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Detecting spatiotemporal nonlinear dynamics in resting state of human brain based on fMRI datasets

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ABSTRACT

In this work, a nonlinear dynamics method, coupled map lattices, was applied to functional magnetic resonance imaging (fMRI) datasets to examine the spatiotemporal properties of resting state blood oxygen level-dependent (BOLD) fluctuations. Spatiotemporal Lyapunov Exponent (SPLE) was calculated to study the deterministic nonlinearity in resting state human brain of nine subjects based on fMRI datasets. The results show that there is nonlinearity and determinism in resting state human brain. Furthermore, the results demonstrate that there is a spatiotemporal chaos phenomenon in resting state brain, and suggest that fluctuations of fMRI data in resting state brain cannot be fully attributed to nuclear magnetic resonance noise. At the same time, the spatiotemporal chaos phenomenon suggests that the correlation between voxels varies with time and there is a dynamic functional connection or network in resting state human brain.

1. Introduction

Functional magnetic resonance imaging (fMRI) has emerged as a useful and noninvasive technique for studying the function of the brain. Using magnetic resonance technique, researchers have found that it is possible to indirectly detect changes in blood-oxygenation levels that are a result of neuronal activation. In the past decade, fMRI has provided a powerful approach to study the structure-function relationship in the human brain. Most of studies concentrated on detecting or estimating brain regions involved in specific cognitive or sensor-motor tasks.

Conscious rest has been widely used as a baseline condition in positron emission tomography (PET) and fMRI neuroimaging experiments. In most cases, rest state is defined as a state that differs from the active state both in terms of conditions (open/closed eyes, absence/presence of a stimulus input) and instructions given to the subject. A rest state can therefore be used in a wide variety of experiments. However, it is an ill-defined mental state because it may vary both from one subject to another and within the same subject [1].

The complex behavior of the hemodynamic response is a global phenomenon and the reconstruction of the dynamics recorded in fMRI data should make use of the vast amount of spatial information acquired [2]. Electroencephalography (EEG) and magneto-encephalography (MEG) analysis can achieve higher accuracy (performance) by combining spatial and temporal approaches [3,4]. Compared with EEG of low spatial resolution, fMRI datasets offer millimeter spatial resolution with temporal resolutions of the order of seconds. It can offer more spatial information than EEG/MEG. Hence, spatiotemporal analysis is an important analytic tool of fMRI datasets in brain research [5].

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As a linear spatiotemporal analysis method, correlation analysis has been widely used in the study of functional connectivity based on fMRI datasets. It assumes that the relevant information about the interactions of brain regions is reflected by a linear relationship between the values of two signals at the same time [6,7]. However, this hypothesis has not thoroughly been investigated. Recent studies indicated the nonlinear nature of BOLD response [8]. Many nonlinear models between stimulation and fMRI response are established [9,10]. These nonlinearities are believed to be caused by viscoelastic properties of blood vessels [8,11], and nonlinearities at the neuronal level, such as the adaptive behavior of neuronal activity [12–16]. The BOLD response is more sensitive to subtleties of neuronal activity than previously suggested in the literature [17].

Even though there has been an effort to study nonlinear dynamics of brain using Electroencephalogram (EEG) [4,18–20], very little work has been done in applying method of nonlinear dynamics to fMRI, particularly during the resting state. Fractional Gaussian noise property of fMRI datasets is analyzed using Hurst exponent [21]. An extension of the delta-epsilon approach is applied to fMRI data to evaluate whether a time course of a candidate pixel provides additional information concerning the time evolution of reference pixel time series [22]. The nonlinearity arising from the finite dimensional dynamics is then characterized using patterns of singularities in the complex plane. A finite embedding dimension is a measure of the determinism of the system, which can be quantified using information theoretic measures like Lempel-Ziv complexity [23]. Using spatial embedding of fMRI datasets, local spatiotemporal chaos in baseline [24] has been reported, but the significance of nonlinearity has not been tested on fMRI datasets by using surrogate data. Though the nonlinearity analysis of fMRI dataset in human brain has attracted many researchers, most of works on nonlinear analysis of fMRI are carried on single time series voxel by voxel, as is traditionally done in the nonlinear signal processing literature. In addition, because of no significant stimulation in resting state human brain, it is difficult to detect the nonlinearity by the relationship between stimulation and its fMRI response.

In this work, a nonlinear dynamics method, coupled map lattices (CML), was applied to fMRI datasets of resting state human brain. The Spatiotemporal Lyapunov Exponent (SPLE) was calculated for fMRI datasets and the nonlinearity of fMRI datasets was tested by using surrogate data generated from the fMRI datasets. The positive SPLE was confirmed by a finite embedding dimension which is a measure of the determinism of fMRI datasets in resting state brain. The results demonstrate that there is a spatiotemporal chaos phenomenon in resting state brain, and suggest that the fluctuations in resting state brain cannot be fully taken as nuclear magnetic resonance (NMR) noise, but can be the spatiotemporal properties inhered in resting state brain. At the same time, the deterministic nonlinear dynamics can get an estimation of spatiotemporal correlation of resting state brain, and the correlation between voxels varies with time and there is a dynamic functional connection or network in resting state brain.

2. Method

Lyapunov exponents can measure the divergence (or convergence) of nearby trajectories. Although there have been a number of algorithms which attempt to estimate the underlying dynamics recently, most of these algorithms are not suitable for a spatiotemporal dataset such as fMRI but can only be applied to single time series.

2.1. Spatiotemporal Lyapunov Exponent

Ricard V. SolÉ and Jordi Bascompte presented a method [25] to evaluate the SPLE numerically when very short time series are obtained from a spatially distributed dynamical system. This method bases on the concept of coupled map lattices. Coupled map lattices have been widely used as models of spatiotemporal chaos in physics, chemistry and biology.

A dynamical system is given by a set of nonlinear equations as follows:

$$x^j_{n+1}(\mathbf{k}) = F^j_\mu(\mathbf{x}_n(\mathbf{k})) + C^j_\gamma(\mathbf{x}_n(\mathbf{k})), \tag{1}$$

where $\mathbf{j} = \mathbf{1}, \ldots, \mathbf{s}, \mathbf{x} = (x^1_n, \ldots, x^s_n)$ and $F^j_\mu(\mathbf{x}), C^j_\gamma(\mathbf{x}) \in C^2(U)$. U is a compact set and $U \subset \mathbf{R}^s$. This set of maps is then defined on a two-dimensional lattice

$$\Lambda^2(L) = \{\mathbf{k} = (\alpha, \beta) | 1 \leqslant \alpha, \beta \leqslant L\}. \tag{2}$$

If we have a time series defined as the set:

$$\Gamma^j(\mathbf{k}) = \{x^j_1(\mathbf{k}), \ldots, x^j_m(\mathbf{k})\} \quad \forall \mathbf{k} \in \Lambda^2(L). \tag{3}$$

Using the lagging method, a phase space of new d-dimensional sets can be reconstructed as follows:

$$\Gamma^j_d(\mathbf{k}) = \{X^j_i(\mathbf{k}) = (x^j_i(\mathbf{k}), \ldots, x^j_{i+d-1}(\mathbf{k}))\}, \tag{4}$$

where $i = 1, \ldots, m - d + 1$ and d is an embedding dimension. Now we consider the global set defined as the union of all local orbits:

$$\Gamma_d(\Lambda) = \bigcup_{k \in \Lambda(L)} \Gamma^j_d(\mathbf{k}) \tag{5}$$

This set is then constructed by (m- (d-1))L^2-points.

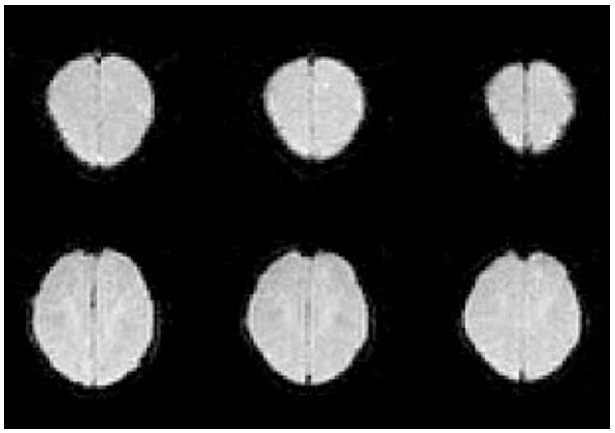

Fig. 1. The interested slices of resting state fMRI datasets from human brain.

For each vector $X_i^j(\mathbf{k})$, we search those lattice points $\mathbf{h} \in \Lambda^2(L)$, $(\mathbf{h} \neq \mathbf{k})$ so that the inequality

$$\|X_i^j(\mathbf{k}) - X_i^j(\mathbf{h})\| = \left[\sum_{u=i}^{i+d-1} (x_u^j(\mathbf{k}) - x_u^j(\mathbf{h}))^2\right]^{1/2} < \varepsilon \tag{6}$$

can hold. Here, ε is the maximum initial separation. Then the Spatiotemporal Lyapunov Exponent will be evaluated by:

$$\lambda_s(d) = \frac{1}{N_p} \sum_{i=1}^{m-d} \sum_{\langle \mathbf{k},\mathbf{h} \rangle} \ln \left[\frac{\|X_{i+1}^j(\mathbf{k}) - X_{i+1}^j(\mathbf{h})\|}{\|X_i^j(\mathbf{k}) - X_i^j(\mathbf{h})\|}\right], \tag{7}$$

where N_p is the total number of $\langle \mathbf{k}, \mathbf{h} \rangle$ pairs.

By simulation, the method of numerical SPLE estimation is used to study Logistic CML, Lotka-Volterra CML and Host-parasitoid CML, which show that low-dimensional chaos can be detected and a consistent estimation of λ_s with other methods is attained [25].

Spatiotemporal Lyapunov Exponent would indicate divergence of the orbits in the attractor and hence be an index of the spatiotemporal correlation between voxels under consideration.

New evidence suggests that essential feature of brain activities can be characterized by low-dimensional dynamics and self-organized spatial patterns of activity. In this way, the brain can switch flexibly between different coherent states [20]. Now, we use this numerical SPLE estimating method to research the spatiotemporal properties of resting state fluctuations for fMRI datasets.

2.2. fMRI data acquisition and analysis

Gradient-echo echo planar imaging (EPI) data were acquired from nine healthy volunteers in resting state with closing eyes, stopping thinking if any idea came up. The datasets were obtained on a 1.5T PHILIPS MEDICAL SYSTEMS Gyroscan NT scanner (TR = 700 ms, Flip angle = 70° and FOV = 23 cm, with five transection slices covering the visual cortex (SCVC) and other five transection slices covering the motor cortex (SCMC), 5mm slice thickness, matrix size: 64×64). After discarding initial scans (to allow for magnetic saturation effects), each time-series is comprised of 600 vol images.

The data were preprocessed with using SPM2 (Statistical Parametric Mapping) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm2). The time series were realigned, corrected for movement-related effects. A mask containing only brain voxels was generated by a threshold. Because of no calculation carrying on between slices and in order to retain as much information as possible, no further preprocess was done. Before calculating the Spatiotemporal Lyapunov Exponent, the datasets were normalized by their maximums. Then, the Spatiotemporal Lyapunov Exponents were calculated to slices numbered by 2, 3, and 4. Fig. 1 shows the images of interested slices. The upper row shows the interested slices covering motor cortex of brain and the lower row shows the interested slices covering the visual cortex, respectively. In order to test the nonlinearity of fMRI datasets, surrogate data were generated from fMRI datasets and also calculated the SPLEs using the same algorithm.

3. Results

The effect of embedding dimension is well illustrated in Fig. 2 for fMRI dataset from one resting state subject. There exists a plateau after a certain embedding dimension $d = 8$. Because of small time series, the plateau shows some slow decay as the

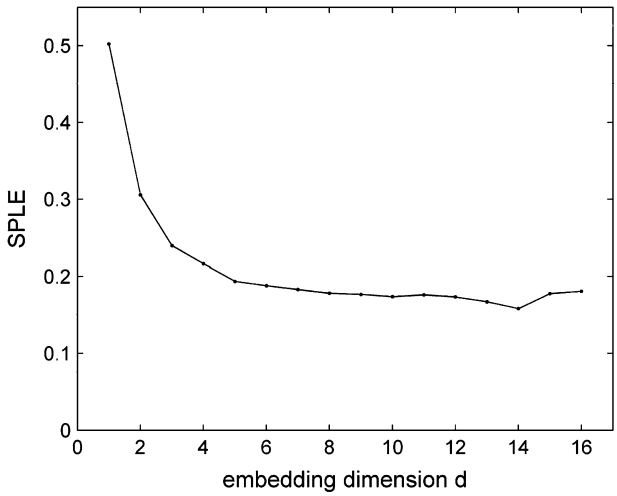

Fig. 2. The effect of embedding dimension.

embedding dimension increases. When the embedding dimensions are within the scope of 8–12, a characteristic rate of decay is observed: $(\lambda_s(d) - \lambda_s(d+1)) \leqslant 0.01$. For other subjects, similar plateaus can be observed as the embedding dimension d increases.

Fig. 3 shows the time evolution of the SPLEs for the fMRI dataset from one resting state subject. In Fig. 3, there is no significant variety with time for the SPLEs to be observed. For other subjects, the results are similar.

In order to evaluate the uniformity of the variety with time for the SPLEs, we define the time-relative-uniformity TRU as follows:

$$\mathrm{TRU} = \frac{\mathrm{SPLE}_{\max} - \mathrm{SPLE}_{\min}}{\mathrm{SPLE}_{\mathrm{mean}}}, \tag{8}$$

where $\mathrm{SPLE}_{\max}$, $\mathrm{SPLE}_{\min}$ and $\mathrm{SPLE}_{\mathrm{mean}}$ are the maximum, minimum and mean of the SPLEs evolving with time for one slice of a resting state subject, respectively. The results show in Table 1. Though all of the TRUs are within 0.6–12%, most of them are less than 5%. Therefore, there is no significant temporal variety of the SPLEs to be observed.

The final SPLEs of all interested slices for nine subjects are showed in Table 2. The most important characteristic is that all SPLEs, which are estimated from the fMRI datasets in resting state subjects, are positive.

Surrogate data are artificially generated for mimicking some properties of the data under study. In the case of testing for nonlinearity, the surrogate data should have the same Fourier spectrum and autocorrelation function ('linear properties') as the raw data under study. This kind of surrogate data is designed to test the null hypothesis that the signal consists of linearly filter Gaussian noise. The popular algorithm for generating this kind of surrogate data can be described in the following

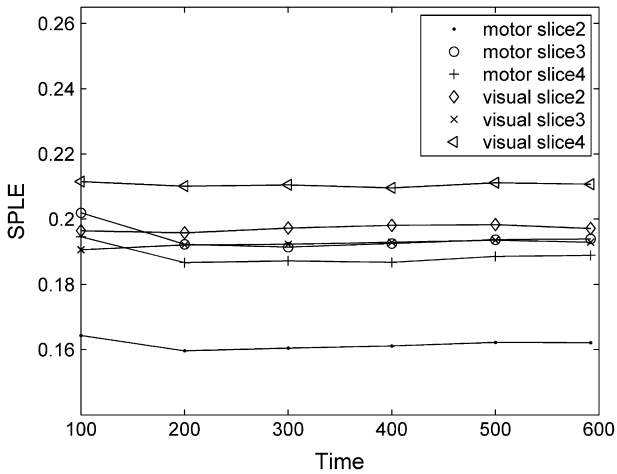

Fig. 3. The temporal evolution of the SPLEs for resting state fMRI dataset. The embedding dimension $d = 8$, and $\varepsilon = 0.02$.

Table 1
The TRU for the SPLEs of fMRI datasets in resting state brain

	Slice2 of SCMC (%)	Slice3 of SCMC (%)	Slice4 of SCMC (%)	Slice2 of SCVC (%)	Slice3 of SCVC (%)	Slice4 of SCVC (%)
Subject1	1.69	1.57	4.39	0.60	0.75	1.14
Subject2	4.48	4.97	9.16	3.67	2.72	6.04
Subject3	3.40	5.51	4.62	1.76	0.89	1.58
Subject4	2.97	8.04	9.75	3.05	1.00	4.83
Subject5	1.95	3.03	2.12	1.15	1.74	2.74
Subject6	8.31	8.13	11.58	6.88	1.32	2.64
Subject7	5.42	0.91	8.35	1.79	0.94	3.76
Subject8	2.91	5.41	4.20	1.27	1.51	0.92
Subject9	2.01	5.64	2.02	2.11	2.62	1.10

Table 2
The SPLEs of fMRI datasets in resting state brain

	Slice2 of SCMC	Slice3 of SCMC	Slice4 of SCMC	Slice2 of SCVC	Slice3 of SCVC	Slice4 of SCVC
Subject1	0.1782	0.2297	0.2259	0.1754	0.2006	0.1750
Subject2	0.1503	0.1505	0.1516	0.1050	0.1456	0.1749
Subject3	0.2283	0.2150	0.2177	0.2206	0.2263	0.2246
Subject4	0.2774	0.2694	0.2562	0.2494	0.2499	0.2428
Subject5	0.2030	0.2361	0.2520	0.2784	0.2571	0.2764
Subject6	0.1708	0.1834	0.2601	0.1694	0.1820	0.1978
Subject7	0.2133	0.2261	0.2488	0.2523	0.2514	0.2347
Subject8	0.1621	0.1940	0.1889	0.1971	0.1930	0.2107
Subject9	0.2451	0.2540	0.2306	0.2571	0.2614	0.2593

way [18]: first, compute the Fourier transform (FT) of the original data. Usually, the Fourier spectrum of the original data has complex amplitude at each frequency. Second, randomize the phases of the Fourier spectrum. Each complex amplitude of the Fourier spectrum is multiplied by $e^{i\phi}$, where ϕ is independently chosen from $[0,2\pi]$ for each frequency. In order for the inverse Fourier transform to be real (no imaginary components), the phases of the Fourier spectrum must be symmetrized, so that $\phi(f) = -\phi(-f)$. Then a new complex spectrum in frequency domain can be obtained with the same absolute values as the Fourier spectrum of original data. Third, generate the surrogate data. The new complex spectrum can be transformed back into the time domain by the inverse Fourier transform (IFT) and thus the surrogate data, which is a realization of linear stochastic process with the same power spectrum as the original data, can be obtained.

To test nonlinearity of the fMRI dataset, 29 surrogate datasets ($p < 0.05$) were generated with the same power spectrum as the fMRI dataset and also calculated the SPLEs by use of the same method. Fig. 4 shows the time evolutions of the SPLEs for the fMRI dataset and its 29 surrogate data. There are significant differences to be observed between the fMRI dataset and its 29 surrogate data.

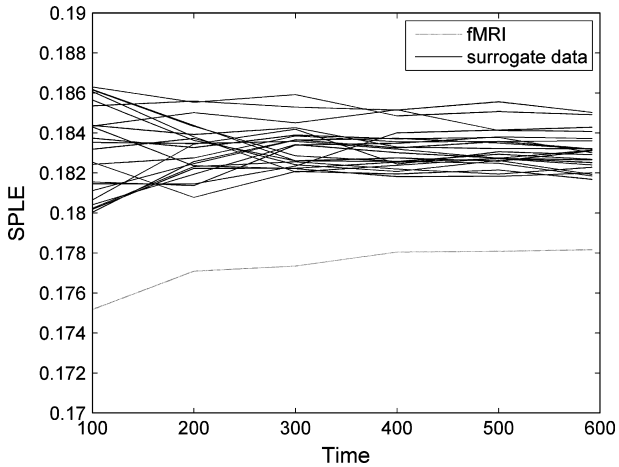

Fig. 4. The SPLEs of raw fMRI dataset and its surrogate datasets.

4. Discussion

It is demonstrated [25] that one can easily distinguish among fixed points, periodic and chaotic orbits. As embedding dimension d is increased, the existence of plateau after a certain $d = d_0$ indicates the presence of low-dimensional dynamics. For small time series, the plateau often shows some slow decay. When deterministic chaos is present, a characteristic rate of decay is observed: $\lambda_s(d) - \lambda_s(d) \leqslant 0.01$. For noisy time series or periodic time series, no such plateau can be obtained. In Fig. 2, the existence of plateau as d increases shows that the fluctuation of fMRI data in resting state brain is neither noise, nor the periodic signal. Therefore the fluctuations of fMRI data in resting state brain cannot be fully attributed to NMR noise.

In order to test nonlinearity, the SPLE was utilized as the discriminating statistic. A surrogate data method was used to verify the characteristics of resting state fMRI datasets. The results of significant difference between the fMRI datasets and their surrogate datasets lead us to conclude that the fluctuations of resting state fMRI datasets of human brain are: (1) not filtered noise; (2) not linear. We could positively show that nonlinear behavior presents in our data. In other words, dynamics in resting state fMRI datasets is nonlinear, at least in our experiment. Therefore, it is shown again that fluctuations of fMRI dataset in resting state brain (absence of explicit brain activation) cannot be fully attributed to NMR noise and that the noise structure of the fMRI data may provide insights into the brain. Significant difference between the fMRI datasets and their surrogate datasets can also exhibit some determinism in the resting state brain. So the resting state of brain conveys valuable information on basal neural activity. This is consistent with the recent reports [23,26].

For the formalism such as those used in this paper, a full study of regular lattices has shown (for several dimensions) the robustness of low-dimensional dynamics emerging from local disorder. In this sense, the collective behavior is shown to be robust with respect to external noise, small changes in the local dynamics and modification in the initial and boundary conditions. In these situations, averages over many short local orbits are expected to yield equivalent information [25]. The dynamics at short temporal scales can be characterized with the aid of Spatiotemporal Lyapunov Exponent. The fact that no significant temporal variation of the SPLEs is observed exhibits that there is brief dynamics stability in the resting state brain.

According to the chaotic theory [27], the Lyapunov Exponents are related to the average rates of convergence and/or divergence of nearby trajectories in phase space. Systems that exhibit a limit cycle as their attractor extractor exhibit no positive Lyapunov exponents, and thus periodic or quasiperiodic signals such as cardiac pulsation and respiratory movement impossibly exhibit any positive Lyapunov exponents. When at least one Lyapunov exponent is positive, then the system at hand is chaotic, and the initial sphere will evolve to some complex ellipsoid structure reflecting the exponential divergence of nearby initial conditions along at least one direction on the attractor. This "sensitivity" to the initial conditions results in an inability to predict the evolution of trajectory beyond an interval of time. When no positive Lyapunov exponent exists, then no exponential divergence exists, and thus the long-term predictability of system at hand is guaranteed. In our study, all SPLEs among different regions of the brain in resting state are positive. This is an important observation showing the fact that there is a phenomenon of spatiotemporal chaos in the resting state brain. Because positive SPLE reflects the exponential divergence of nearby initial conditions, the distance between two voxels in phase space increases with time. In other words, spatiotemporal chaos phenomenon induces correlation between two voxels varying with time. Hence, from the view of dynamics, the correlation between voxels in the resting state brain is not fixed but varies with time. Namely, it is dynamic.

Fluctuations at very low frequencies (0.1 Hz) in fMRI data of resting state brain are spatially correlated within networks corresponding to related brain functions. This low frequency correlation has been utilized in the study of functional connectivity and has been shown to reflect pathologic and/or physiologic alterations [7,28–30]. However, spatiotemporal chaos phenomenon induces the result that correlation between voxels is not fixed and varies with time. Therefore, if there are functional connections or networks in resting state brain, they are necessarily dynamic. In other words, there are dynamic connections or networks in resting state brain. This is one of the reasons that there are more than one spatially distinct resting state networks in a resting state brain dataset [28] and that the nature of the networks can still be debated [31].

Though SPLEs of all subjects are positive, their differences (including TRU) among all subjects in resting state brain are significant ($p < 0.01$). A plausible interpretation is that the resting state is an ill-defined mental state because it may vary both from one subject to another and within the same subject.

5. Conclusion

In this work, the nonlinear dynamics property in resting state human brain is detected by calculating Spatiotemporal Lyapunov Exponent, which based on the coupled map lattices method, to fMRI datasets. The positive SPLE is confirmed by a finite embedding dimension which is a measure of the determinism of fMRI dataset in resting state brain. The results show that spatiotemporal chaos can be detected in resting state human brain. This suggests that the fluctuations in resting state brain cannot be fully attributed to NMR noise, but can be the spatiotemporal properties inhered in resting state human brain. In addition, the deterministic nonlinear dynamics can get an estimation of spatiotemporal correlation of resting state brain, which the correlation between voxels varies with time and there is dynamic functional connection or network in resting state brain.

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