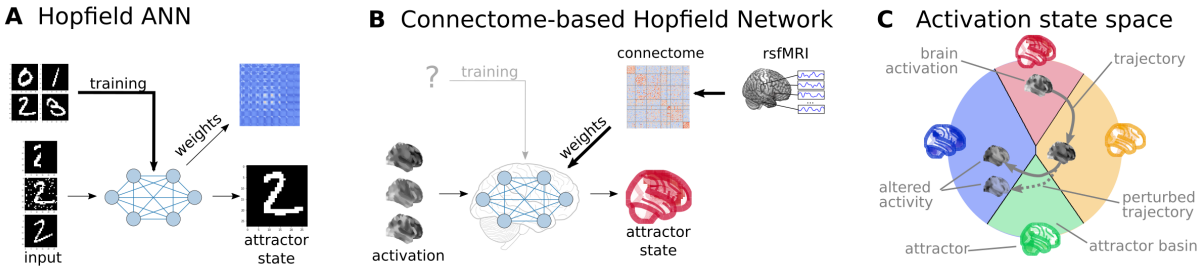

Figure 1: Connectome-based Hopfield networks as models of macro-scale brain dynamics. A Hopfield artificial neural networks (HNNs) are a form of recurrent artificial neural networks that serve as content-addressable ("associative") memory systems. Hopfield networks can be trained to store a finite number of patterns (e.g. via Hebbian learning a.k.a. "fire together - wire together"). During the training procedure, the weights of the HNN are trained so that the stored patterns become stable attractor states of the network. Thus, when the trained network is presented partial, noisy, or corrupted variations of the stored patterns, it can effectively reconstruct the original pattern via an iterative relaxation procedure that converges to the attractor states. B We consider regions of the brain as nodes of a Hopfield network. Instead of training the Hopfield network to specific tasks, we set its weights empirically, with the interregional activity flow estimated via functional brain connectivity. Capitalizing on strong analogies between the relaxation rule of Hopfield networks and the activity flow principle that links activity to connectivity in brain networks, we propose the resulting functional connectome-based Hopfield neural network (*fcHNN*) as a computational model for macro-scale brain dynamics. C The proposed computational framework assigns an energy level, an attractor state and a position in a low-dimensional embedding to brain activation patterns. Additionally, it models how the entire state-space of viable activation patterns is restricted by the dynamics of the system and how alterations in activity and/or connectivity modify these dynamics.

In the present work, we use HNNs to explore the functional connectome's attractor-dynamics with the aid of a streamlined, low-dimensional representation of the energy landscape. Subsequently, we use a diverse set of experimental, clinical, and meta-analytic studies to evaluate our model's ability to reconstruct various characteristics of resting state brain dynamics, as well as its capacity to detect and explain changes induced by experimental tasks or alterations in brain disorders.

Results

Connectome-based Hopfield network as a model of brain dynamics

First, we explored the attractor states of the functional connectome in a sample of n=41 healthy young participants (study 1, see Methods Table 1 for details). We estimated interregional activity flow (Cole *et al.*, 2016; Ito *et al.*, 2017) as the study-level average of regularized partial correlations among the resting state fMRI timeseries of m = 122 functionally defined brain regions (see Methods for details). We then used the standardized functional connectome as the w_{ij} weights of a fully connected recurrent ANN, specifically a continuous-state Hopfield network (Hopfield, 1982; Koiran, 1994), consisting of m neural units, each having an activity $a_i \in [-1,1] \subset \mathrm{R}$. Hopfield networks can be initialized by an arbitrary activation pattern (consisting of m activation values) and iteratively updated (i.e. "relaxed") until their energy converges a local minimum, that is, to one of the finite number of attractor states (see Methods). The relaxation procedure is based on a simple rule; in each iteration, the activity of a region is constructed as the weighted average of the activities of all other regions, with weights defined by the connectivity between them. The average is then transformed by a sigmoidal activation function, to keep it in the desired [-1,1] interval. This can be expressed by the following equation:

$$\dot{a}_i = S\left(\beta \sum_{j=1}^{m} w_{ij}\, a_j - b_i\right) \qquad (1)$$

where $\dot{a}_i$ is the activity of neural unit i in the next iteration and $S(a_j)$ is the sigmoidal activation function ($S(a) = \tanh(a)$ in our implementation) and b_i is the bias of unit i and β is the so-called temperature parameter. For the sake of simplicity, we set $b_i = 0$ in all our experiments. We refer to this architecture as a functional connectivity-based Hopfield Neural Network (*fcHNN*). The relaxation of a *fcHNN* model can be conceptualized as the repeated application of the activity flow principle (Cole *et al.*, 2016; Ito *et al.*, 2017), simultaneously for all regions: $\dot{a}_i = \sum_{j=1}^{m} w_{ij} a_j$. The update rule also exhibits analogies with network control theory (Gu *et al.*, 2015) and the inner workings of neural mass models, as applied e.g. in dynamic causal modeling (Daunizeau *et al.*, 2012).
Hopfield networks assign an energy value to each possible activity configuration (Hopfield, 1982; Koiran, 1994), which decreases during the relaxation procedure until reaching an equilibrium state with minimal energy (Figure 2A, top panel). We used a large number of random initializations to obtain all possible attractor states of the connectome-based Hopfield network in study 1 (Figure 2A, bottom panel).

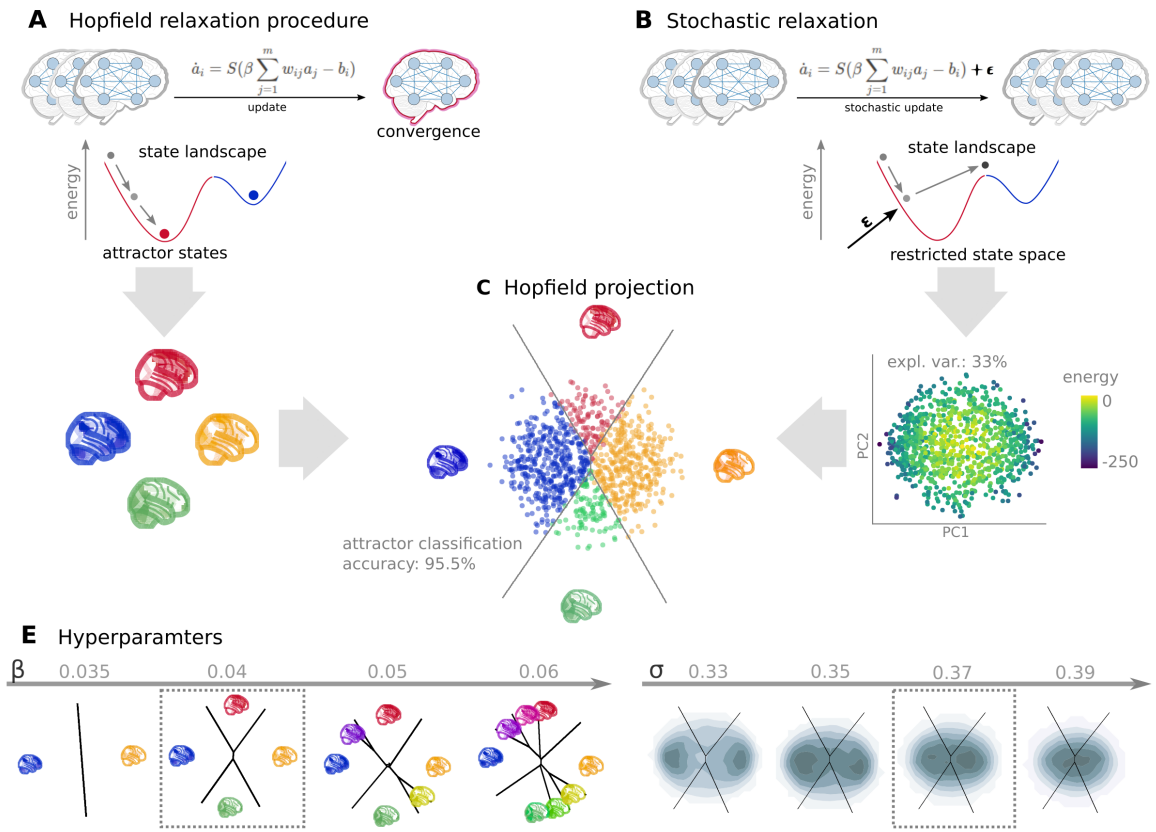

Figure 2: Attractor states and state-space dynamics of connectome-based Hopfield networks **A** Top: During so-called relaxation procedure, activities in the nodes of an *fcHNN* model are iteratively updated based on the activity of all other regions and the connectivity between them. The energy of a connectome-based Hopfield network decreases during the relaxation procedure until reaching an equilibrium state with minimal energy, i.e. an attractor state. Bottom: Four attractor states of the *fcHNN* derived from the group-level functional connectivity matrix from study 1 (n=44). **B** Top: In presence of weak noise (stochastic update), the system does not converge to equilibrium anymore. Instead, activity transverses on the state landscape in a way restricted by the topology of the connectome and the "gravitational pull" of the attractor states. Bottom: We sample the "state landscape" by running the stochastic relaxation procedure for an extended amount of time (e.g. 100.000 consecutive stochastic updates), each point representing an activation configuration or state. To construct a low-dimensional representation of the state space, we take the first two principal components of the simulated activity patterns. The first two principal components explain approximately 58-85% of the variance of state energy (depending on the noise parameter σ, see Supplementary Figure 1). **C** We map all states of the state space sample to their corresponding attractor state, with the conventional Hopfield relaxation procedure (A). The four attractor states are also visualized in their corresponding position on the PCA-based projection. The first two principal components yield a clear separation of the attractive state basins (cross-validated classification accuracy: 95.5%, Supplementary Figure 2). We refer to the resulting visualization as the *fcHNN* projection and use it to visualize *fcHNN*-derived and empirical brain dynamics throughout the rest of the manuscript. **E** At its simplest form, the *fcHNN* framework entails only two free hyperparameters: the temperature parameter β (left) that controls the number of attractor states and the noise parameter of the stochastic relaxation σ. To avoid overfitting these parameters to the empirical data, we set $\beta = 0.04$ and $\sigma = 0.37$ for the rest of the paper (dotted boxes).

Consistent with theoretical expectations, we observed that increasing the temperature parameter β led to an increasing number of attractor states (Figure 2E, left, Supplementary Figure 3), appearing in symmetric pairs (i.e. $a_i^{(1)} = -a_i^{(2)}$). For simplicity, we set the temperature parameter for the rest of the paper to a value resulting in 4 distinct attractor states ($\beta = 0.4$).

*FcHNN*s, without any modifications, always converge to an equilibrium state. To incorporate stochastic fluctuations in neuronal activity (Robinson *et al.*, 2005), we introduced weak Gaussian noise to the f*cHNN* relaxation procedure. This procedure, referred to as stochastic relaxation, prevents the system from reaching equilibrium and, somewhat similarly to stochastic DCM (Daunizeau *et al.*, 2012), induces complex system dynamics (Figure 2B).

In order to enhance interpretability, we obtained the first two principal components (PCs) of the states sampled from the stochastic relaxation procedure. The resulting two-dimensional embedding (Figure 2B, bottom plot) exhibited high consistency across different values of β and σ (Figure 2E). For all subsequent analyses, we set $\sigma = 0.37$ (based a coarse optimization procedure aimed at reconstructing the bimodal distribution of empirical data, Figure 2E right). On the low-dimensional embedding, which we refer to as the *fcHNN* projection, we observed a clear separation of the attractor states (Figure 2C), with the two symmetric pairs of attractor states located at the extremes of the first and second PC. To map the attractor basins on the space spanned by the first two PCs (Figure 2C), we obtained the attractor state of each point visited during the stochastic relaxation and fit a multinomial logistic regression model to predict the attractor state from the first two PCs. The resulting model accurately predicted attractor states of arbitrary brain activity patterns, achieving a cross-validated accuracy of 96.5%. The attractor basins were visualized by using the decision boundaries obtained from this model. (Figure 2C). We propose the 2-dimensional *fcHNN* projection depicted on (Figure 2C) as a simplified representation of brain dynamics, and use it as a basis for all subsequent analyses in this work.

Reconstruction of resting state brain dynamics

The spatial patterns of the obtained attractor states exhibit high neuroscientific relevance and closely resemble previously described large-scale brain systems. (Figure 3A). The first pair of attractors (mapped on PC1, horizontal axis) resemble the two complementary "macro" systems described, among others, by Golland *et al.* (2008) and Cioli *et al.* (2014) as well as the two "primary" brain states observed by Chen *et al.* (2018) and the 'unimodal-to-transmodal' principal gradient of Margulies *et al.* (2016) and Huntenburg *et al.* (2018). A common interpretation of these two patterns is that they represent (i) an "extrinsic" system linked to the immediate sensory environment and (ii) an "intrinsic" system for higher-level internal context. The other pair of attractors spans an orthogonal axis, and resemble to patterns commonly associated with perception–action cycles (Fuster, 2004), and described as a gradient across sensory-motor modalities (Huntenburg *et al.*, 2018), recruiting regions associated with active inference (e.g. motor cortices) and perceptual inference (e.g. visual areas).

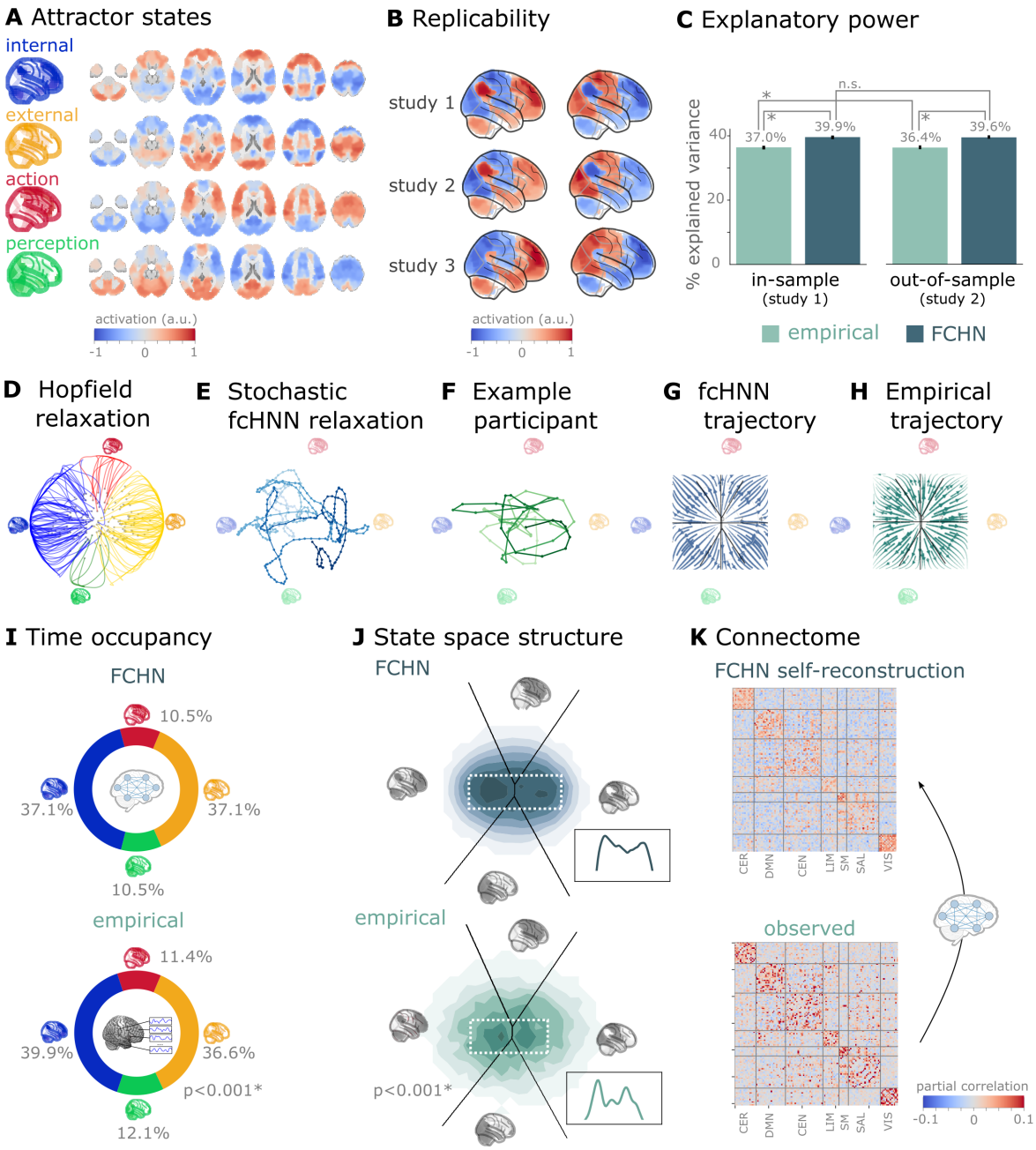

Figure 3: Connectome-based Hopfield networks reconstruct characteristics of real resting state brain activity.

A The four attractor states of the *fcHNN* model from study 1 reflect brain activation patterns with high neuroscientific relevance, representing sub-systems previously associated with "internal context" (blue), "external context" (yellow), "action" (red) and "perception" (green) (Golland *et al.*, 2008; Cioli *et al.*, 2014; Chen *et al.*, 2018; Fuster, 2004; Margulies *et al.*, 2016). **B** The attractor states show excellent replicability in two external datasets (study 2 and 3, mean correlation 0.93). **C** The *fcHNN* projection (first two PCs of the *fcHNN* state space) explains significantly more variance ($p<0.0001$) in the real resting state fMRI data than principal components derived from the real resting state data itself and generalizes better ($p<0.0001$) to out-of-sample data (study 2). Error bars denote 99% bootstrapped confidence intervals. **D** The *fcHNN* of study 1 seeded with real activation maps (gray dots) of an example participant. All activation maps converge to one of the four attractor states during the relaxation procedure (without noise) and the system reaches equilibrium. Trajectories are colored by attractor state. **E** Illustration of the stochastic relaxation procedure in the same *fcHNN* model, seeded from a single starting point (activation pattern). The system does not converge to an attractor state but instead transverses the state space in a way restricted by the topology of the connectome and the "gravitational pull" of the attractor states. The shade of the trajectory changes with an increasing number of iterations. The trajectory is smoothed with a moving average over 10 iterations for visualization purposes. **F** Real resting state fMRI data of an example participant from study 1, plotted on the *fcHNN* projection. The shade of the trajectory changes with increasing number of iterations. **G** Flow map of the mean trajectories (i.e. the timeframe-to-

timeframe transition direction) in *fcHNN*-generated data, as compared to a shuffled null model representing zero temporal autocorrelation. The flow map reveals that the "gravitational pull" of the attractor states gives rise to a characteristic temporal autocorrelation structure. **H** A similar pattern can be found in real data (flow analysis of all participants from study 1 pooled, as compared to a shuffled null model representing zero temporal autocorrelation). **I** The *fcHNN* analysis accurately predicts ($p<0.0001$) the fraction of time spent on the basis of the four attractor states in real restring state fMRI data (study 1) and, **J**, reconstructs the characteristic bimodal distribution of the real resting state data. **K** Stochastic *fcHNN*s are capable of "self-reconstruction": the timeseries resulting from the stochastic relaxation procedure mirror the co-variance structure of the functional connectome the *fcHNN* model was initialized with.

The discovered attractor states demonstrate remarkable replicability (mean Pearson's correlation 0.93) across the discovery dataset (study 1) and two independent replication datasets (study 2 and 3, Figure 3C). Moreover, they were found to be robust to noise added to the connectome (Supplementary Figure 7).
Further analysis in study 1 showed that connectome-based Hopfield models accurately reconstructed multiple characteristics of true resting-state data. First, the two axes of the *fcHNN* projection accounted for a substantial amount of variance in the real resting-state fMRI data in study 1 (mean $R^2 = 0.399$) and generalized well to out-of-sample data (study 2, mean $R^2 = 0.396$) (Figure 3E). Remarkably, the explained variance of the *fcHNN* projection significantly exceeded that of a PCA performed directly on the real resting-state fMRI data itself ($R^2 = 0.37$ and 0.364 for in- and out-of-sample analyses).
Second, *fcHNN* analyses accurately reconstructed various aspects of true resting state brain dynamics. Panel D on Figure 3 shows that, with the conventional Hopfield relaxation procedure, individual activation maps converge to one of the four attractor states. When weak noise is introduced to the system (stochastic relaxation, panel E), the system does not converge to an attractor state, but the resulting path is still influenced by the attractor states' gravity. The empirical timeseries data exhibits a similar pattern not only visually (panel F), but also when quantifying the average trajectories of flow, as compared to null-models of zero temporal autocorrelation (randomized timeframe order), reflecting the "gravitational pull" of attractor states (Figure 3 G and H, see Methods for analysis details).
During stochastic relaxation, the *fcHNN* model was found to spend approximately three-quarters of the time on the basis of the first two attractor states and one-quarter on the basis of the second pair of attractor states (approximately equally distributed between pairs). We observed strikingly similar temporal occupancies in the real data Figure 3D), statistically significant with various null models (Supplementary Figure 4). Fine-grained details of the bimodal distribution observed in the real resting-state fMRI data were also convincingly reproduced by the *fcHNN* model (Figure 3F and Figure 2E).
Finally, *fcHNN*s were found to generate signal that preserves the covariance structure of the real functional connectome, indicating that dynamic systems of this type (including the brain) inevitably "leak" their underlying structure into the activity time series, strengthening the construct validity of our approach (Figure 3D).

An explanatory framework for task-based brain activity

Next to reproducing various characteristics of spontaneous brain dynamics, *fcHNN*s can also be used to model responses to various perturbations. We obtained task-based fMRI data from a study by Woo *et al.* (2015) (study 4, n=33, see Figure 3), investigating the neural correlates of pain and its self-regulation.
We found that activity changes due to pain (taking into account hemodynamics, see Methods) were characterized on the *fcHNN* projection by a shift towards the attractor state of action/execution (permutation test for mean projection difference by randomly swapping conditions, $p<0.001$, Figure 4A, left). Energies, as defined by the *fcHNN*, were also significantly different between the two conditions ($p<0.001$), with higher energies during pain stimulation.
When participants were instructed to up- or downregulate their pain sensation (resulting in increased and decreased pain reports and differential brain activity in the nucleus accumbens, NAc (see Woo *et al.* (2015) for details), we observed further changes of the location of momentary brain activity patterns on the *fcHNN* projection ($p<0.001$, Figure 4A, right), with downregulation pulling brain dynamics towards the attractor state of internal context and perception. Interestingly, self-regulation did not trigger significant energy changes ($p=0.36$).

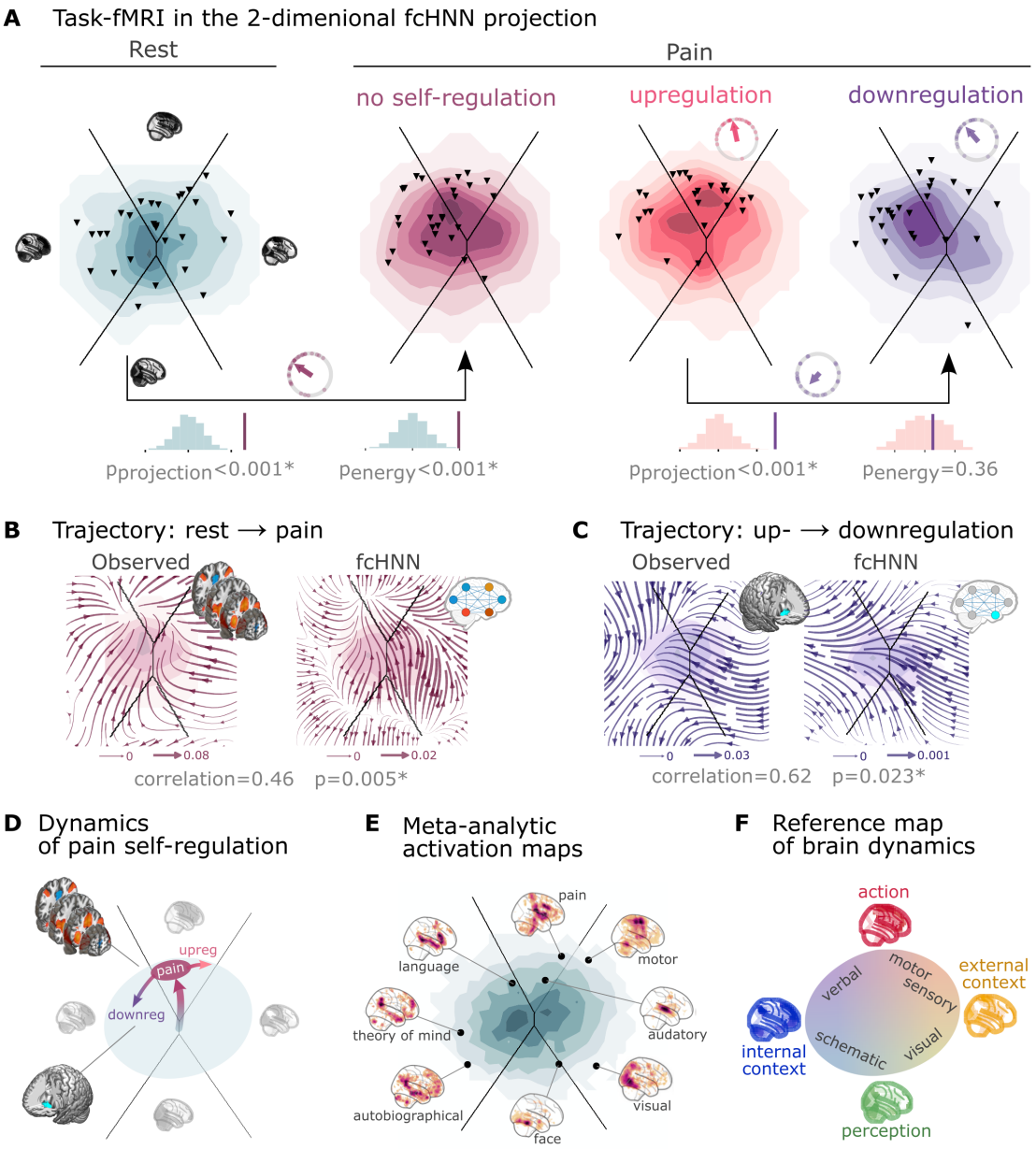

Figure 4: Empirical Hopfield-networks reconstruct real task-based brain activity.
A Functional MRI time-frames during pain stimulation from study 4 (second *fcHNN* projection plot) and self-regulation (third and fourth) are distributed differently on the *fcHNN* projection than brain states during rest (first projection, permutation test, p<0.001 for all). Energies, as defined by the Hopfield model, are also significantly different between rest and the pain conditions (permutation test, p<0.001), with higher energies during pain stimulation. Triangles denote participant-level mean activations in the various blocks (corrected for hemodynamics). Small circle plots show the directions of the change for each individual (points) as well as the mean direction across participants (arrow), as compared to the reference state (downregulation for the last circle plot, rest for all other circle plots). **B** Flow-analysis (difference in the average timeframe-to-timeframe transition direction) reveals a non-linear difference in brain dynamics during pain and rest (left). When introducing weak pain-related signal in the *fcHNN* model during stochastic relaxation, it accurately reproduces these non-linear flow differences (right). **C** Simulating activity in the Nucleus Accumbens (NAc) (the region showing significant activity differences in Woo *et al.* (2015)) reconstructs the observed non-linear flow difference between up- and downregulation (left). **D** Schematic representation of brain dynamics during pain and its up- and downregulation, visualized on the *fcHNN* projection. In the proposed framework, pain does not simply elicit a direct response in certain regions, but instead, shifts spontaneous brain dynamics towards the "action" attractor, converging to a characteristic "ghost attractor" of pain. Down-regulation by NAc activation exerts force towards the attractor of internal context, leading to the brain less frequent "visiting" pain-associated states. **E** Visualizing meta-analytic activation maps (see Supplementary Table 1 for details) on the *fcHNN* projection captures intimate relations between the corresponding tasks and **F** serves as a basis for a *fcHNN*-based theoretical interpretative framework for spontaneous and task-based brain dynamics. In the proposed framework, task-

based activity is not a mere response to external stimuli in certain brain locations but a perturbation of the brain's characteristic dynamic trajectories, constrained by the underlying functional connectivity. From this perspective, "activity maps" from conventional task-based fMRI analyses capture time-averaged differences in these whole brain dynamics.

Next, we conducted a "flow analysis" on the *fcHNN* projection, quantifying how the average timeframe-to-timeframe transition direction differs on the *fcHNN* projection between conditions (see Methods). This analysis unveiled that during pain (Figure 4B, left side), brain activity tends to gravitate towards a distinct point on the projection on the boundary the basins of the internal and action attractors, which we term the "ghost attractor" of pain (similar to Vohryzek *et al.* (2020)). In case of downregulation (as compared to upregulation), brain activity is pulled away from the pain-related "ghost attractor" (Figure 4C, left side), towards the attractor of internal context.

Our *fcHNN* was able to accurately reconstruct these non-linear dynamics by adding a small amount of realistic "control signal" (similarly to network control theory Liu *et al.* (2011) Gu *et al.* (2015)). To simulate the alterations in brain dynamics during pain stimulation, we acquired a meta-analytic pain activation map (Zunhammer *et al.*, 2021) (n=603) and incorporated it as a control signal added to each iteration of the stochastic relaxation procedure. The ghost attractor found in the empirical data was present across a relatively wide range of signal-to-noise (SNR) values (Supplementary Figure 5). Results with SNR=0.005 are presented on Figure 4B, right side (Pearson's r = 0.46, p=0.005 based on randomizing conditions on a per-participant basis).

The same model was also able to reconstruct the observed non-linear differences in brain dynamics between the up- and downregulation conditions (Pearson's r = 0.62, p=0.023) without any further optimization (SNR=0.005, Figure 4C, right side). The only change we made to the model was the addition (downregulation) or subtraction (upregulation) of control signal in the NAc (the region in which (Woo *et al.*, 2015) observed significant changes between up- and downregulation), introducing a signal difference of ΔSNR=0.005 (the same value we found optimal in the pain-analysis). Results were reproducible with lower NAc SNRs, too (Supplementary Figure 6).

To provide a comprehensive picture on how tasks and stimuli other than pain map onto the *fcHNN* projection, we obtained various task-based meta-analytic activation maps from Neurosynth (see Methods) and plotted them on the *fcHNN* projection (Figure 4E). This analysis reinforced and extended our interpretation of the four investigated attractor states and shed more light on how various functions are mapped on the axes of internal vs. external context and perception vs. action. In the coordinate system of the fcHNN projection, visual processing is labeled "external-perception", sensory-motor processes fall into the "external-active" domain, language, verbal cognition and working memory belongs to the "internal-active" region and long-term memory as well as social and autobiographic schemata fall into the "internal-perception" regime (Figure 4F).

Clinical relevance

We obtained data from n=172 autism spectrum disorder (ASD) and typically developing control (TDC) individuals, acquired at the New York University Langone Medical Center, New York, NY, USA (NYU) and generously shared in the Autism Brain Imaging Data Exchange dataset (study 7: ABIDE, (Di Martino *et al.*, 2014). After excluding high-motion cases (see Methods), we visualized the distribution of time-frames on the *fcHNN*-projection separately for the ASD and TDC groups (Figure 5A). First, we assigned all timeframes to one of the 4 attractor states with the *fcHNN* from study 1 and found several significant differences in the mean activity on the attractor basins (see Methods) of the ASD group as compared to the respective controls (Figure 5B). Strongest differences were found on the "action-perception" axis (Table 1), with increased activity of the sensory-motor and middle cingular cortices during "action-execution" related states and increased visual and decreased sensory and auditory activity during "perception" states, likely reflecting the widely acknowledged, yet poorly understood, perceptual atypicalities in ASD (Hadad & Schwartz, 2019). ASD related changes in the internal-external axis were characterized by more involvement of the posterior cingulate, the precuneus, the nucleus accumbens, the dorsolateral prefrontal cortex (dlPFC), the cerebellum (Crus II, lobule VII) and inferior temporal regions during activity of the internalizing subsystem (Table 1). While similar, default mode network (DMN)-related changes have often been attributed to an atypical integration of information about the “self” and the “other” (Padmanabhan *et al.*, 2017), a more detailed *fcHNN*-analysis may help to further disentangle the specific nature of these changes.

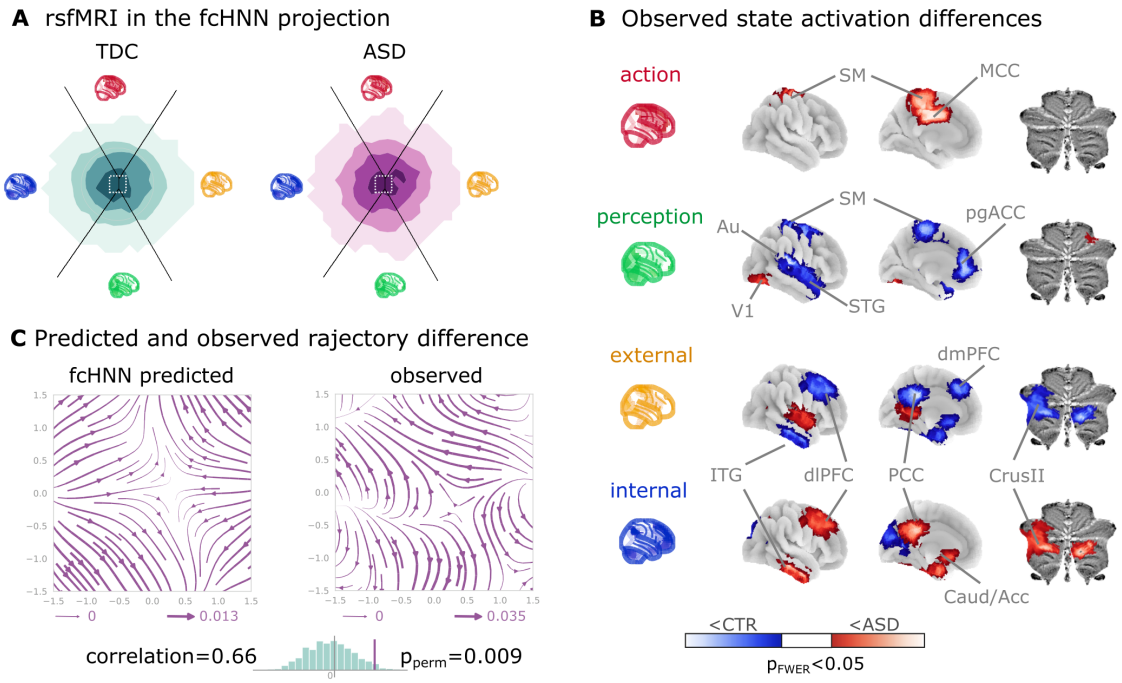

Figure 5: Connectome-based Hopfield analysis of autism spectrum disorder.
A The distribution of time-frames on the *fcHNN*-projection separately for ASD patients and typically developing control (TDC) participants. **B** We quantified attractor state activations in the Autism Brain Imaging Data Exchange datasets (study 7) as the individual-level mean activation of all time-frames belonging to the same attractor state. This analysis captured alterations similar to those previously associated to ASD-related perceptual atypicalities (visual, auditory and somatosensory cortices) as well as atypical integration of information about the "self" and the "other" (default mode network regions). All results are corrected for multiple comparisons across brain regions and attractor states (122*4 comparisons) with Bonferroni-correction. See Table 1 and Supplementary Figure 8 for detailed results. **C** The comparison of data generated by *fcHNN*s initialized with ASD and TDC connectomes, respectively, revealed a characteristic pattern of differences in the system's dynamics, with increased pull towards (and potentially a higher separation between) the action and perception attractors and a lower tendency of trajectories going towards the internal and external attractors. ***Abbreviations***: MCC: middle cingulate cortex, ACC: anterior cingulate cortex, pg: perigenual, PFC: prefrontal cortex, dm: dorsomedial, dl: dorsolateral, STG: superior temporal gyrus, ITG: inferior temporal gyrus, Caud/Acc: caudate-accumbens, SM: sensorimotor, V1: primary visual, A1: primary auditory, SMA: supplementary motor cortex, ASD: autism spectrum disorder, TDC: typically developing control.

Table 1: The top ten largest changes in average attractor-state activity between autistic and control individuals. Mean attractor-state activity changes are presented in the order of their absolute effect size. All p-values are based on permutation tests (shuffling the group assignment) and corrected for multiple comparisons (via Bonferroni's correction). For a comprehensive list of significant findings, see Supplementary Figure 8.

region	attractor	effect size	p-value
primary auditory cortex	perception	-0.126	<0.0001
middle cingulate cortex	action	0.109	<0.0001
cerebellum lobule VIIb (medial)	internal context	0.104	<0.0001
mediolateral sensorimotor cortex	perception	-0.099	0.00976
precuneus	action	0.098	<0.0001
middle superior temporal gyrus	perception	-0.098	<0.0001
frontal eye field	perception	-0.095	<0.0001
dorsolateral sensorimotor cortex	perception	-0.094	0.00976
posterior cingulate cortex	action	0.092	<0.0001
dorsolateral prefrontal cortex	external context	-0.092	<0.0001

Thus, we contrasted the characteristic trajectories derived from the *fcHNN* models of the two groups (initialized with the group-level functional connectomes). Our *fcHNN*-based flow analysis predicted that in ASD, there is an increased likelihood of states returning towards the middle from the internal-external axis and an increased likelihood of states transitioning towards the extremes of the action-perception axis (Figure 5C). We observed a highly similar pattern in the real data (Pearson's correlation: 0.66), statistically significant after permutation testing (shuffling the group assignment, p=0.009).

Discussion

In this study, we have introduced and validated a simple yet robust network-level generative computational framework that elucidates how activity propagation within the functional connectome orchestrates large-scale brain dynamics, leading to the spontaneous emergence of brain states, gradients and characteristic dynamic responses to perturbations.

The construct validity of our model is rooted in the activity flow principle, first introduced by Cole *et al.* (2016). The activity flow principle states that activity in a brain region can be predicted by a weighted combination of the activity of all other regions, where the weights are set to the functional connectivity of those regions to the held-out region. This principle has been shown to hold across a wide range of experimental and clinical conditions (Cole *et al.*, 2016; Ito *et al.*, 2017; Mill *et al.*, 2022; Hearne *et al.*, 2021; Chen *et al.*, 2018). The proposed approach is based on the intuition that the repeated, iterative application of the activity flow equation exhibits close analogies with a type of recurrent artificial neural networks, known as Hopfield networks (Hopfield, 1982).

Hopfield networks have been widely acknowledged for their relevance for brain function, including the ability to store and recall memories (Hopfield, 1982), self-repair (Murre *et al.*, 2003), a staggering robustness to noisy or corrupted inputs (Hertz *et al.*, 1991; see also Supplementary Figure 7) and the ability to produce multistable dynamics organized by the "gravitational pull" of a finite number of attractor states (Khona & Fiete, 2022). While many of such properties of Hopfield networks have previously been proposed as a model for micro-scale neural systems (see Khona & Fiete (2022) for a review), the proposed link between macro-scale activity propagation and Hopfield networks allows transferring the vast body of knowledge on Hopfield networks to the study of large-scale brain dynamics.

Integrating Cole's activity flow principle with the HNN architecture mandates the initiation of network weights with functional connectivity values, specifically partial correlations as suggested by Cole *et al.* (2016). Considering the functional connectome as weights of an already trained neural network distinguishes our methodology not only from conventional biophysical and phenomenological computational modeling strategies, which usually rely on the structural connectome to model polysynaptic connectivity (Cabral *et al.*, 2017), but also from "neuroconnectionist" approaches that employ explicit training procedures (Doerig *et al.*, 2023).

In contrast to finely detailed biophysical models with many free parameters, the basic form of the *fcHNN* approach comprises solely two, easily interpretable "hyperparameters" (temperature and noise) and yields notably consistent outcomes across an extensive range of these parameters (Supplementary Figure 1, 3, 4, 5, 6). To underscore the potency of this simplicity and stability, in the present work, we avoided any unnecessary parameter optimization. It is likely, however, that extensive parameter optimization could further improve the performance of the model.

The proposed model is different from, but compatible with, linear network control theory-based (Gu *et al.*, 2015) approaches. The fact that *fcHNNs* work with direct activity flow estimates, means however, that we do not have to tackle the challenge of modelling the structural-functional coupling (Seguin et al., 2023). Further, the *fcHNN* approach allows us to leverage on knowledge about the underlying ANN architecture. Specifically, Hopfield attractor dynamics provide a mechanistic account for the emergence of large-scale canonical brain networks and brain states (Zalesky *et al.*, 2014), and shed light to the origin of characteristic task-responses that are accounted by "ghost attractors" in the system (Deco & Jirsa, 2012; Vohryzek *et al.*, 2020).

As fcHNNs do not need to be trained to solve any explicit tasks, they are well suited to examine spontaneous brain dynamics. However, it is worth mentioning that, like any other ANNs, *fcHNN*s can also be further trained via established ANN training techniques (e.g. via the Hebbian learning rule) to "solve" various tasks or to match altered dynamics during development or in clinical populations. In this promising future direction, the training procedure itself becomes part of the model, providing testable hypotheses about the formation, and various malformations, of brain dynamics.

Given its simplicity, it is remarkable, if not surprising, how accurately the *fcHNN* model is able to reconstruct and predict brain dynamics under a wide range of conditions. Particularly interesting is the result that the two-dimensional *fcHNN* projection can explain more variance in real resting state fMRI data than the first two principal components derived from the data itself. A plausible explanation for the remarkable reconstruction performance is that, through their known noise tolerance, *fcHNN*s are able to capture essential principles of the underlying dynamic processes even if our empirical measurements are corrupted by noise and low sampling rate. Indeed, *fcHNN* attractor states were found to be robust to noisy weights (Supplementary Figure 7) and highly replicable

across datasets acquired at different sites, with different scanners and imaging sequences (study 2 and 3). The observed level of replicability allowed us to re-use the *fcHNN* model constructed with the connectome of study 1 for all subsequent analyses, without any further fine-tuning or study-specific parameter optimization.

Conceptually, the notion of a global attractor model of the brain network is not new (Deco & Jirsa, 2012). The present work shows, however, that the brain as an attractor network necessarily 'leaks' its code in form of the partial correlation across the regional timeseries, posing fcHNNs as the preferred technique to uncover its large-scale attractor states. We demonstrate that the reconstructed attractor states are not solely local minima in the state-space but act as a driving force for the dynamic trajectories of brain activity. Attractor-dynamics may be the main driving factor for the spatial and temporal autocorrelation structure of the brain, recently described to be predictive of network topology in relation to age, subclinical symptoms of dementia, and pharmacological manipulations with serotonergic drugs (Shinn *et al.*, 2023). Nevertheless, attractor states should not be confused with the conventional notion of brain states (Chen *et al.*, 2015) and large-scale functional gradients (Margulies *et al.*, 2016). In the *fcHNN* framework, attractor states can rather be conceptualized as "Platonic idealizations" of brain activity, that are continuously approximated - but never reached - by the brain, resulting in re-occurring patterns (brain states) and smooth gradual transitions (large-scale gradients).

Relying on previous work, we can establish a relatively straightforward (although somewhat speculative) correspondence between attractor states and brain function, mapping brain activation on the axes of internal vs. external context (Golland *et al.*, 2008; Cioli *et al.*, 2014), as well as perception vs. action (Fuster, 2004). This four-attractor architecture exhibits an appealing analogy with Friston's free energy principle (Friston *et al.*, 2006) that postulate the necessary existence of subsystems for active and perceptual inference as well as a hierarchically organized (i.e. external and internal) subsystems that give rise to consciousness (Ramstead *et al.*, 2023; Lee *et al.*, 2023).

Both conceptually and in terms of analysis practices, resting and task states are often treated as separate phenomena. However, in the *fcHNN* framework, the differentiation between task and resting states is considered an artificial dichotomy. Task-based brain activity in the *fcHNN* framework is not a mere response to external stimuli in certain brain locations but a perturbation of the brain's characteristic dynamic trajectories, with increased preference for certain locations on the energy landscape ("ghost attractors"). In our analyses, the *fcHNN* approach capture and predict participant-level activity changes induced by pain and its self-regulation and gave a mechanistic account for how relatively small activity changes in a single region (NAc) may result in a significantly altered pain experience.

Brain dynamics can not only be perturbed by task or other types of experimental or naturalistic interventions, but also by pathological alterations. Here we have demonstrated (study 7) that *fcHNN*-based analyses can characterize and predict altered brain dynamics in autism spectrum disorder (ASD). The observed ASD-associated changes in brain dynamics are indicative of a reduced ability to flexibly switch between perception and internal representations, corroborating previous findings that in ASD, sensory-driven connectivity transitions do not converge to transmodal areas (Hong *et al.*, 2019). Such findings are in line with previous reports of a reduced influence of context on the interpretation of incoming sensory information in ASD (e.g. the violation of Weber's law) (Hadad & Schwartz, 2019).

Together, our findings open up a series of exciting opportunities for the better understanding of brain function in health and disease.

First, the 2-dimensional *fcHNN* projection offers a streamlined framework not only for the visualization, but also for the *interpretation*, of brain activity patterns, as it conceptualizes changes related to various behavioral or clinical states or traits as a shift in brain dynamics in relation to brain attractor states.

Second, *fcHNN* analyses may provide insights into the causes of changes in brain dynamics, by for instance, identifying the regions or connections that act as an "Achilles heel" in generating such changes. Such analyses could, for instance, aid the differentiation of primary causes and secondary effects of particular activity or connectivity changes in various clinical conditions.

Third, the *fcHNN* approach can provide testable predictions about the effects of pharmacological interventions as well as non-invasive brain stimulation (e.g. transcranial magnetic or direct current stimulation, focused ultrasound, etc) and neurofeedback. Obtaining the optimal stimulation or treatment target within the *fcHNN* framework (e.g. by means of network control theory (Liu *et al.*, 2011)) is one of the most promising future directions with the potential to significantly advance the development of novel, personalized treatment approaches.

In this initial work, we presented the simplest possible implementation of the *fcHNN* concept. It is clear that the presented analyses exploit only a small proportion of the richness of the full state-space dynamics reconstructed by the *fcHNN* model. There are many potential ways to further improve the utility of the *fcHNN* approach. Increasing the number of reconstructed attractor states (by increasing the temperature parameter), investigating higher-dimensional dynamics, fine-tuning the hyperparameters, testing the effect of different initializations and perturbations are all important direction for future work, with the potential to further improve the model's accuracy and usefulness.

Conclusion

To conclude, here we have proposed a lightweight, high-level computational framework that accurately captures and predicts brain dynamics under a wide range of conditions. The framework models large-scale activity flow in the brain with a recurrent artificial neural network architecture that, instead of being trained to solve specific tasks or mimic certain dynamics, is simply initialized with the empirical functional connectome. The framework identifies neurobiologically meaningful attractor states and provides a model for how these restrict brain dynamics. The proposed framework, referred to as the connectome-based Hopfield neural network (*fcHNN*) model, can accurately reconstruct and predict brain dynamics under a wide range of conditions, including resting states, task-induced activity changes and brain disorders. *FcHNN*s establish a conceptual link between connectivity and activity, provide a mechanistic account for the emergence of brain states, gradients and autocorrelation structure and offer a simple, robust, and highly interpretable computational alternative to conventional descriptive approaches to investigating brain function. The generative nature of the proposed model opens up a series of exciting opportunities for future research, including predicting the effect, and understanding the mechanistic bases, of various interventions; thereby paving the way for designing novel treatment approaches.

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Analysis source code
https://github.com/pni-lab/connattractor

Project website
https://pni-lab.github.io/connattractor/

Data availability
Study 1, 2 and 4 is available at openneuro.org (ds002608, ds002608, ds000140). Data for study 3 is available upon request. Data for study 5-6 is available at the github page of the project: https://github.com/pni-lab/connattractor. Study 7 is available at https://fcon_1000.projects.nitrc.org/indi/abide/, preprocessed data is available at http://preprocessed-connectomes-project.org/.

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Methods

Data

We obtained functional MRI data from 7 different sources (Table 1). We included three resting state studies with healthy volunteers (study 1, study 2, study 3, $n_{total} = 118$), one task-based study (study 4, $n_{total} = 33$ participants, 9 runs each), an individual participant meta-analytic pain activation map of pain (study 5, $n_{total} = 603$ from 20 different studies), 8 task-based activation patterns obtained from coordinate-based meta-analyses via Neurosynth (study 6, 14371 studies in total, see Supplementary Table 1) and a resting state dataset focusing on ASD from the ABIDE (Autism Brain Imaging Data Exchange, study 6, $n_{total} = 1112$, Di Martino *et al.* 2014).

Table 1: Datasets and studies. The table includes details about the study modality, analysis aims, sample size used for analyses, mean age, gender ratio, and references.

study	modality	analysis	n	age (mean±sd)	%female	references
study 1	resting state	discovery	41	26.1±3.9	37%	Spisak *et al.* (2020)
study 2	resting state	replication	48	24.9±3.5	54%	Spisak *et al.* (2020)
study 3	resting state	replication	29	24.8±3.1	53%	Spisak *et al.* (2020)
study 4	task-based	pain self-regulation	33	27.9 ± 9.0	66%	Woo *et al.* (2015)
study 5 (Metaanalysis)	task-based	IPD meta-analysis pain map	603 (20 studies)	26.3 ± 5.9	39%	Zunhammer *et al.* (2021)
study 6 (Neurosynth)	task-based	coordinate-based meta-analyses	14371 studies in total	N/A	N/A	Yarkoni *et al.* (2011)
study 7 (ABIDE, NYU sample)	resting state	Autism Spectrum Disorder	ASD: 98 TDC: 74	15.3±6.6	20.9%	Di Martino *et al.* (2014)

Study 1 was used to evaluate the ability of the proposed approach to reconstruct resting state brain activity. Study 2 and 3 served as replications studies for these analyses. Study 1, 2 and 3 is well suited to examine replicability and generalizability; data in these three studies was acquired in 3 different centers from 2 different countries, by different research staff, with different scanners (Philips, Siemens, GE) and different imaging sequences. Further details on study 1-3 are described in Spisak *et al.* (2020). The ability of the proposed approach to model task-based perturbation of brain dynamics was evaluated in Study 4, which consisted of nine task-based fMRI runs for each of the 33 healthy volunteers. In all runs, participants received heat pain stimulation. Each stimulus lasted 12.5 seconds, with 3-second ramp-up and 2-second ramp-down periods and 7.5 seconds at target temperature. Six levels of temperature were administered to the participants (level 1: 44.3°C; level 2: 45.3°C; level 3: 46.3°C; level 4: 47.3°C; level 5: 48.3°C; level 6: 49.3°C). In this analysis we used run 1 (passive experience), run 3 (down-regulation) and run 7 (up-regulation). Participants were asked to cognitively "increase" (regulate-up) or "decrease" (regulate-down) pain intensity. See Woo *et al.* (2015) for details. Pain control signal for our task-based trajectory analyses on data from study 4 was derived from our participant-level meta-analysis of 20 pain fMRI studies (study 5). For details, see Zunhammer *et al.* (2021). To obtain fMRI activation maps for other tasks, we used Neurosynth (D. (2011)), a web-based platform for large-scale, automated synthesis of functional magnetic resonance imaging (fMRI) data. We performed 8 different coordinate-based meta-analyses with the terms "motor", "auditory", "visual", "face", "autobiographical", "theory mind", "language" and "pain" (Supplementary Table 1) and obtained the Z-score maps from a two-way ANOVA, comparing the coordinates reported for studies with and without the term of interest, and testing for the presence of a non-zero association between term use and voxel activation. In study 7 (ABIDE), we obtained preprocessed regional timeseries data from the Preprocessed Connectome Project (Craddock *et al.*, 2013), as shared (https://osf.io/hc4md) by Dadi *et al.* (2019). All preprocessed timeseries data were obtained with the 122-region version of the BASC (Bootstrap Analysis of Stable Clusters) brain atlas (Bellec *et al.*, 2010).

Preprocessing and timeseries extraction

Functional MRI data from studies 1-4 was preprocessed with our in-house analysis pipeline, called the RPN-pipeline (https://github.com/spisakt/RPN-signature). The RPN-pipeline is based on PUMI (Neuroimaging Pipelines Using Modular workflow Integration, https://github.com/pni-lab/PUMI), a nipype-based (Gorgolewski *et al.*, 2011) workflow management system. It capitalizes on tools from FSL (Jenkinson *et al.*, 2012), ANTS

(Avants *et al.*, 2011) and AFNI (Cox, 1996), with code partially adapted from the software tools C-PAC (Craddock *et al.*, 2013) and niworkflows (Esteban *et al.*, 2019), as well as in-house python routines. We run the containerized version of the pipeline with default parameters, as in Spisak *et al.* (2020).
Brain extraction from both the anatomical and the structural images, as well as tissue-segmentation from the anatomical images was performed with FSL bet and fast. Anatomical images were linearly and non-linearly co-registered to the 1mm-resolution MNI152 standard brain template brain with ANTs (see https://gist.github.com/spisakt/0caa7ec4bc18d3ed736d3a4e49da7415 for parameters).
Functional images were co-registered to the anatomical images with the boundary-based registration technique of FSL flirt. All resulting transformations were saved for further use. The preprocessing of functional images happened in the native image space, without resampling. Realignment-based motion-correction was performed with FSL mcflirt. The resulting six head motion estimates (3 rotations, 3 translations), their squared versions, their derivatives and the squared derivatives (known as the Friston-24-expansion, Friston *et al.* (1996)) were calculated to be used as nuisance signals. Additionally, head motion was summarized as framewise displacement (FD) timeseries, according to Power's method (Power *et al.*, 2012), to be used in data censoring and exclusion. After motion-correction, outliers (e.g. motion spikes) in timeseries data were attenuated using AFNI despike. The union of the eroded white-matter maps and ventricle masks were transformed to the native functional space and used for extracting noise-signal for anatomical CompCor correction (Behzadi *et al.*, 2007).
In a nuisance regression step, 6 CompCor parameters (the 6 first principal components of the noise-region timeseries), the Friston-24 motion parameters and the linear trend were removed from the timeseries data with a general linear model. On the residual data, temporal bandpass filtering was performed with AFNI's 3DBandpass to retain the 0.008–0.08Hz frequency band. To further attenuate the impact of motion artifacts, potentially motion-contaminated time-frames, defined by a conservative FD>0.15mm threshold, were dropped from the data (known as scrubbing, Satterthwaite *et al.* (2013)). Participants were excluded from further analysis if more than 50% of frames were scrubbed.
The 122-parcel version of the BASC (Multi-level bootstrap analysis of stable clusters) multi-resolution functional brain atlas (Bellec *et al.*, 2010) was individualized; it was transformed to the native functional space of each participant and masked by the grey-matter mask obtained from the anatomical image, to retain individual grey-matter voxels only. Voxel-timeseries were averaged over these individualized BASC regions.

Functional connectome

Regional timeseries were ordered into large-scale functional modules (defined by the 7-parcel level of the BASC atlas) for visualization purposes. Next, in all datasets, we estimated study-level mean connectivity matrices by regularized partial correlation, via the Graphical Lasso algorithm that estimates a sparse precision matrix by solving a Lasso problem and an L1 penalty for sparsity, as implemented in nilearn (Abraham *et al.*, 2014). Diagonal elements of the matrices were set to zero.

Connectome-based Hopfield networks

Hopfield networks, a type of artificial neural network, consist of a single layer of m fully connected nodes (Hopfield, 1982), with activations $\boldsymbol{a} = (a_1, \dots, a_m)$. Hopfield networks assign an energy to any arbitrary activity configurations:

$$E = -\frac{1}{2}\boldsymbol{a}^T\boldsymbol{W}\boldsymbol{a} + \boldsymbol{a}^T\boldsymbol{b} \qquad (1)$$

where W is the weight matrix with element $w_{i,j}$ denoting the weight between nodes i and j and $\boldsymbol{b}$ is the bias, which is set to $\boldsymbol{b} = 0$ for all experiments.
During the so-called relaxation process, the activities of the nodes are iteratively updated until the network converges to a stable state, known as an attractor state. The dynamics of the network are governed by the equation referenced as eq. (1) of the main text, or in matrix form:

$$\dot{\boldsymbol{a}} = S(\beta\boldsymbol{W}\boldsymbol{a} - \boldsymbol{b}) \qquad (2)$$

where $\dot{\boldsymbol{a}} = (\dot{a_1}, \dots, \dot{a_m})$ is the activity in the next iteration and $S(.)$ is the sigmoidal activation function ($S(a) = tanh(a)$ in our implementation) and β is the temperature parameter. During the stochastic relaxation procedure, we add weak Gaussian noise to each node's activity at every iteration:

$$\dot{\boldsymbol{a}} = S(\beta\boldsymbol{W}\boldsymbol{a} - \boldsymbol{b} + \epsilon), \qquad (3)$$

where $\epsilon \sim \mathcal{N}(\mu, \sigma)$, with σ regulating the amount of noise added and μ set to 0, by default.
In this work we propose functional connectome-based Hopfield neural networks (*fcHNN*s) as a model for large-scale brain dynamics. *FcHNN*s are continuous-state Hopfield neural networks with each node representing a brain region and weights initialized with a group-level functional connectivity matrix. The weights are scaled to zero mean and unit standard deviation.
In studies 1-3, we obtained the finite number of attractor states for all *fcHNN*s by repeatedly (10^5 times) initializing the *fcHNN* with random activations and relaxing them until convergence.

fcHNN projection

We mapped out the *fcHNN* state-space by initializing our *fcHNN* model with a random input, and applying the stochastic update step for 10^5 iterations and storing all visited activity configurations. We performed a principal component analysis (PCA) on the state samples, and proposed the first two principal component (PCs) as the coordinate system for the *fcHNN* projection. Using a Multinomial Logistic Regression, we predicted to which attractor state each of the state samples converges to, using the first two PCs as features. The model's performance was evaluated with 10-fold cross-validation. We visualized the attractor states position in the projection as well as the decision boundaries between the attractor states, based on this regression model. We set $\beta = 0.04$, which results in 4 attractor states given the connectome of study 1. We generated *fcHNN* projections in study 1 with four different σ values (0.33, 0.35, 0.37, 0.39) and fixed σ at 0.37 for all subsequent analyses. The value of σ was selected based on visual inspection of the state space distribution and its similarity to real fMRI data in the *fcHNN* projection (see Figure 3).

Replicability

We obtained the four attractor states in study 1, as described above. We then constructed two other *fcHNN*s, based on the study-mean functional connectome obtained in studies 2 and 3 and obtained all attractor states of these models, with the same parameter settings ($\beta = 0.04$ and $\sigma = 0.37$) as in study 1. In both replication studies we found four attractor states. The spatial similarity of attractor states across studies was evaluated by Pearson's correlation coefficient.

Evaluation: resting state dynamics

Analogously to the methodology of the *fcHNN* projection, we performed PCA on the preprocessed fMRI time-frames from study 1 (based on the empirical regional timeseries data). To compare the explanatory power of the first two PCs derived from *fcHNN*-generated data and real fMRI data, we fitted linear regression models which used the first two *fcHNN* or real data-based PCs as regressors to reconstruct the real fMRI time-frames. In-sample explained variances and the corresponding confidence intervals were calculated for both models with bootstrapping (100 samples). To evaluate the out-of-sample generalization of the PCs (*fcHNN*- and real data-based) from study 1, we calculated how much variance they can explain in study 2.
To calculate fractional time occupancies of the attractor states in real timeseries vs simulated data, we used each real and simulated timeframe as an input to the *fcHNN* of study 1 and obtained the corresponding attractor state. Statistical inference on the similarity of the real fractional occupancies and the *fcHNN* prediction was performed with two different null models. Null model #1 was constructed by a spatial autocorrelation preserving randomization of all time-frames in the real data. Null model #2 was constructed by random sampling from a multivariate normal distribution, with the covariance matrix set based on the functional connectome (partial correlations). More detail on the null-models can be found in Supplementary figure 4.
To confirm that the real and *fcHNN* temporal sequences (from the stochastic relaxation) on display similar temporal autocorrelation properties, we compared both to their randomly shuffled variant with a "flow analysis". First we calculated the direction on the projection plane between each successive TR (a vector on the *fcHNN* projection plane for each TR transition), both for the empirical and the shuffled data. Next, we obtained a two-dimensional binned means for both the x and y coordinates of these transition vectors (pooled across all participants), calculated over a 2-dimensional grid of 100×100 uniformly distributed bins in the [-6,6] range (arbitrary units) and applied a Gaussian smoothing with a σ of 5 bins. Finally, we visualized the difference between the binned-mean trajectories of the empirical and the shuffled data as a “streamplot”, with the Python package matplotlib. The same approach was repeated with the *fcHNN*-generated data.

Evaluation: task-based dynamics

We used study 4 to evaluate the ability of the *fcHNN* approach to capture and predict task-induced alterations in large-scale brain dynamics. First, runs 1, 3 and 7 from all participants, which investigated the passive experience and the down- and up-regulation of pain, respectively, was preprocessed with the same workflow used to preprocess studies 1-3. Regional timeseries data was grouped to "pain" and "rest" blocks, with a 6-second delay to adjust for the hemodynamic response function. All activation timeframes were transformed to the *fcHNN* projection plane obtained from study 1. Within-participant differences of the average location on the *fcHNN* projection was calculated and visualized with radial plots, showing the participant-level mean trajectory on the projection plane from rest to pain, denoted with circles, as well as the group level trajectory (arrow). The significance of the position difference and energy difference of the participant-level mean activations in the projection plane was tested with a permutation test. We used the L2 norm of the two-dimensional position difference and the absolute energy difference, respectively, as test statistics. The permutation tests were run with 1000 permutations, randomly swapping the conditions.
To further highlight the difference between the task and rest conditions, a "flow analysis" was performed to investigate the dynamic trajectory differences between the conditions rest and pain. The analysis method was identical to the flow analysis of resting sate data. First we calculated the direction in the projection plane between each successive TR during the rest conditions (a vector on the *fcHNN* projection plane for each TR transition). Next, we obtained a two-dimensional binned means for both the x and y coordinates of these transition vectors (pooled across all participants), calculated over a 2-dimensional grid of 100 ×100 uniformly distributed bins in the [-6,6] range (arbitrary units) and applied Gaussian smoothing with a σ 5 bins. The same procedure was repeated for the pain condition and the difference in the mean directions between the two conditions was visualized as “streamplots” (using Python’s matplotlib). We used the same approach to quantify the difference in characteristic state transition trajectories between the up- and downregulation conditions. The empirically estimated trajectory differences (from real fMRI data) were contrasted to the trajectory differences predicted by the *fcHNN* model from study 1.
To obtain *fcHNN*-simulated state transitions in resting conditions, we used the stochastic relaxation procedure (Eq. 3), with μ set zero. To simulate the effect of pain-related activation on large-scale brain dynamics, we set μ_i during the stochastic relaxation procedure to a value representing pain-elicited activity in region i. The region-wise activations were obtained calculating the parcel-level mean activations from the meta-analytic pain activation map from (Zunhammer *et al.*, 2021), which contained Hedges' g effect sizes from an individual participant-level meta-analysis of 20 pain studies, encompassing a total of n=603 participants. The whole activation map was scaled with five different values ranging from 10^{-3} to 10^{-1}, spaced logarithmically, to investigate various signal-to-noise scenarios. We obtained the activity patterns of 10^5 iterations from this stochastic relaxation procedure and calculated the state transition trajectories with the same approach used with the empirical data. Next we calculated the simulated difference between the rest and pain conditions and compared it to the actual difference through a permutation test with 1000 permutations, using Pearson's correlation coefficient as test statistic. From the five investigated signal-to-noise values, we chose the one that provided the highest similarity to the real pain vs. rest trajectory difference.
When comparing the simulated and real trajectory differences between pain up- and downregulation, we used the same procedure, with two differences. First, when calculating the simulated state transition vectors for the self-regulation conditions, we used the same procedure as for the pain condition, but introduced and additional signal in the nucleus accumbens, with a negative and positive sign, for up- and downregulation, respectively. We did not optimize the signal-to-noise ratio for the nucleus accumbens signal but, instead, simply used the value optimized for the pain vs. rest contrast (For a robustness analysis, see Supplementary figure 6).

Clinical data

To demonstrate the sensitivity of the *fcHNN* approach to clinically relevant alterations of large-scale brain dynamics in Autism Spectrum Disorder (ASD), we obtained data from n=172 individuals, acquired at the New York University Langone Medical Center, New York, NY, USA (NYU) as shared in the Autism Brain Imaging Data Exchange dataset (study 7: ABIDE, (Di Martino *et al.*, 2014). We focused on the largest ABIDE imaging center to ensure that our results are not biased by center effects. We excluded high motion cases similarly to our approach in studies 1-4, i.e. by ignoring ("scrubbing") volumes with FD>0.15 and excluding participants with more than 50% of data scrubbed. Timeseries data was pooled and visualized on the *fcHNN* projection of study 1, separately for ASD and control participants. Next, for each participant, we grouped the timeframes from the regional timeseries data according to the corresponding attractor states (obtained with the *fcHNN* model from study 1) and averaged timeframes corresponding to the same attractor state to calculated participant-level mean attractor activations. We assessed mean attractor activity differences between the patient groups with a permutation test, randomly re-assigning the group labels 50000 times. We adjusted the significance threshold with a Bonferroni-correction, accounting for tests across 4 states and 122 regions, resulting in $\alpha = 0.0001$. Finally, we have calculated the trajectory differences between the two groups, as predicted by the group-specific *fcHNN*s

(initialized with the ASD and TCD connectomes), and - similarly to the approach used in study 4 - we contrasted the *fcHNN* predictions to the trajectory differences observed in the real rsfMRI data. As in the previous flow analyses, we tested the significance of the similarity between the predicted and observed trajectory differences with a permutation test (1000 permutations), by shuffling group labels.

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