Linear models replicate the energy landscape and dynamics of resting-state brain activity

Yuki **Hosaka**[1], Takemi **Hieda**[1], Kenji **Hayashi**[1], Koji **Jimura**[2], Teppei **Matsui**[1]

1. Graduate School of Brain Science, Doshisha University, Kyotanabe, Kyoto, 610-0394, Japan
2. Department of Informatics, Gumma University, Maebashi, 371-8510 Japan

Corresponding Author:
Teppei Matsui (tematsui@mail.doshisha.ac.jp)

Conflicts of Interests: None declared.

Acknowledgments
Data were provided in part by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University.

Funding Sources
This study was supported by JSPS KAKENHI (Grant No.24H02331 to TM, 21K06384 to KH, 24K10471 and 20K07727 to KJ). JST-CREST (Grant. No. JPMJCR22N4 to TM).

Abstract

The brain is constantly and spontaneously active even in the absence of sensory stimulation or motor tasks. The spatiotemporal dynamics of this resting-state brain activity are commonly assumed to be non-stationary and non-linear. It has been proposed that dynamic features (e.g., brain states) extracted from measured resting-state brain activity can better explain subject-specific phenotypes (e.g., fluid intelligence score) than static features. However, several recent studies reported that some analysis methods used to extract dynamic features from resting-brain activity as measured by functional magnetic resonance imaging (fMRI) do not truly reflect non-stationarity and/or non-linear statistical properties of the data. In this study, we examined energy landscape analysis (ELA) to assess whether dynamic features extracted by ELA accurately represent the non-stationary and/or non-linear aspects of resting-brain fMRI activity. To specify the statistical properties being extracted, we applied ELA to both real fMRI data and surrogate data generated by linear and stationary models. We found that ELA results obtained with both the real and simulated data were almost indistinguishable, suggesting that the features extracted by ELA can be explained by covariance and autocorrelation structures. These results corroborate a recent proposal that resting-state fMRI activity can be adequately described by linear models.

Introduction

Brain activity in the resting state, as measured by fMRI, is widely investigated for its potential applications in the non-invasive diagnosis of neuropsychiatric and neurological disorders (1). A common assumption regarding the dynamics of resting-brain activity is that it can be explained by transitions between multiple brain states (2, 3). Recent studies have reported that dynamic features (e.g., brain states) extracted from measured resting-state brain activity can better explain subject-specific phenotypes (e.g., fluid intelligence score) than static features (4, 5).

However, it remains an open question whether resting-brain dynamics indeed consist of multiple states. Recent statistical examinations cast doubt on common analysis techniques, such as sliding-window correlation analysis (4, 6) or point process analysis (7), used to extract possible brain states from resting-state fMRI data. Careful examination using surrogate data, which retains the statistical properties of the original data but are produced by stationary and linear models, revealed that results obtained by these analysis methods are entirely reproducible using surrogate data (6, 8–10). Because surrogate data are linear and stationary by construction, these studies indicate that sliding-window analysis or point process analysis cannot be regarded as evidence of the non-stationarity, or multiple brain-states, of resting brain dynamics.

Energy landscape analysis (ELA) (11, 12) is an alternative widely recognized method for extracting stable brain-states from resting-brain activity. Inspired by statistical mechanics, ELA utilizes the maximum entropy method to recover the energy landscape of resting-brain activity, whose local minima correspond to the basins of attraction (i.e., stable states). Recent studies have reported that subject-level information (e.g., psychiatric conditions and cognitive scores) is reflected in the transition patterns among the states extracted by ELA (13, 14). Although the results of ELA are naturally interpreted with the view that resting-brain dynamics are non-stationary, it is unknown whether ELA captures the non-stationarity of resting-brain activity data. In the present study, we addressed this question by examining ELA using surrogate data.

Materials and methods

Dataset

For analyses of representative data, we used an example fMRI data provided by Ezaki *et al.* (11). The data consisted of time courses from seven regions of interest (ROIs) within the cingulo-opercular network (CON), comprising 9,560 volumes with a repetition time (TR) of 0.72 s. For population analysis, we used the S1200 release of resting-state fMRI distributed by the Human Connectome Project (HCP; http://humanconnectomeproject.org/) (15). The data were preprocessed to obtain ROI-based timecourses (4000 volumes × 264 ROIs × 1002 subjects; TR, 0.72 s; see (10) for details). From 264 ROIs defined in (16), we selected seven ROIs related to CONs, 11 ROIs related to the fronto-parietal network (FPN) and 12 ROIs related to the default mode network (DMN), whose centers were closest to the CON, FPN and DMN ROIs defined in (17). We concatenated data from two subjects, yielding 501 real data samples in total.

Generation of surrogate data

For each sample of real data, we applied three types of linear, stationary models to generate simulated data that retained certain statistical properties of the real data (9, 10). The first model retained only the covariance structure of the real data (Static Null). Simulated data for Static Null were generated using a multivariate Gaussian distribution with covariance matrices set to those of the real data. The second model was a first-order autoregressive randomization null model (ARR). The lag of the ARR null was set to 1. Thus, ARR assumed that the fMRI data at time t is the sum of the linear transformation (A_1) of the fMRI data at time $t-1$ and zero-mean multivariate Gaussian noise with a covariance matrix (Σ). The parameters for the autoregressive equation (Σ, A_1) were fitted as described previously (9). Simulated data for ARR were generated using a randomly selected time point from the real fMRI data as the seed and by iteratively applying the autoregressive equation. The third model was a phase randomization null model (PR). PR retained the complete autoregressive structures of the real data as well as the covariance structures (9). Simulated data for the PR null were generated by first applying a discrete Fourier transform (DFT) to the real fMRI data. Random phases were then added to the Fourier-transformed data, and inverse DFT was applied. The added phases were independently generated for each frequency but were the same across brain regions (9).

Energy landscape analysis (ELA)

ELA was performed as described previously (11) using Matlab2023a (MathWorks,

Natick, MA) with code provided by (11). Briefly, for both real and simulated data, fMRI time courses were binarized to -1 and 1. This implies that, for data with N ROIs, each volume could assume one of 2^N states. After binarization, a pairwise maximum entropy model was fitted to each sample of real or simulated data, yielding an energy landscape. Basins of attraction of the energy landscapes were obtained by fitting dysconnectivity graphs (see (11) for details).

Comparison of ELA results obtained with real and simulated data

Energy landscapes were compared by calculating Pearson's correlation between an energy landscape of each sample of real data and an energy landscape obtained from the corresponding simulated data.

For comparing the dynamics of real and simulated data, we calculated a transition matrix describing the probability of switching (or staying) between basins of attraction. To obtain the transition matrix, each volume in the data was assigned to one of the basins of attraction, yielding a time course of state switching. Then, the probabilities of switching/staying from one basin to another in successive volumes were calculated. Comparisons of transition matrices were done in two methods. In the first method, we selected simulated data with basins of attraction identical to those of the corresponding real data. We then calculated an elementwise Pearson's correlation between the two matrices using all elements or only off-diagonal elements. In the second method, for each sample of simulated data, we obtained the state-switching time course using basins of attraction obtained from the corresponding real data. We then calculated the transition matrix of the simulated data and compared it with that of the real data using elementwise Pearson's correlation (using all elements or only off-diagonal elements). Note that Pearson's correlation using off-diagonal elements was calculated for those data that had more than three basins of attraction.

Because each sample of simulated data had a corresponding sample of real data, statistical testing was performed using a paired *t*-test. We report only uncorrected *p*-values because correction for multiple comparisons was not deemed essential for the purpose of this study.

Data and code availability

The data used in this study are available from the website of (11) or from HCP. Code for reproducing essential results will be made available for download upon publication of the manuscript at https://github.com/teppei-matsui/EL. All codes used for the analysis will be provided upon reasonable request to the corresponding author.

Results

Energy landscape reflects the covariance structure of resting-brain activity

First, we compared the energy landscapes obtained with real data and simulated data constructed by stationary null models. Figure 1a shows the energy landscapes of example real data used in a previous study (11) and the simulated data constructed from it. This example demonstrates that the energy landscapes of the real and simulated data were highly correlated and almost perfectly overlapped for all the null models tested (Static Null, R = 0.988; ARR, R = 0.975; PR, R = 0.982) (Fig. 1a). These results indicate that linear and stationary models taking into account the second-order statistics of the data are enough to capture the shape of the energy landscape.

Transition patterns among states reflect the autocorrelation of resting-brain activity

Next, we examined whether the transition patterns among the energy minima could be captured by the null models. For this example data, we found that the basins of attraction in the energy landscapes were identical for the real and simulated data. Figure 1b shows the transition probability matrices describing the state-switching dynamics of the real and simulated resting brain activities. Unlike the shape of the energy landscape, transition probabilities obtained with the static null showed low correlations with those obtained with the real data (R = 0.107). In contrast, the transition probabilities obtained with ARR and PR showed extremely high correlations with the real transition probabilities (ARR, R = 0.998; PR, R = 0.999). The correlation between transition matrices was higher for ARR and PR than for Static Null even when excluding diagonal elements (Static Null, R = 0.618; ARR, R = 0.961; PR = 0.886). The relatively high positive correlation for Static Null was likely due to the relative frequency of states reflected in the covariance structure. These results indicate that the dynamics of the transitions between energy minima can be effectively captured by linear autoregressive models.

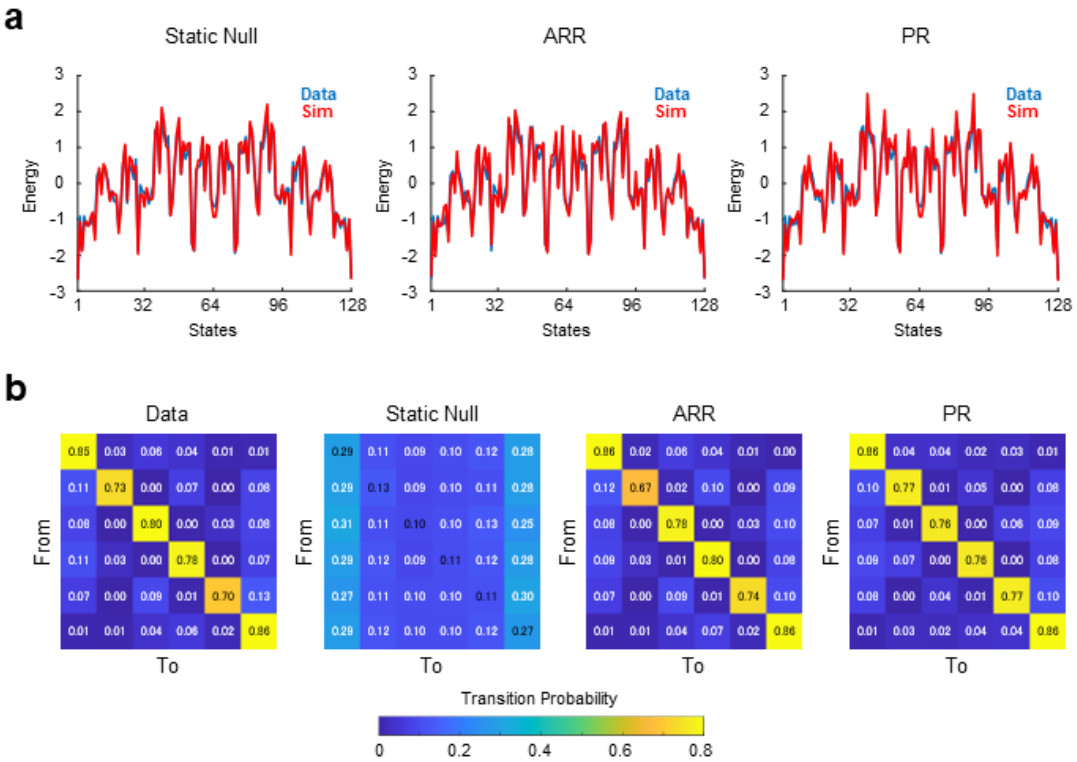

Figure 1. Energy landscapes and transition probability matrices for example and simulated data calculated from it. a. Plots of energy landscapes. Energy landscapes for real data (blue) and simulated data (red) are overlaid for each type of simulated data. **b.** Matrices of transition probability between energy minima (basins). Note that energy minima were identical for the real data and all simulated data.

Test of reproducibility in a large database

Next, to confirm whether these observations also hold in other datasets, we compared energy landscapes of real and simulated data using a publicly available large-scale database of resting-state fMRI provided by HCP. From this database we obtained 501 samples of CON activities. Correlation coefficients of energy landscapes of the real and simulated data were high for all tested null models (Fig. 2a). Although the differences were small, the correlation values were the highest for Static Null and lowest for ARR [Static Null, 0.871 ± 0.068 (mean ± s.d.); ARR, 0.818 ± 0.085; PR, 0.864 ± 0.070; $p < 0.10^{-10}$ (uncorrected) for all pairwise comparisons, paired *t*-test]. These results suggest that the shape of the energy landscape of resting-state fMRI data can be largely captured by stationary and linear statistical properties.

For simulations yielding identical energy landscapes (32, 17, and 34 out of 501

simulations for Static Null, ARR, and PR, respectively), correlation coefficients between transition matrices obtained from data and simulations were high for ARR [R = 0.994 ± 0.006 (mean ± s.d.) with diagonal elements; R = 0.751 ± 0.311 without diagonal elements] and PR (R = 0.992 ± 0.011 with diagonal elements; R = 0.711 ± 0.417 without diagonal elements) but not for Static Null (R = 0.113 ± 0.125 with diagonal elements; R = 0.545 ± 0.532 without diagonal elements).

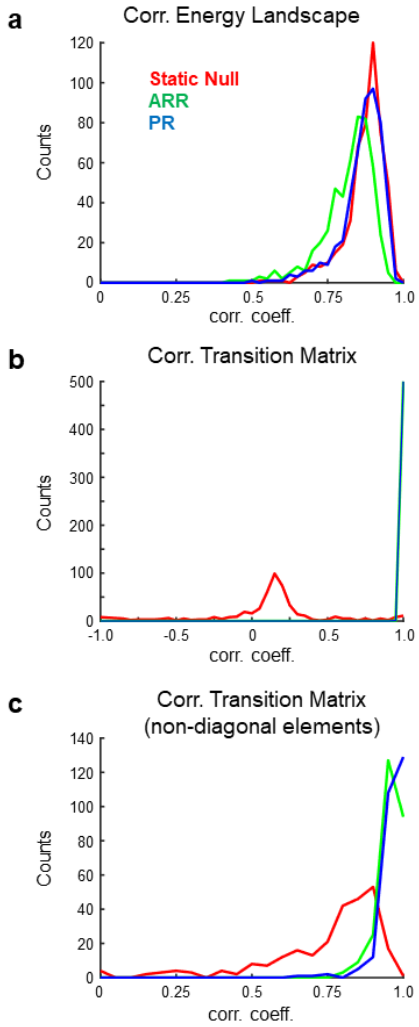

Figure 2. Results of population analysis based on HCP. a. Distribution of correlation coefficients between energy landscapes calculated from real and simulated data. **b.** Distribution of correlation coefficients between transition matrices calculated from real and simulated data. Note that the correlations were calculated using all elements of the transition matrices. **c.** Distribution of correlation coefficients between transition matrices calculated from real and simulated data using only non-diagonal elements of the transition matrices.

To further examine the similarity of dynamics between data and simulations, based on the high similarities of energy landscapes between them (Fig. 2a), we calculated transition probability matrices in each sample of simulated data using the basins of attraction calculated from the corresponding real data. Transition matrices calculated with simulated data were highly correlated with those calculated with ARR (R = 0.999 ± 0.002 with diagonal elements) and PR (R = 0.999 ± 0.003 with diagonal elements) but not with Static Null (R = 0.096 ± 0.390 with diagonal elements) (Fig. 2b). No significant difference was found between ARR and PR [$p > 0.015$ (uncorrected), paired *t*-test]. Correlations calculated only using non-diagonal elements in ARR and PR were still higher than those in Static Null (Fig. 2c), although Static Null had positive overall correlations (R = 0.747 ± 0.203 without diagonal elements). Though the difference was small, correlation values were significantly higher for PR (R = 0.956 ± 0.037 without diagonal elements) than ARR (R = 0.963 ± 0.043 without diagonal elements) [$p < 0.004$ (uncorrected), paired *t*-test]. Similar results were obtained for FPN and DMN (Table 1). Overall, these results confirmed the reproducibility of the observation made with the example data (Fig. 1).

Network	**Model**	**Corr. Ene. Land.**	**Corr. Trans. Mat.**	**Corr. Trans. Mat. w/o Diag.**
FPN	Static Null	0.859 (0.042)	0.164 (0.406)	0.788 (0.124)
FPN	ARR	0.793 (0.052)	0.993 (0.019)	0.929 (0.082)
FPN	PR	0.849 (0.043)	0.994 (0.014)	0.941 (0.064)
DMN	Static Null	0.838 (0.049)	0.191 (0.258)	0.725 (0.165)
DMN	ARR	0.772 (0.061)	0.992 (0.023)	0.919 (0.098)
DMN	PR	0.829 (0.050)	0.994 (0.012)	0.937 (0.068)

Table 1. Summary of results for FPN and DMN. Network, type of brain network. Model, models used to obtain simulated data. Corr. Ene. Land., correlation coefficient between the energy landscape obtained with the real data and that obtained with simulated data. Corr. Trans. Mat., correlation coefficient between the transition matrix obtained with real data and that obtained with simulated data. Corr. Trans. Mat. w/o Diag., correlation coefficient between the transition matrix obtained with real data and that obtained with simulated data calculated using non-diagonal elements of transition matrices. Values are shown as mean (s.d.).

Discussion

We found that two key results of ELA, the energy landscape and transition matrices describing the state-switching dynamics, can be explained by the stationary null models taking into account the covariance and the autocorrelation, respectively, of the real resting-brain activity data. The fact that Static Null reproduced the energy landscape suggests that the energy landscape reflects the covariance structure of the resting-state fMRI data. The absence of a significant difference between ARR and PR for explaining the transition matrix suggests that first-order autocorrelation is sufficient to explain the state-switching dynamics. Thus, the present results suggest that ELA is unlikely to be able to provide evidence of the non-stationarity, or multiple states, of resting brain activity.

We would like to note that the absence of non-linearity or non-stationarity in the features obtained with ELA does not diminish its utility in describing resting-brain activity. The present results, nevertheless, indicate that the results obtained by ELA, in particular the brain states, need to be interpreted with care (see (18) for related discussions).

From a broader perspective, the present results align with a recent proposal that macroscopic resting brain activities are best described with linear models (19). However, it should be noted that, due to the large measurement noise in fMRI, nonlinear and non-stationary features may be masked by noise in fMRI data. Future animal studies using measurements with higher signal-to-noise ratio, such as calcium imaging (20, 21), would be useful to determine whether macroscopic resting-brain dynamics are truly linear and stationary.

Conclusions

Using surrogate data analyses, we found that the features of resting-state fMRI activity extracted by ELA, namely the shape of the energy landscape and the transition patterns among the energy minima, can be largely explained by stationary and linear statistical properties of the data. This finding supports the idea that resting-state fMRI activities are well described by linear models.

References

1. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8(9):700-11.
2. Vidaurre D, Smith SM, Woolrich MW. Brain network dynamics are hierarchically organized in time. Proc Natl Acad Sci U S A. 2017;114(48):12827-32.
3. Noro Y, Li R, Matsui T, Jimura K. A method for reconstruction of interpretable brain networks from transient synchronization in resting-state BOLD fluctuations. Front Neuroinform. 2022;16:960607.
4. Hutchison RM, Womelsdorf T, Allen EA, Bandettini PA, Calhoun VD, Corbetta M, et al. Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage. 2013;80:360-78.
5. Liégeois R, Li J, Kong R, Orban C, Van De Ville D, Ge T, et al. Resting brain dynamics at different timescales capture distinct aspects of human behavior. Nat Commun. 2019;10(1):2317.
6. Matsui T, Murakami T, Ohki K. Neuronal Origin of the Temporal Dynamics of Spontaneous BOLD Activity Correlation. Cereb Cortex. 2018.
7. Liu X, Chang C, Duyn JH. Decomposition of spontaneous brain activity into distinct fMRI co-activation patterns. Front Syst Neurosci. 2013;7:101.
8. Laumann TO, Snyder AZ, Mitra A, Gordon EM, Gratton C, Adeyemo B, et al. On the Stability of BOLD fMRI Correlations. Cereb Cortex. 2016.
9. Liégeois R, Laumann TO, Snyder AZ, Zhou J, Yeo BTT. Interpreting temporal fluctuations in resting-state functional connectivity MRI. Neuroimage. 2017;163:437-55.
10. Matsui T, Pham TQ, Jimura K, Chikazoe J. On co-activation pattern analysis and non-stationarity of resting brain activity. Neuroimage. 2022;249:118904.
11. Ezaki T, Watanabe T, Ohzeki M, Masuda N. Energy landscape analysis of neuroimaging data. Philos Trans A Math Phys Eng Sci. 2017;375(2096).
12. Watanabe T, Hirose S, Wada H, Imai Y, Machida T, Shirouzu I, et al. Energy landscapes of resting-state brain networks. Front Neuroinform. 2014;8:12.
13. Watanabe T, Rees G. Brain network dynamics in high-functioning individuals with autism. Nat Commun. 2017;8:16048.
14. Kang J, Jeong SO, Pae C, Park HJ. Bayesian estimation of maximum entropy model for individualized energy landscape analysis of brain state dynamics. Hum Brain Mapp. 2021;42(11):3411-28.
15. Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K, et al. The WU-Minn Human Connectome Project: an overview. Neuroimage. 2013;80:62-79.

16. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, et al. Functional network organization of the human brain. Neuron. 2011;72(4):665-78.
17. Fair DA, Cohen AL, Power JD, Dosenbach NU, Church JA, Miezin FM, et al. Functional brain networks develop from a "local to distributed" organization. PLoS Comput Biol. 2009;5(5):e1000381.
18. Matsui T, Yamashita KI. Static and Dynamic Functional Connectivity Alterations in Alzheimer's Disease and Neuropsychiatric Diseases. Brain Connect. 2022.
19. Nozari E, Bertolero MA, Stiso J, Caciagli L, Cornblath EJ, He X, et al. Macroscopic resting-state brain dynamics are best described by linear models. Nat Biomed Eng. 2024;8(1):68-84.
20. Li R, Ohki K, Matsui T. Ketamine-induced 1-Hz oscillation of spontaneous neural activity is not directly visible in the hemodynamics. Biochem Biophys Res Commun. 2023;678:102-8.
21. Matsui T, Murakami T, Ohki K. Mouse optical imaging for understanding resting-state functional connectivity in human fMRI. Commun Integr Biol. 2018;11(4):e1528821.