

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

METHODS

Thursday 4th April, 2024

Keywords

1 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 Table ??) 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. \[2014\]](#)).

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. \[2015b\]](#) 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, n=603). For details, see [Zunhammer et al. \[2021\]](#). To obtain fMRI activation maps for other tasks, we used Neurosynth ([Tor 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” (Table ??) 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](#)].

2 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 $FD > 0.15\text{mm}$ 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.

3 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 [Varoquaux et al., 2010], as implemented in nilearn [Abraham et al., 2014]. Diagonal elements of the matrices were set to zero.

4 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 $\mathbf{a} = (a_1, \dots, a_m)$. Hopfield networks assign an energy to any arbitrary activity configurations:

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

where \mathbf{W} is the weight matrix with element $w_{i,j}$ denoting the weight between nodes i and j and \mathbf{b} is the bias, which is set to $\mathbf{b} = 0$ 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. of the main text, or in matrix form:

$$\mathbf{a}' = S(\beta \mathbf{W} \mathbf{a} - \mathbf{b}) \quad (2)$$

where $\mathbf{a}' = (a'_1, \dots, a'_m)$ is the activity in the next iteration and $S(\cdot)$ 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:

$$\mathbf{a}' = S(\beta \mathbf{W} \mathbf{a} - \mathbf{b} + \epsilon), \quad (3)$$

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 (**fcHNNs**) as a model for large-scale brain dynamics. **FcHNNs** 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 **fcHNNs** by repeatedly (times) initializing the **fcHNN** with random activations and relaxing them until convergence.

5 **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 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).

6 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.

7 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 random sampling from a multivariate normal distribution, with the covariance matrix set based on the functional connectome (partial correlations). Null model #2 was constructed by a spatial autocorrelation preserving randomization of all time-frames in the real data. More detail on the null-models can be found in Figure ??.

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.

8 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 state 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 ((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 0 to 1, spaced logarithmically, to investigate various signal-to-noise scenarios. We obtained the activity patterns of 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 an 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 Figure ??).

9 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 (Table 1: **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 calculate 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 **fcHNNs** (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.

References

- Adriana Di Martino, Chao-Gan Yan, Qingyang Li, Erin Denio, Francisco X Castellanos, Kaat Alaerts, Jeffrey S Anderson, Michal Assaf, Susan Y Bookheimer, Mirella Dapretto, et al. The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Molecular psychiatry*, 19(6):659–667, 2014.
- Tamas Spisak, Balint Kincses, Frederik Schlitt, Matthias Zunhammer, Tobias Schmidt-Wilcke, Zsigmond T. Kincses, and Ulrike Bingel. Pain-free resting-state functional brain connectivity predicts individual pain sensitivity. *Nature Communications*, 11(1), January 2020. ISSN 2041-1723. doi:[10.1038/s41467-019-13785-z](https://doi.org/10.1038/s41467-019-13785-z). URL <http://dx.doi.org/10.1038/s41467-019-13785-z>.

- Choong-Wan Woo, Mathieu Roy, Jason T. Buhle, and Tor D. Wager. Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain. *PLoS Biology*, 13(1):e1002036, January 2015a. ISSN 1545-7885. doi:[10.1371/journal.pbio.1002036](https://doi.org/10.1371/journal.pbio.1002036). URL <http://dx.doi.org/10.1371/journal.pbio.1002036>.
- Matthias Zunhammer, Tamás Spisák, Tor D Wager, and Ulrike Bingel. Meta-analysis of neural systems underlying placebo analgesia from individual participant fmri data. *Nature communications*, 12(1):1391, 2021.
- Choong-Wan Woo, Mathieu Roy, Jason T Buhle, and Tor D Wager. Distinct brain systems mediate the effects of nociceptive input and self-regulation on pain. *PLoS biology*, 13(1):e1002036, 2015b.
- Wager Tor D. Neurosynth: a new platform for large-scale automated synthesis of human functional neuroimaging data. *Frontiers in Neuroinformatics*, 5, 2011. ISSN 1662-5196. doi:[10.3389/conf.fninf.2011.08.00058](https://doi.org/10.3389/conf.fninf.2011.08.00058). URL <http://dx.doi.org/10.3389/conf.fninf.2011.08.00058>.
- Cameron Craddock, Sharad Sikka, Brian Cheung, Ranjeet Khanuja, Satrajit S Ghosh, Chaogan Yan, Qingyang Li, Daniel Lurie, Joshua Vogelstein, Randal Burns, et al. Towards automated analysis of connectomes: The configurable pipeline for the analysis of connectomes (c-pac). *Front Neuroinform*, 42(10.3389), 2013.
- Kamalaker Dadi, Mehdi Rahim, Alexandre Abraham, Darya Chyzyk, Michael Milham, Bertrand Thirion, Gaël Varoquaux, Alzheimer’s Disease Neuroimaging Initiative, et al. Benchmarking functional connectome-based predictive models for resting-state fmri. *NeuroImage*, 192:115–134, 2019.
- Pierre Bellec, Pedro Rosa-Neto, Oliver C Lyttelton, Habib Benali, and Alan C Evans. Multi-level bootstrap analysis of stable clusters in resting-state fmri. *Neuroimage*, 51(3):1126–1139, 2010.
- Krzysztof Gorgolewski, Christopher D Burns, Cindee Madison, Dav Clark, Yaroslav O Halchenko, Michael L Waskom, and Satrajit S Ghosh. Nipype: a flexible, lightweight and extensible neuroimaging data processing framework in python. *Frontiers in neuroinformatics*, 5:13, 2011.
- Mark Jenkinson, Christian F Beckmann, Timothy EJ Behrens, Mark W Woolrich, and Stephen M Smith. Fsl. *Neuroimage*, 62(2):782–790, 2012.
- Brian B Avants, Nicholas J Tustison, Gang Song, Philip A Cook, Arno Klein, and James C Gee. A reproducible evaluation of ants similarity metric performance in brain image registration. *Neuroimage*, 54(3):2033–2044, 2011.
- Robert W Cox. Afni: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical research*, 29(3):162–173, 1996.
- Oscar Esteban, Christopher J Markiewicz, Ross W Blair, Craig A Moodie, A Ilkay Isik, Asier Erramuzpe, James D Kent, Mathias Goncalves, Elizabeth DuPre, Madeleine Snyder, et al. fmriprep: a robust preprocessing pipeline for functional mri. *Nature methods*, 16(1):111–116, 2019.
- Karl J Friston, Steven Williams, Robert Howard, Richard SJ Frackowiak, and Robert Turner. Movement-related effects in fmri time-series. *Magnetic resonance in medicine*, 35(3):346–355, 1996.
- Jonathan D Power, Kelly A Barnes, Abraham Z Snyder, Bradley L Schlaggar, and Steven E Petersen. Spurious but systematic correlations in functional connectivity mri networks arise from subject motion. *Neuroimage*, 59(3):2142–2154, 2012.
- Yashar Behzadi, Khaled Restom, Joy Liau, and Thomas T Liu. A component based noise correction method (compcor) for bold and perfusion based fmri. *Neuroimage*, 37(1):90–101, 2007.
- Theodore D Satterthwaite, Mark A Elliott, Raphael T Gerraty, Kosha Ruparel, James Loughhead, Monica E Calkins, Simon B Eickhoff, Hakon Hakonarson, Ruben C Gur, Raquel E Gur, et al. An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *Neuroimage*, 64:240–256, 2013.
- Gaël Varoquaux, Flore Baronnet, Andreas Kleinschmidt, Pierre Fillard, and Bertrand Thirion. Detection of brain functional-connectivity difference in post-stroke patients using group-level covariance modeling. In *Medical Image Computing and Computer-Assisted Intervention–MICCAI 2010: 13th International Conference, Beijing, China, September 20–24, 2010, Proceedings, Part I 13*, pages 200–208. Springer, 2010.
- Alexandre Abraham, Fabian Pedregosa, Michael Eickenberg, Philippe Gervais, Andreas Mueller, Jean Kossaifi, Alexandre Gramfort, Bertrand Thirion, and Gaël Varoquaux. Machine learning for neuroimaging with scikit-learn. *Frontiers in neuroinformatics*, 8:14, 2014.
- John J Hopfield. Neural networks and physical systems with emergent collective computational abilities. *Proceedings of the national academy of sciences*, 79(8):2554–2558, 1982.