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Dynamic multi-scale modes of resting state brain activity detected by entropy field decomposition

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Abstract

The ability of functional magnetic resonance imaging (fMRI) to non-invasively measure fluctuations in brain activity in the absence of an applied stimulus offers the possibility of discerning functional networks in the “resting state” of the brain. However, the reconstruction of brain networks from these signal fluctuations poses a significant challenge because they are generally non-linear, non-Gaussian, and can overlap in both their spatial and temporal extent. Moreover, because there is no explicit input stimulus there is no signal model with which to compare the brain responses. A variety of techniques have been devised to address this problem but the predominant approaches are based on the presupposition of statistical properties of complex brain signal parameters which are unprovable but facilitate the analysis. In this paper we address this problem with a new method called the entropy field decomposition for estimating structure within spatio-temporal data. This method is based upon a general information field theoretic formulation of Bayesian probability theory incorporating prior coupling information that allows the enumeration of the most probable parameter configurations without the need for unjustified statistical assumptions. This approach facilitates the construction of brain activation modes directly from the spatial-temporal correlation structure of the data. These modes and their associated spatial-temporal correlation structure can then be used to generate space-time activity probability trajectories called functional connectivity pathways which provide a characterization of functional brain networks.

Keywords

fMRI; resting state fMRI; brain functional connectivity; resting state networks; entropy spectrum pathways; entropy field decomposition

Introduction

Functional magnetic resonance imaging (fMRI) has revolutionized neuroscience research by providing a method by which to non-invasively observe spatial and temporal variations in

brain activity. The initial and still dominant fMRI approach is to measure changes in the blood oxygenation level dependent (BOLD) signal in response to well controlled input stimuli designed to probe specific brain systems. This is the so-called “task-based” fMRI. More recently, however, as significant advances in MRI scanner technologies have facilitated the acquisition of high spatial and temporal resolution whole brain fMRI data, an increasing number of studies have returned to the study of brain activity in the absence of external stimulation, the so-called “resting state” condition (Biswal, Yetkin, Haughton, & Hyde, 1995). In resting state fMRI (rsfMRI), one seeks to identify synchronous fluctuations in the BOLD signal that characterize “modes” of brain activity. However, these rsfMRI data present a unique and significant analysis challenge that has yet to be adequately solved, and thus severely limits the utility of the method. The existence of an input stimuli in task-based fMRI implementations provides a reference against which to assess signal changes and facilitates the application of the vast array of analysis methods available for signal detection and parameter estimation. Resting state fMRI data, on the other hand, has no such input, and thus there is a fundamental problem of defining the question to be asked of the data. Brain activity as observed by rsfMRI is generally characterized by spatially and temporally coherent signal changes that reflect “modes” of brain function. These changes can occur on multiple spatial and temporal scales. What exactly is the signal? And how, exactly, is a brain “mode” defined?

In this paper we approach this problem using a new data analysis method developed to address the general problem of detecting non-linear and non-Gaussian spatial-temporal variations in multivariate data. Our method is based on two recent and complimentary general approaches to data analysis, information field theory (IFT) (Enßlin, Frommert, & Kitaura, 2009), which reformulates Bayesian theory in terms of field theory in order to incorporate the important and often overlooked conditions that ensure the continuity of underlying parameter spaces that are to be estimated from discrete data, and entropy spectrum pathways (ESP) (Frank & Galinsky, 2014), which uses the principle of maximum entropy (Jaynes, 1957a, 1957b) to incorporate prior information on the structure of the underlying space in order to estimate measures of connectivity. Incorporation of ESP into IFT is found to produce quantized modes of signal behavior that can then be ranked according to their significance. This method is called the entropy field decomposition (EFD) and it provides a quantitative theory for the estimation of complicated coherent spatial-temporal signal structures in the absence of a signal model (Frank & Galinsky, 2015). A key feature of the EFD theory is that it does not assume either that the signal or noise is Gaussian or that the parameter relationships are linear. Indeed, the power of the method is its ability to automatically detect non-Gaussian and non-linear signal behaviour such as that characteristic of rsfMRI signals.

Here we demonstrate that the most modest and conservative declaration of prior information and model assumptions is sufficient to formulate the rsfMRI data question in a precise theoretical form that lends itself to an efficient and accurate computational method for assessing brain activity. This not only enables the construction of a well-posed meaning for brain modes derived from rsfMRI signals, but also provides a rapid and accurate computational method for direct estimation of these modes. It is shown that a range of modes exist at different spatial-temporal scales. These modes emerge from the data as a

consequence of their space-time coupling structure and the requirement for logical consistency that ensures that they are the most likely space-time paths (i.e., modes) consistent with the data and the prior information, and nothing else, and as such are described by relatively few parameters.

2 Theory

The *entropy field decomposition (EFD)* is developed within the very general framework of information field theory (IFT) (Enßlin et al., 2009) which is not only a fully Bayesian method, but makes explicit the important distinction between the discrete nature of data measurements and the continuity of the underlying field. The utility of IFT has been demonstrated in a wide range of signal estimation problems related to cosmology (Frommert & Enßlin, 2009; Enßlin & Weig, 2010; Frommert & Enßlin, 2010; Enßlin & Frommert, 2011). The EFD method incorporates prior local coupling information into IFT through the theory of entropy spectrum pathways (Frank & Galinsky, 2014) which characterizes and ranks global information pathways based on these local couplings.

Consider the case where the data $\{d(x_j, t_i)\}$ consist of n measurements in time $t_i, i = 1, \dots, n$ at N spatial locations $x_j, j = 1, \dots, N$ (or equivalently $\{d(\xi_l)\}$, where $\xi_l, l = 1, \dots, nN$ defines a set of space-time locations). The spatial locations are assumed to be arranged on a Cartesian grid and the sampling times are assumed to be equally spaced. Neither of these is required in what follows, but merely simplify and clarify the analysis. For most applications we are interested in, the data d are assumed to be 4-dimensional, composed of temporal variations in the signal from a volumetric (three spatial dimensions) imaging experiment. Each data point is of the form

$$d(x_j, t_i) = \hat{R}s(x_j, t_i) + e_{i,j} \quad (1)$$

where $\hat{R}$ is an operator that represents the response of the measurement system to a signal $s(x_j, t_i)$, and $e_{i,j}$ is the noise with the covariance matrix $\Sigma_e = \langle ee^\dagger \rangle$.

From the Bayesian viewpoint, the goal is to estimate the unknown signal from the peak in the joint posterior probability, given the data d and any available prior information I . The posterior distribution can be written via Bayes theorem, as

$$\underbrace{p(s | d, I)}_{\text{Posterior}} = \frac{\overbrace{p(d, s | I)}^{\text{Joint probability}}}{\underbrace{p(d | I)}_{\text{Evidence}}} = \frac{\overbrace{p(d | s, I)}^{\text{Likelihood}} \overbrace{p(s | I)}^{\text{Prior}}}{p(d | I)} \quad (2)$$

For the case of a known model, the denominator is a constant and the posterior distribution is just the product of the likelihood and the prior distribution. With a non-informative, or

“flat” prior, the posterior distribution is just the likelihood, and thus the peak in the posterior distribution is equivalent to the maximum of the likelihood.

Information field theory (Enßlin et al., 2009) re-expresses the probabilistic (or Bayesian) prescription in the language of field theory. The description in terms of fields is important in that, although the data in Eqn 1 consist of discrete samples in both space and time, the underlying signal s is assumed to be *continuous* in space-time, and thus characterized by a field $\psi(x, t) \equiv \psi(\xi)$ such that

$$s(\xi_l) = \int \psi(\xi) \delta(\xi - \xi_l) d\xi \quad (3)$$

By formulating the problem in terms of space-time coordinates $\xi = \{x, t\}$ where x are the spatial coordinates and t is the time coordinates, the “lattice” of points ξ_j , and any quantities derived or constructed from it, are (or can be) space-time quantities. This characterization is particularly important in the present context because we seek to not only detect, but in effect, define *quantitatively*, what is meant by “modes” of space-time variations. As we will show, this can be accomplished well within the context of field theory because the general notion of spatio-temporal patterns can be codified as spatio-temporal modes of a self-interacting field.

The IFT formalism proceeds by identifying the terms in Eqn 2 with the corresponding structures of field theory:

$$H(d, \psi) = - \ln p(d, \psi | I) \quad \text{Hamiltonian} \quad (4a)$$

$$p(d | I) = \int d\psi e^{-H(d, \psi)} = Z(d) \quad \text{Partition function} \quad (4b)$$

so that the Bayes Theorem providing the posterior distribution Eqn 2 becomes

$$p(\psi | d, I) = \frac{e^{-H(d, \psi)}}{Z(d)} \quad (5)$$

From the general results of IFT (Enßlin et al., 2009) applied to a signal of the form Eqn 1, the information Hamiltonian can be written

$$H(d, \psi) = H_0 - j^\dagger \psi + \frac{1}{2} \psi^\dagger D^{-1} \psi + H_l(d, \psi) \quad (6)$$

where H_0 is essentially a normalizing constant that can be ignored, D is a propagator, j is an information source, and H_i is an interaction term. If $H_i = 0$, Eqn 6 describes a *free* theory, whereas if $H_i \neq 0$, then it describes an *interacting* theory. The free theory provides only an initial step in the analysis of data that possesses spatio-temporal variations, for it implicitly assumes that the field components do not interact with one another. In most “real life” cases, such as in rsfMRI data, one would expect more complex spatio-temporal dynamics in which the modes interact with one another.

Interactions are incorporated into IFT by the inclusion of an interaction Hamiltonian (Enßlin et al., 2009)

$$H_i = \sum_{n=1}^{\infty} \frac{1}{n!} \int \cdots \int \Lambda_{\xi_1 \dots \xi_n}^{(n)} \psi(\xi_1) \cdots \psi(\xi_n) d\xi_1 \cdots d\xi_n \quad (7)$$

We keep the terms with $n = 1$ and $n = 2$ assuming that they can be regarded as perturbative corrections to the source and the propagator terms. This interaction Hamiltonian includes anharmonic terms resulting from interactions between the eigenmodes of the free Hamiltonian and may be used to describe non-Gaussian signal or noise, a nonlinear response (i.e., mode-mode interaction) or a signal dependent noise (i.e. due to mode-noise interaction).

The classical solution at the minimum of the Hamiltonian ($\delta H / \delta \psi = 0$) is

$$\psi(\xi) = D \left(j - \sum_{n=1}^{\infty} \frac{1}{n!} \int \cdots \int \Lambda_{\xi \xi_1 \dots \xi_n}^{(n+1)} \psi(\xi_1) \cdots \psi(\xi_n) d\xi_1 \cdots d\xi_n \right) \quad (8)$$

Note that the matrix Λ is written in terms of space-time coordinates ξ and thus characterizes space-time interactions.

A powerful feature of IFT is that it is a Bayesian theory, and so prior information can be included in a straightforward logical fashion. One type of information that proves to be very informative is that of the nearest-neighbor coupling, which can be used to discern the most probable pathways of information through a disordered lattice. This is the basis for the ESP theory (Frank & Galinsky, 2014) which ranks the optimal paths within a disordered lattice according to their path entropy. This is accomplished by constructing a matrix that characterizes the interactions between locations i and j on the lattice called the *coupling matrix*:

$$Q_{ij} = e^{-\gamma_{ij}} \quad (9)$$

The γ_{ij} are Lagrange multipliers that define the interactions and can be seen as local potentials that depend on some function of the space-time locations ξ_i and ξ_j on the lattice. The eigenvector $\phi^{(k)}$ associated with the k 'th eigenvalue λ_k of Q

$$\sum_j Q_{ij} \phi_j^{(k)} = \lambda_k \phi_i^{(k)} \quad (10)$$

generates the transition probability from location i to location j of the k 'th path

$$p_{ijk} = \frac{Q_{ji} \phi_i^{(k)}}{\lambda_k \phi_j^{(k)}} \quad (11)$$

For each transition matrix Eqn 11 there is a unique stationary distribution associated with each path k :

$$\mu^{(k)} = [\phi^{(k)}]^2 \quad (12)$$

that satisfies

$$\mu_i^{(k)} = \sum_j \mu_j^{(k)} p_{ijk} \quad (13)$$

the first of which, $\mu^{(1)}$, corresponds to the maximum entropy stationary distribution (Jaynes, 1957a, 1957b). Note that Eqn 13 is written to emphasize that the squaring operation is performed on a pixel-wise basis (i.e., for each i and j). Considering only $\mu^{(1)}$, note that if the Lagrange multipliers take the form

$$\gamma_{ij} = \begin{cases} 0 & \text{connected} \\ \infty & \text{not connected} \end{cases} \Rightarrow Q_{ij} = e^{-\gamma_{ij}} = \begin{cases} 1 \\ 0 \end{cases} \quad (14)$$

then Q becomes simply an adjacency matrix A . The maximum entropy distribution constructed from this adjacency matrix is the maximum entropy random walk (Burda, Duda, Luck, & Waclaw, 2009). In the ESP theory it is the more general coupling matrix Q , rather than the adjacency matrix A , that is the fundamental quantity that encodes the coupling information (Frank & Galinsky, 2014). Another significant result of the ESP theory is that it ranks *multiple paths*, and these paths can be constructed from *arbitrary* coupling schemes through Q_{ij} . Each of the stationary distributions is associated with a path in which the localization of information is related to the eigenstructure of the disordered lattice. This

localization phenomenon, first observed in the maximum entropy random walk (Burda et al., 2009), and shown to persist with the spectrum of ESP eigenvectors (Frank & Galinsky, 2014), is an important feature of the ESP formalism, since it results in a localization of probabilities which in real life systems tend to be compact and thus amenable to a parsimonious representation of the estimated parameters.

The ESP prior can be incorporated into the estimation scheme by using the coupling matrix Q_{ij} (Eqn 9) so that the prior distribution for the signal, given the coupling matrix, is

$$p(s | Q) = \frac{1}{|2\pi Q|^{1/2}} \exp \left(-\frac{1}{2} s_i^\dagger Q_{ij} s_j \right) \quad (15)$$

The exponent in Eqn 15 can be rewritten using Eqn 10 as $\psi_i^\dagger \mathcal{Q}_{ij} \psi_j$ where ψ are the signals expressed in terms of ϕ , the eigenvectors of Q that comprise the ESP basis (Frank & Galinsky, 2014) and $\mathcal{Q}$ is a diagonal matrix containing eigenvalues of the maximum entropy pathways. (An explicit form of this representation is given below in Eqn 18). It is instructive to note that in the simple case of Gaussian noise with this ESP prior the propagator D in the information Hamiltonian Eqn 6 becomes

$$D = \left[Q + \hat{R}^\dagger \Sigma_e^{-1} \hat{R} \right]^{-1} \quad (16)$$

Without interactions $H_i = 0$ and using a linearly dependent data response-over-noise weighted information source

$$j = \hat{R}^\dagger \Sigma_e^{-1} d \quad (17)$$

the propagator Eqn 16 just provides recasting of the noise corrected propagator in the ESP basis in terms of an interaction free IFT model. Hence the ESP eigenmodes can be viewed also as free modes of the IFT when noise corrected coupling matrix Q is used as a propagator. However, in general, and in the specific applications examined below, these assumptions are violated and this simple description does not hold. The general EFD formalism, and the algorithm described below, does not depend on this description and no assumption of Gaussian noise is made.

But we would like to stress one small but very important point that can be easily overlooked. By the ESP construction the coupling matrix Q may depend on the data in rather complex ways, and hence, the IFT model expressed by Eqn 6, even in the absence of interactions, does *not* possess the property of Gaussianity that is viewed as a major limitation of many data analysis models in fields ranging from brain imaging to weather related data processing

to cosmic microwave background data assimilation. Gaussianity is not assumed in the EFD approach by its very construction.

An important practical implication of this ESP guided form of IFT is that ESP ranking of eigenmodes allows the reduction of problem dimensions by writing a Fourier expansion using $\{\phi^{(k)}\}$ as the basis functions

$$\psi(\xi_l) = \sum_k^K \left[a_k \phi^{(k)}(\xi_l) + a_k^\dagger \phi^{\dagger, (k)}(\xi_l) \right] \quad (18)$$

and keeping the number of modes K significantly smaller than the overall size of the problem nN by examining the importance of the eigenvalues λ_k and comparing them to the noise covariance $|\Sigma_\phi|$. Note that, as a consequence of Eqn 10, these basis functions are unique once the coupling matrix has been defined. Furthermore, the localization phenomena peculiar to the ESP eigenvectors distinguishes the eigenfunctions used in Eqn 18 from other harmonic bases.

In many practical applications temporal variations are well-characterized by frequency modes and thus instead of using the ESP expansion in the whole space-time domain in Eqn 18, it may often be beneficial to use the ESP basis only for spatial coordinates $\{x_i\}$ while keeping the traditional Fourier polynomial expansion in the temporal $\{t_j\}$ domain

$$\psi(x_i, t_j) = \sum_{k,l} \left[a_{k,l} e^{i\omega_l t_j} \phi^{(k,l)} + a_{k,l}^\dagger e^{-i\omega_l t_j} \phi^{\dagger, (k,l)} \right] \quad (19)$$

Note that the coupling matrix Q is now different at different frequencies ω_l , hence, spatial ESP basis functions $\phi^{(k,l)}$ depend on frequency as well. Except for the appearance of the second index in this form of expansion, the rest of the approach, including the information Hamiltonian Eqn 20 and the form of the interaction terms Eqn 25, can easily be recast using this new basis.

The information Hamiltonian Eqn 6 can then be written in ESP basis (Eqn 18) as

$$H(d, a_k) = -j_k^\dagger a_k + \frac{1}{2} a_k^\dagger \Lambda a_k + \sum_{n=1}^{\infty} \frac{1}{n!} \sum_{k_1}^K \cdots \sum_{k_n}^K \tilde{\Lambda}_{k_1 \dots k_n}^{(n)} a_{k_1} \cdots a_{k_n} \quad (20)$$

where matrix Λ is the diagonal matrix $\text{Diag}\{\lambda_1, \dots, \lambda_K\}$, composed of the eigenvalues of the noise corrected coupling matrix, and j_k is the amplitude of k th mode in the expansion of the source j

$$j_k = \int j \phi^{(k)}(\xi) d\xi \quad (21)$$

Expression for the classical solution Eqn 8 for the mode amplitudes a_k then becomes

$$\Lambda a_k = \left(j_k - \sum_{n=1}^{\infty} \frac{1}{n!} \sum_{k_1}^K \cdots \sum_{k_n}^K \tilde{\Lambda}_{kk_1 \dots k_n}^{(n+1)} a_{k_1} \cdots a_{k_n} \right) \quad (22)$$

The new interaction terms $\tilde{\Lambda}^{(n)}$ are expressed through integrals over ESP eigenmodes

$$\tilde{\Lambda}_{k_1 \dots k_n}^{(n)} = \int \cdots \int \Lambda_{\xi_1 \dots \xi_n}^{(n)} \phi^{k_1}(\xi_1) \cdots \phi^{k_n}(\xi_n) d\xi_1 \cdots d\xi_n \quad (23)$$

The interaction terms $\Lambda^{(n)}$ should be specified in order to be able to estimate amplitudes a_k of the self-interacting modes. The simplest way to take into account the interactions would be an assumption of only local interactions. This can be easily accomplished by factorization $\Lambda^{(n)}$ in a product of delta functions $\alpha^{(n)} \delta(\xi_1 - \xi_2) \cdots \delta(\xi_1 - \xi_n)$, here $\alpha^{(n)} < 1$ are constants. This results in a simple but not particularly useful expression for $\tilde{\Lambda}_{k_1 \dots k_n}^{(n)}$

$$\tilde{\Lambda}_{k_1 \dots k_n}^{(n)} = \alpha^{(n)} \int \phi^{k_1}(\xi) \cdots \phi^{k_n}(\xi) d\xi \quad (24)$$

which after substituting it into e.g. Eqn 22 just provides the expression for the classical local-only interacting field (Enßlin et al., 2009) recast in the reduced dimensions ESP eigenmodes basis.

A more general and practical expression for estimating the amplitudes of interacting modes can be constructed by assuming that the nonlinear interactions between different modes will reflect the coupling. A natural way to take coupling into account would be through factorization of $\Lambda^{(n)}$ in powers of the coupling matrix, i.e. we can assume that

$$\Lambda_{\xi_1 \dots \xi_n}^{(n)} = \frac{\alpha^{(n)}}{n} \sum_{p=1}^n \prod_{\substack{m=1 \\ m \neq p}}^n Q_{\xi_p \xi_m} \quad (25)$$

which results in

$$\tilde{\Lambda}_{k_1 \dots k_n}^{(n)} = \frac{\alpha^{(n)}}{n} \sum_{p=1}^n \left(\frac{1}{\lambda_{k_p}} \prod_{m=1}^n \lambda_{k_m} \right) \int \left(\prod_{r=1}^n \phi^{k_r}(\xi) \right) d\xi \quad (26)$$

Here values of the coefficients $\alpha^{(n)}$ should be chosen sufficiently small to ensure the convergence of the classical solution Eqn 22. From a practical standpoint values of $\alpha^{(n)} \lesssim 1 / \max (j_k^n / \lambda_k)$ provide a good starting estimate for further adjustments.

This expression is correct up to the third ($n = 3$) order but discards various chain-like factorizations (e.g. $Q_{\xi_1 \xi_2} Q_{\xi_2 \xi_3} \dots Q_{\xi_{n-1} \xi_n}$) for higher ($n > 3$) orders. These chain-like terms may be included as well by re-expanding required nonlinear combinations of ESP basis functions through the same basis. We would like to emphasize that this task is not impracticable as in many “real life” applications the ESP eigenmodes are expected to be compactly localized because of the unique localization properties of the ESP eigenvectors (Frank & Galinsky, 2014). Therefore, nonlinear expressions that involve various powers of ESP eigenmodes can be expected to decay significantly faster than nonlinear terms.

This formalism provides a well defined quantitative definition of a “mode” in terms of an eigen-expansion of fields in the ESP basis. Each mode makes a contribution to the total posterior probability Eqn 5 through the Hamiltonian in Eqn 6. The reconstructed space-time modes are volumetric time series that represent the activation patterns in the brain. These modes can be ranked according to various criteria, such as power, which is the criterion used in this paper. This EFD approach is very versatile because of the flexibility in the choice of both the prior information (in the construction of Q) and the coupling scheme. For example, it is possible to use either frequencies or amplitudes (or both) for coupling.

2.1 Space-time tractography and connectivity eigenmodes

Current methods for the detection of brain networks focus on the estimation of spatio-temporal patterns of activation, just as we have presented in the preceeding section. However, the general nature of the EFD facilitates further analysis that has the potential to provide more detailed information on the nature of brain activity. The general EFD framework constructs the modes from spatio-temporal patterns in parameters that are generally tensorial in nature. A useful feature of EFD with tensorial parameters is its ability to construct long-range space-time correlations through the generation of spatially continuous parameter pathways, or tracts, by the incorporation of our recently developed tractography method which employs a geometrical optics approach guided by ESP (GO-ESP; (Galinsky & Frank, 2015)). Although this approach was developed in the context of mapping neural pathways from diffusion weighted MRI data, the method actually makes no assumption about the type of data, and can be viewed as a general procedure for constructing the optimal estimates of the space-time trajectories traversed by a systems parameters. We call this general procedure *space-time tractography* and refer to the resulting pathways as space-time tracts. These tracts provide additional information about the detected modes that is not directly apparent from the modes themselves, but is embedded in the estimated spatio-temporal patterns, in a similar way that neural connectivity can be seen to be additional

information embedded with the tensor field of estimated voxel diffusion profiles. In the case of functional tractography, these tracts reveal how the activation evolves with time by tracking the location of the maximum space-time correlation.

From a logical perspective, this tractography through space-time paths can be viewed simply as an extension of the EFD by noting that Hamilton's Principle of Least Action for a light ray traveling a path $r(s)$ of unit speed (parameterized by the arc-length ds that satisfies $ds^2 = dr(s) \cdot dr(s)$, and of unit speed, $|r| = 1$) between points a and b in three-dimensional space can be expressed in terms of the stationarity condition $\delta S_o = 0$ of the action

$$S_o = \int_a^b L_o(r, \dot{r}) ds \quad \text{where} \quad L_o(r, \dot{r}) = n(r) \sqrt{\dot{r} \cdot \dot{r}} \quad (27)$$

where L_o is the Lagrangian and $n(r)$ is the spatially dependent index of refraction and we use the subscript o to denote the "optics" analogy. With this Lagrangian, the Principle of Stationary Action implies the eikonal equation of ray optics and thus links the Lagrangian formulation and the geometrical optics approach to tractography (Galinsky & Frank, 2015). The tract trajectories are generated by the partition function

$$Z_o = \int \mathcal{D}_\phi \exp \{ - S_o \} \quad (28)$$

One possible way to implement this general principle is to define a Hamiltonian $\mathcal{H}_m(\mathbf{x}, \mathbf{k})$ as the averaged temporal correlation function of the space-time signal

$$\mathcal{H}_m(\mathbf{x}, \mathbf{k}) = \frac{1}{T^2} \int \int s_m(\mathbf{x}, t') s_m(\mathbf{x} + \mathbf{k}, t' + t) dt dt' \quad (29)$$

where $s_m(\mathbf{x}, t)$ is the m -th mode signal and $T = t_n - t_1$. Then the trajectory is integrated starting from the seed point to follow the maximum correlation with

$$\frac{d\mathbf{x}}{dt} = \frac{\partial \mathcal{H}_m}{\partial \mathbf{k}}, \quad \frac{d\mathbf{k}}{dt} = - \frac{\partial \mathcal{H}_m}{\partial \mathbf{x}}. \quad (30)$$

where $\mathbf{k}$ is the conjugate variable of the spatial coordinate $\mathbf{x}$ (i.e., the momentum). Tracts are then constructed from the space-time trajectory of the maximum correlations in precisely the same manner as through the diffusion sensitivity and spatial coordinate space in our formulation of the tractography problem in diffusion tensor imaging (DTI) (Galinsky & Frank, 2015). In practice, the computation of $\mathcal{H}_m(\mathbf{x}, \mathbf{k})$ comes essentially "for free" in that the temporal pair correlation function is already computed as part of the EFD processing

scheme. From a practical perspective, the most straightforward implementation of tractography is to assume that tracts traverse the high probability regions of the parameters estimated using the EFD procedure outlined above, using the probability surfaces of the ranked modes as seed points allows us to generate the space-time paths for each mode.

Tractography results produce a multitude of pathways that can be difficult to interpret or categorize in a succinct fashion. This is true as well in tractography generated from diffusion weighted data (Galinsky & Frank, 2015). Here we introduce a useful quantitative characterization of the paths based upon the eigenmodes of the connectivity matrix generated from all of the starting and ending points of each tract. These are called *space-time connectivity eigenmodes* and represent the trajectory of maximum space-time correlation within a given mode. These eigenmodes can be ranked according to their associated eigenvalues. The principal eigenmode is thus the one associated with the largest eigenvalue, and interpreted as the primary, or most probable, pathway in the data.

We previously introduced this procedure for constructing parameter probability pathways in a different context (Frank, Galinsky, & Wurman, 2015). The use of spatio-temporal correlations to construct functional pathways has also been previously demonstrated by Ding (Ding et al., 2013)

3 Implementation

The general EFD formalism is very flexible and allows for multiple spatial and temporal correlation orders to be incorporated, and can include a wide range of prior information, such as physiological models for the fMRI signal. However, for this initial paper we limit our implementation to nearest neighbor interactions (in both space and time) and a Gaussian noise model. Nevertheless, this rather straightforward implementation is sufficient to demonstrate the power and utility of the method. Two slightly different implementations were used, the first was using a complete spatial-temporal ESP basis for signal expansion Eqn 18, and the second was based on spatial ESP but employed Fourier expansion in the temporal domain Eqn 19. All the algorithms implemented in this paper were written in standard ANSI C/C++. The spatio-temporal EFD procedure used in this paper for estimating the signal modes consisted of the following steps:

1. Generate coupling matrix Eqn 9 using simple nearest neighbor coupling $Q(\xi_i, \xi_j) = \alpha(\xi_i)\alpha(\xi_j)A_{ij}$, where A_{ij} is the space-time adjacency matrix, i.e. A_{ij} equals 1 if i and j are nearest neighbors in space or time domains, and 0 otherwise.
2. Find ESP eigenvalues λ_k and eigenvectors $\phi^{(k)}$ for the coupling matrix $Q(\xi_i, \xi_j)$ solving the eigenvalue problem Eqn 10.
3. Use ESP eigenvalues λ_k and eigenvectors $\phi^{(k)}$ to construct the information Hamiltonian Eqn 20, where Λ is simply the diagonal matrix $\text{Diag}\{\lambda_1, \dots, \lambda_K\}$ of ESP eigenvalues, and the interaction terms $\Lambda^{(n)}$ are constructed from ESP eigenvalues and eigenvectors with the help of Eqn 26.

4. Finally, the amplitudes a_k that describe both spatially and temporally interacting modes of the information Hamiltonian Eqn 20 are found from the nonlinear expression for the classical solution Eqn 22.

Although the alternative implementation (corresponding to Eqn 19) follows the above estimation steps, it nevertheless has several important differences worth mentioning. First, instead of generating nearest neighbor coupling in both space and time domains, it employs the frequency dependent spatial coupling matrix $Q(x_i, x_j, \omega_l)$ taking nearest neighbor coupling only in the spatial domain (here x_i and x_j are spatial coordinates and ω_l is a frequency). Second, the strength of coupling for each frequency depends on the temporal pair correlation function. There are different ways to introduce this temporal correlation dependence. We used the following form of coupling matrix

$$Q(x_i, x_j, \omega_0) = \mathcal{R}_{ij}^m d(x_i, \omega_0) d(x_j, \omega_0), \quad (31)$$

$$Q(x_i, x_j, \omega_l) = \mathcal{R}_{ij}^m \left(\phi^{(1)}(x_i, \omega_0) d(x_j, \omega_l) + \phi^{(1)}(x_j, \omega_0) d(x_i, \omega_l) \right), \quad (32)$$

here $\mathcal{R}_{ij}$ is either the mean

$$\mathcal{R}_{ij} = \frac{1}{T} \int_0^T \int_0^T (d(x_i, t - \tau) d(x_j, \tau) d\tau dt) \quad (33)$$

or the maximum

$$\mathcal{R}_{ij} = \max_t \int d(x_i, t - \tau) d(x_j, \tau) d\tau \quad (34)$$

of the temporal pair correlation function computed for spatial nearest neighbors i and j , $\phi^{(1)}(x_j, \omega_0)$ is the eigenmodes that corresponds to the largest eigenvalue of $Q(x_i, x_j, \omega_0)$, and the exponent $m = 0$ is used to attenuate the importance of correlations.

The additional implementation steps can be summarized then as follows:

1. Generate the temporal pair correlation functions $\mathcal{R}_{ij}$ for every i and j pair of spatial nearest neighbors.
2. Compute the mean (or largest) correlation value for each pair and use this as a coupling coefficient from the propagator to find the spatial eigenmodes $\phi(x_j, \omega_0)$ with zero frequency ω_0 (that is, the mean field) by solving the eigenvalue problem Eqn 10 for the coupling matrix $Q(x_i, x_j, \omega_0)$ from Eqn 31.

3. Use the zero frequency spatial eigenmodes $\phi(x_i, \omega_0)$ to construct coupling matrices $Q(x_i, x_j, \omega)$ in Eqn 32 and solve the eigenvalue problem Eqn 10 for each ω_f frequency.
4. Generate the information Hamiltonian Eqn 20 by summation of input from interaction terms Eqn 26 and solve for the mode amplitudes a_k in a way similar to the last two items of the spatio-temporal approach.

The first three steps determine the values of mean field at every spatial position and then determine the spatio-temporal eigenmodes in spatial-frequency (i.e. Fourier) space assuming non-interacting fields. The last step determines the interactions between these eigenmodes. The final results are space/time localization patterns that are our *definition* of the “modes” of the data.

We would like to strongly emphasize that the above implementation is but one manifestation of the method. Because the coupling matrix Q can be constructed in a variety of ways, and higher order terms can be included to incorporate more complex interactions between signal and noise components, the method provides the framework to explore a wide range of implementations presumed suitable in different applications. However, the key point is that, while the particular implementations may differ, the *logic* remains unchanged, and is represented by Bayes Theorem Eqn 5 with well defined parameters in the construction of the information Hamiltonian Eqn 6 that must always be explicitly enunciated. In the results shown in this paper no special processing was performed. There are no preliminary noise reduction and smoothing filters, no preprocessing steps for dimensionality reduction, etc. There are no hidden *ad hoc* features. And it is particularly important to note that the spatial and temporal dimensions are handled in a unified manner as simply different dimensions in a general space-time problem.

4 Results

A few specific demonstrations of the EFD method on increasingly complex problems will serve to illustrate the methods basic approach, objectives, definitions, and capabilities. The problem of ultimate interest in this paper - the non-linear, non-Gaussian, spatially and temporally overlapping fluctuations in rsfMRI data - constitute the most complex case. Therefore, two simple demonstrations of the method on simulated *task-based* fMRI paradigms are helpful in illustrating some of the features of the EFD approach as well as providing some intuitive insight into this general methodology. This is followed by a more complicated numerical simulation with spatially overlapping regions with different non-linear, non-Gaussian characteristics that provides a demonstration on simulated data that has characteristics most relevant to rsfMRI data. This is followed by the application of the mode estimation procedure to actual rsfMRI data. And finally we demonstrate the application of space-time tractography to these EFD estimated rsfMRI modes.

4.1 Demonstration on simulated 2D task-based fMRI data

In the first example, we compare EFD directly with ICA on a numerical phantom that, despite its simplicity, is a good model for an idealized brain activation: two partially overlapping ellipsoidal spatially “activated” regions with two different low SNR square

wave signals in Gaussian noise. The signals from the two regions were assumed to be additive. These data are shown in the top row of Figure 1. The EFD analysis is shown in the middle row. The cutoff for defining “relevant” modes was determined by the ratio of the mode powers and was set to -30 dB signal attenuation. In the EFD processing of this data very minimal user input was required. Mode amplitudes were used for correlations (a user controllable option) and the mean field was used for coupling. Only two modes are detected and these are seen to correspond to the correct spatial regions with the correct temporal profiles. EFD has thus identified the correct space-time regions of the signals.

On the other hand, the ICA results shown in the bottom row of Figure 1 are erroneous. The components are a mixture in both space and time of the two true modes. While the algorithm undoubtedly constructs two “independent” components, this example clearly illustrates that this is a poor model for even this simple brain activation model, and thus most likely for actual brain activation data. Indeed, the signal modes are *not* independent in that they share at least some portion of the same space-time region. Requiring them to be maximally independent is thus forcing on them a property they do not intrinsically have. A similar example has previously demonstrated this problem in which spatially and temporally dependent signals are incorrectly detected when using spatial and temporal ICA, respectively, (Calhoun, Adali, Pearlson, & Pekar, 2001)

The EFD procedure, on the other hand, simply constructs the most probable pathways in space-time based on the *measured* correlations in the data. Because of the localization properties of ESP (first observed in the maximum entropy random walk (Burda et al., 2009)), there are in fact very few space-time parameter configurations consistent with the prior coupling information. The “modes” thus represent the configurations that are consistent with the data and the most probable. The second example with a more complicated signal waveform is shown in Figure 2. We would like to reiterate that the simplicity of this example was for demonstrative purposes but emphasize that the EFD method does not *assume* Gaussian noise nor simple additivity of the signal.

For the second task-based example, we provide a demonstration of the capabilities of EFD in detecting non-linear signals using the same numerical phantom as in the first example but turning one of the activations slowly on then slowly off during the course of the numerical experiment. The results of this numerical experiment are shown in Figure 2. The additional complication of the non-linearity in the second waveform does not deter EFD from detecting the correct two modes.

The data in this numerical example, shown in the top row of Figure 2. The “activated” regions are two partially overlapping ellipsoidal patches (called regions 1 and 2, Figure 2A) with distinct time series. That is, all voxels in a given patch have the same time series but these time series are different in the two patches. The signal in region 1 (Figure 2B) consists of a 4 cycle square wave with “on” and “off” periods having equal length (20 time points). The activation is “on” at the first time point. The time course in region 2 (Figure 2D) is more complicated, and consists of an 8 cycle square wave with equal on/off periods (10 time points) that has been shifted one-quarter cycle relative to the time course in regions 1 and multiplied by a Fermi filter so that activation smoothly turns on then off during the duration

of the acquisition. Gaussian noise was added and scaled so that the *SNR* of the data was 10. The signals from the two regions were assumed to be additive. The time course from the region where region 1 and region 2 overlap is shown in Figure 2C.

4.2 Demonstration on simulated 3D non-periodic, overlapping data

The capabilities of our method on data more relevant for the analysis of rsfMRI data, mixing different time varying signals inside several spatial domains, is demonstrated in the simulation shown in Figure 3, which consists of a central sphere (white) located at the origin ($\{x, y, z\} = \{0, 0, 0\}$) oscillating at a single, periodic frequency, surrounded by six spherical or ellipsoidal regions along the principal axes $\{x_1, 0, 0\}$, $\{-x_2, 0, 0\}$, $\{0, y_1, 0\}$, $\{0, -y_2, 0\}$, $\{0, 0, z_1\}$, $\{0, 0, -z_2\}$. The signals are the same throughout the volume of any particular domain. In addition, Gaussian noise has been added. Three spheres (red, green, blue), spatially separated from the central sphere, each oscillate at a single, distinct frequency, though at different maximum amplitudes. Three ellipsoids (magenta, yellow and cyan) overlap the central sphere and have non-periodic time courses (again with different maximum amplitudes) created by filtering a sinusoidal amplitude with a Fermi filter, which turns the signal on and off smoothly in time. Both the periodic and non-periodic objects overlap spatially, such that in the center area of the white sphere, signals from four different objects are mixed (one periodic signal from the white sphere itself and three different nonperiodic signals from magenta, yellow and cyan ellipsoids). This example illustrates the important fact that extracted EFD modes need not be orthogonal. This is crucial in many, if not most, applications, such as in the case of rsfMRI data below, where one would not expect the data modes to be orthogonal.

Three panels of Figure 4 show spatial and temporal patterns for extracted non-periodic ellipsoids overlapped with the central sphere. The temporal profiles for all spheres correspond to SNR from 6.8 to 7 (we used Gaussian $\sigma=0.1$ in this example). Figure 5 shows the signal extracted from the area of the central sphere where four different signals are mixed.

4.3 Mode estimation results on real data

The EFD methods was testing on two previously published data sets from two different studies: the NYU CSC TestRetest (NYU-TRT) resource (Shehzad et al., 2009), and data collected at the UCSD Center for FMRI (CFMRI) on the effects of caffeine on the resting state data ((Wong, Olafsson, Tal, & Liu, 2013)).

The EFD analysis employed interacting and frequency normalized modes with mode amplitudes used for correlation. The analysis produced 23 modes above the threshold of .001 of the maximum mode amplitude, ranked according to the mode power. The computational implementation allows for the frequency bandwidth to be limited by a simple Gaussian filter $\exp(-\lambda\omega^2)$ or a Fermi-Dirac filter $1/(\exp((\omega - \omega_0)/T) + 1)$ (or their combination). The frequency band-width is specified by a parameter β such that the frequency with the number $1/\sqrt{\beta}$ will be e-fold suppressed. However, in the examples presented in this paper, no frequency filters were used. So once the coupling was specified, no additional processing was used. A sensitivity threshold on the mode power of -30 dB is

used to determine which modes are significant. This produces around 30 significant modes per subject. We emphasize that no additional processing, noise correction, or filtering other than that described in section 3 was used.

As a first test of the EFD method on real data, we applied it to a four subjects from the publically available resting state fMRI data in the NYU CSC TestRetest (NYU-TRT) resource (Shehzad et al., 2009). These data has been used previously in numerous reproducibility and reliability studies e.g., (Shehzad et al., 2009; Zuo, Kelly, et al., 2010; Zuo, Di Martino, et al., 2010; Wang et al., 2011; Fiecas et al., 2013). While a full study quantifying the reproducibility and test-retest reliability of our method relative to existing techniques is beyond the scope of this current paper, these data provide a useful test-bed for comparison with the current standard state-of-the-art ICA method as implemented in the FSL MELODIC package (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012).

Four subjects were chosen from the NYU-TRT database, for which two trials for each subject are available. The standard preprocessing of the raw rsfMRI time-series in FSL used for ICA analysis by local users was applied to each of these datasets. These corrections consist of elimination of the first few (5) time samples, motion correction and affine registration using the MCFLIRT facility in FSL to a standard anatomical template (MNI152_T1_2mm brain) (Jenkinson, Bannister, & Smith, 2002). Both the ICA and EFD analysis were subsequently performed on these data. While both methods produce multiple “modes”, our focus for purposes of reproducibility and comparison with ICA is on the Default Mode Network (DMN) because it is the most well recognized and ubiquitous network, in addition to being of significant interest in a wide range of neuroscience investigations. The results, are shown in Figures 6 to 9, demonstrated the ability of EFD to consistently detect the Default Mode Network across subjects and for the same subject at different scan sessions.

As a second test of our methods we utilized data previously published from the UCSD Center for fMRI (CFMRI) on the effects of caffeine on the resting state data ((Wong et al., 2013)). However, only the data from subjects not administered with caffeine are used here. These data were acquired on a 3T GE Discovery MR750 whole body system using an eight channel receiver head coil. Whole brain BOLD resting-state data were acquired over thirty axial slices using an echo planar imaging (EPI) sequence (flip angle = 70°, slice thickness=4mm, slice gap=1mm, FOV=24cm, TE= 30 ms, TR = 1.8 s, matrix size = 64 × 64 × 30). Further details are available in (Wong et al., 2013). All data were pre-processed using the standard pre-processing analysis 1pathway at the CFMRI (as described in (Wong et al., 2013)). Nuisance terms were removed from the resting-state BOLD time series through multiple linear regression. These nuisance regressors included: i) linear and quadratic trends, ii) six motion parameters estimated during image co-registration and their first derivatives, iii) RETROICOR (2nd order Fourier series) (Glover, Li, & Ress, 2000) and RVHRCOR (Chang & Glover, 2009) physiological noise terms calculated from the cardiac and respiratory signals, and iv) the mean BOLD signals calculated from white matter and CSF regions and their first respective derivatives, where these regions were defined using partial volume thresholds of 0.99 for each tissue type and morphological erosion of two voxels in each direction to minimize partial voluming with gray matter. These preprocessing steps

effectively estimate R , the system response, in Eqn 1. All data volumes were co-registered using an in-house non-linear warping method.

These results of the application of both EFD and ICA to the identification of four well known brain networks (Default Mode, Executive, Salience, and Visual) (Yeo et al., 2011) in three subjects is shown in Figures 10 to 13. The ICA results tended to have a greater spatial distribution of detected activity and appeared significantly noisier. This made discrimination of actual activated regions more problematic. Well separated activation regions in the EFD results could sometimes be seen in the ICA results at a lower ICA threshold and for this reason the ICA results in Figure 10 are thresholded at a slightly lower level than the EFD results for this demonstration. As the EFD method defines and normalizes modes by calculating the equilibrium probabilities, hence, includes coupling from neighboring areas, this difference in thresholds between the EFD and ICA is not a surprise – the procedure of finding a stationary distribution is expected to provide higher signal-to-noise ratio as a byproduct.

These results demonstrate an interesting and useful feature of the EFD procedure - its ability to accurately localize fluctuations in space and time sufficiently well that results from a single subject are meaningful and show significant activation regions.

A further test of both the feasibility and reproducibility of the method was to construct from all 10 subjects in the CFMRI study the average networks for each of the 7 standard brain networks described in (Yeo et al., 2011). To construct these average networks, each of the networks in the template file containing the 7 parcellated brain networks as defined by Yeo (Yeo et al., 2011) were correlated with all EFD modes generated in each subject. The best match to each of the 7 modes in each subject (as determined by the maximum correlation coefficient) were averaged across all subjects. These average networks are shown in Figures 14 and 15 and demonstrate reasonable representations of these well-known modes. While these preliminary results show a clear indication of our methods reproducibility and reliability, future work will need to be performed to further quantify these at the group level with larger data sample sizes.

Our experience has shown that even for the “major” modes, subtle but significant variations in activation patterns are common between subjects. In fact, the definitions of the major modes is far from well defined in the literature. For example, the sensorimotor mode in (Lee et al., 2012) contains the insula, whereas that in (Heine et al., 2012) does not. There is currently no precise consensus on these mode definitions. The analysis of EFD modes from 10 subjects in this paper clearly revealed that in addition to the activated regions typically referred to as the “major modes” there were often supplementary regions that appeared, often in different combinations with the major modes. We therefore tended to observe what might be termed different “flavors” of the major modes. Moreover, modes with much more complex combinations of activations in cortical regions were not uncommon. For this reason, averaging over similar modes in different subjects can be problematic, as it tends to emphasize the “major” components but can diminish the more subtle variations in individual subjects. This is evident in comparing some of the results in individual subjects Figures 10 to 13 with the average networks in Figures 14 and 15

The complexity of the activation patterns suggests that the identification of specific “networks” can be somewhat problematic, or at least more complicated than looking just at broadly activated regions, since modes can be composed of multiple combinations of activations within the separate brain regions. Moreover, it is common for activations to be weighted more towards one hemisphere. This weighting would be an additional characterization in a more comprehensive scheme for defining networks. This would suggest a more comprehensive scheme for the classification of brain modes based on these combinations of brain regions activated in each mode. One simple but reasonable method for doing this is shown for a single subject in Figure 17. The power from each mode was registered to the standard MNI template MNI152_T1_2mm brain and multiplied by a standard brain region template file, in this case the MNI 9 network template MNI-maxprob-thr25-2mm). The number of voxels above a threshold within each of the separate template regions are counted and a histogram for each network is constructed. This histogram constitutes one definition of a network. The interdependencies of the different brain regions is more easily seen by constructing the correlation of the histogram. The information in this correlation plot is redundant with the histogram but is a more visually intuitive depiction of the interactions between the separate brain regions.

It is also worth also reiterating the fact that not only are the spatial patterns of activations complicated but so are the time series in the detected modes as well. Example time series from three arbitrarily chosen modes in the CFMRI data are shown in Figure 16 and demonstrate the complicated nature of the detected waveforms. The fact both the spatial and temporal patterns can be quite complicated emphasizes the problematic nature of methods that require users to visually identify certain waveforms as “noise”, rather than signal (Smith et al., 2013).

4.4 Space-time tractography and connectivity eigenmodes on real data

Space-time tractography results for the DMN in Subjects 6, 8, and 10 of the UCSD caffeine study are shown in Figure 18. The associated first eigenmodes are shown in Figure 19. While a thorough analysis of these results is beyond the scope of this initial study, a few observations are notable. In each case there are clear bilateral connections between the frontal pole and the paracingulate gyrus (green). These trajectories are reflected in the principal eigentracs as regions that can be interpreted as the major trajectories for the activation development. In addition, there are a number of pathways (red) that appear to exhibit strong interhemispheric connectivity and these also result in well defined eigenmode pathways. These tracts and their eigenmodes are rich in information and future work will focus on a better understanding of their content, as well as the significance of the additional eigenmodes that can be constructed from these tracts.

We note at this juncture that in the example shown here the tractography procedure is independent of the procedure for estimating the modes. The mode results are simply used as seed points. However, this need not be the case. A more general approach would be to simultaneously estimate both the modes and the tracts, in a similar spirit with which we have addressed the problem in diffusion tensor imaging (DTI) data analysis, where we have estimated both the local diffusion and the global tract structure simultaneously (Galinsky &

Frank, 2015). This is beyond the scope of the current paper and will be addressed in a future work.

5 Discussion

The analysis problem presented by rsfMRI data is, in some sense, a classic example of a data analysis problem that has become ubiquitous with the advancement of modern scientific instruments and been addressed by a range of methods (Ghil et al., 2002; Christakos, 1991; Plis et al., 2007; Min & Wynter, 2011; Wallace, Smith, & Bretherton, 1992; Lamus, Haemaelaenen, Temereanca, Brown, & Purdon, 2012; Bijma, de Munck, & Heethaar, 2005; Plaut & Vautard, 1994; Uhl, Friedrich, & Haken, 1995, 1993). These data consist of high spatial and temporal resolution noisy volumes within which non-linear and non-Gaussian processes produce complicated signal fluctuations. As the data integrity and size increase with better instrumentation, the burden is placed increasingly on the analysis to detect more subtle and complex features in the data. This, in turn, requires greater care in developing a rigorous framework that facilitates a clear statement of the problem and its assumptions, as well as the ability to incorporate relevant prior information. From a logical perspective, this means the development of a probabilistic (i.e., Bayesian) framework for which these criteria are guaranteed. This is particularly important in applications with signals and noise that are non-linear, non-Gaussian, and overlapping, as there is significant danger in the application of techniques that, while perhaps standard in other applications, have basic assumptions that make their use problematic in applications such as rsfMRI, although this assumption is currently ubiquitous (e.g., (Kolchinsky et al., 2014)).

There are two broad classes of methods that dominate the analyses currently being used to analyze rsfMRI data, correlation analysis and independent components analysis (ICA). Correlation analysis (Biswal et al., 1995; Lowe, Mock, & Sorenson, 1998; Greicius, Krasnow, Reiss, & Menon, 2003) and its variants (Fransson & Marrelec, 2008; Chang & Glover, 2010) are straightforward but simplistic and can merely show what spatial regions have similar signals. This says nothing about the composition of these signals, which might have non-periodic components embedded within them that correlate with different regions at different times. One approach to this problem is to chop up the signals into shorter time segments (Chang & Glover, 2010) although this begs the question of what time segment length is correct, which in fact can be a moot point if the signal is not periodic even in the short time segment. Furthermore, this method provides no well-defined strategy for separating spatially overlapping signals. It is often claimed that correlation analysis is “conservative” in that very little is assumed about the data model, and this is true if the only question is simply to find voxels with similar signals. However, this question is of limited utility in a system such as the brain where a spatial region can be interacting with multiple other regions in a non-periodic fashion, particularly if there is spatial overlap of any of the regions and the voxels contains a mixture of signals.

Difficulties with traditional approaches such as correlation analysis has led to the popularity of independent components analysis (ICA) which was developed to separate signals that are statistically independent (Bell & Sejnowski, 1995). (See also (Comon, 1994) and references therein). ICA was later applied to fMRI data in order to decompose the fMRI signals into

statistically independent component maps without prior knowledge of their spatial extents or time courses of activation (McKeown et al., 1998). The use of ICA with fMRI data is predicated on a number of assumptions, such as that the activated regions are spatially both sparse and independent (McKeown et al., 1998). A major motivation for the proliferation of ICA methods in signal analysis problems was its success in the “blind source separation” problem (Bell & Sejnowski, 1995). In that particular problem, the authors were considering two well defined (and literally) different sources of sounds (two people speaking) who were presumed to not be talking to one another, and thus “independent”. However, the justification for extending the method to rsfMRI data is less well motivated.

Moreover, the “classical” ICA is implicitly based on the assumption that the signal has no noise. Thus is not a proper probabilistic formulation for which significance of the estimates can be obtained, although a variety of *ad-hoc* procedures are often used to generate significance metrics (see (Beckmann & Smith, 2004) for further discussion and examples). To address this deficiency, probabilistic ICA (PICA) was developed (Beckmann & Smith, 2004) and has become the most widely used method for rsfMRI analysis (and the standard for the Human Connectome Project (Smith et al., 2013)).

However, despite the relative success of ICA in rsfMRI analysis, there remain numerous open questions about its assumptions, implementations, and the interpretation of the results. While ICA has been justified as a principled approach consistent with segregation as a principle of functional organization (i.e., that different parts of the brain do different things (Calhoun et al., 2001)) this can be difficult to reconcile with the observation of Tononi, Sporns, and Edelman (Tononi, Sporns, & Edelman, 1994) that “In brains of higher vertebrates, the functional segregation of local areas that differ in their anatomy and physiology contrasts sharply with their global integration during perception and behavior.” And that integration is composed of a host of interdependencies.

It has also been argued that the primary quality of the data that affects the suitability of ICA is sparsity, rather than independence (Daubechies et al., 2009), conclusions which have, in turn, been challenged (Calhoun et al., 2013). The real problem, however, is that this question is a red herring. Some of the problem stems from semantic ambiguities that become codified into ambiguous methodologies. Terms like “modes”, “sources”, and “components” sound like well defined quantities but in fact are very often not. This is due, in part, to the historical development of techniques, such as in ICA where one of the seminal papers addressed what has become known as the “blind source separation” problem (Bell & Sejnowski, 1995). In that particular problem, the authors were considering two well defined (and literally) different sources of sounds (two people speaking) who were presumed to not be talking to one another, and thus “independent”.

There are also computational difficulties that make the practical application of ICA problematic for such large problems as rsfMRI data. One of the major issues in the ICA analysis of rsfMRI data has been the excessive computational complexity of data with such a potentially high spatio-temporal dimensionality. For this reason, for example, ICA invariably employs a “dimensionality reduction” step (typically using PCA) because the dimensions are far too large to make ICA computationally feasible (Calhoun et al., 2001).

This is particularly true of the spatial dimension where the number of voxels is typically on the order of 10^6 . This problem spawned the ICA variants *spatial ICA* and *temporal ICA* (see, for example, (Calhoun et al., 2001; Tian et al., 2013)) which are predicated on the assumption of spatial and temporal independence, respectively.

It is worth reiterating the well-known fact that the relationship between the BOLD signal and the details of brain physiology is exceedingly complex (Buxton & Frank, 1997; Buxton, Wong, & Frank, 1998; Buxton, Uludağ, Dubowitz, & Liu, 2004; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). In fact, given the complexity of the relationship between the BOLD response and the input task, it might be argued that the EFD method might also be of use in task-based experiments when no physiological model is assumed, since the response will have an “unknown” (i.e., not modeled) relationship to the signal. In this paper we have made no attempt to incorporate any physiological models and therefore our goal is not to disentangle the complex relationship between BOLD and the input function. But it is worth pointing out that the EFD formulation is well suited to incorporating models or prior information about brain physiology that one might have about this relationship.

Recently other techniques have been introduced for the purpose of detecting transient dynamics of spatially and temporally overlapping networks through spatio-temporal regularization (Karahanoğlu, Caballero-Gaudes, Lazeyras, & Van De Ville, 2013; Karahanoğlu & Van De Ville, 2015) but these, too, often rely on a host of assumptions such as Gaussian noise, spatial smoothness, and sparsity of the signal, and incorporate several *ad-hoc* procedures such as empirical selected spatial regularization parameters and temporal regularization tuned for each voxel (Karahanoğlu et al., 2013; Karahanoğlu & Van De Ville, 2015). Moreover, the clustering is performed *post-hoc*, rather than being an integral component of the estimation procedure.

In this paper we have formulated a different approach to the estimation of spatial-temporal variations in non-linear and non-Gaussian data. The EFD method is, in fact, a rather straightforward Bayesian procedure, and thus provides a mechanism for the incorporation of prior information, but written in the language of field theory (Enßlin et al., 2009) that provides well-established methods for the construction of arbitrarily complicated but mathematically well-defined signal interactions. At the heart of the EFD procedure is that prior information in the form of local coupling (in both space and time), when incorporated into a Bayesian field theory, provides a method for the construction of the path entropies in parameter space via the ESP procedure (Frank & Galinsky, 2014). In short, this entropy quantitates the possible parameter space configurations and gives preference to those that can occur in the most number of ways. As such, it is the most conservative description that is consistent with given prior information. And this prior information consists of the local coupling information within the data. The EFD procedure requires that quantities are well defined since they arise from a straightforward logical (i.e., Bayesian) procedure. There is only one “source”, and that is the *information source j* in Eqn 6. The “modes” are the expansion of this source into k (Eqn 21) components with associated amplitudes a_k . By construction, the EFD method is both non-linear and non-Gaussian and naturally handles both space and time merely as different dimensions of the same problem. As a consequence, there are no restrictions for overlap of signals in either time or space, and the method is

capable of disambiguating non-Gaussian, non-linear, non-periodic, spatially and temporally overlapping signals (Frank & Galinsky, 2015) using the *measured* space-time correlations present in the data. In turn, this allows the construction of the functional connectivity pathways for each mode directly from space-time correlation structure of each mode.

The ability of EFD to detect subtle, highly localized (in both space and time) activations has implications for how one defines brain networks. While the detected activations shown in the Results were typically highly localized in well-known brain regions, sometimes they were bilateral, sometimes unilateral, but sometimes they were somewhere in between, being partially weighted more towards one hemisphere than the other. However, standard “brain network” classification schemes are generally ambiguous on this issue. For example, some papers talk about an “executive control network” while others put for both a “right executive control network” and “left executive control network”. Our view of this issue, motivated by the results produced by our method, is that it might be reductionistic to posit modes or regions that are simply just “on”, “off”, “unilateral”, or “bilateral” but are, in reality, perhaps more complicated mixtures of spatial and temporal patterns. This is the essential importance of defining “modes” mathematically in our theoretical development. These are unambiguously defined and independent of any subsequent naming scheme attached to them. The “meaning” of these modes, that is, their classification into named brain networks (e.g., “salience network”), is the job of experience neuroscientists and is an issue that will require significantly more attention in the future.

The EFD procedure produces the most probable space-time patterns, or modes, of the brain activity. These modes indicate regions of the brain that, in simple terms, are working together. The usual way this is described (e.g., (Buckner & Vincent, 2007; Fox & Raichle, 2007)) is that these modes represent *networks* of the brain. However, we have also demonstrated that there is additional information that can be derived from the EFD procedure that further informs this question of, and in fact the definition of, brain networks. This can be accomplished by tracking the space-time correlations for *functional tractography* and offers a powerful new method for characterizing brain activity.

In conclusion, the abilities of EFD to detect subtle space-time patterns and connections in the non-linear and non-Gaussian fluctuations in resting state fMRI data offers a new paradigm for quantifying complex brain activation networks.

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References

- Beckmann CF, Smith SM. Probabilistic independent component analysis for functional magnetic resonance imaging. *IEEE Trans Med Imaging*. 2004 Feb; 23(2):137–152. [PubMed: 14964560]
- Bell A, Sejnowski T. An information maximization approach to blind separation and blind deconvolution. *Neural Comput*. 1995 Nov; 7(6):1129–1159. [PubMed: 7584893]
- Bijma F, de Munck JC, Heethaar RM. The spatiotemporal MEG covariance matrix modeled as a sum of Kronecker products. *NeuroImage*. 2005; 27(2):402–415. [PubMed: 16019231]
- Biswal B, Yetkin F, Haughton V, Hyde J. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*. 1995; 34:537–541. [PubMed: 8524021]
- Buckner R, Vincent J. Unrest at rest: default activity and spontaneous network correlations. *Neuroimage*. 2007; 37:1091–1096. [PubMed: 17368915]
- Burda Z, Duda J, Luck J, Waclaw B. Localization of the maximal entropy random walk. *Phys Rev Lett*. 2009; 102(16):160602. [PubMed: 19518691]
- Buxton RB, Frank LR. A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. *J Cerebr Blood F Met*. 1997; 17(1):64–72.
- Buxton RB, Uluda K, Dubowitz D, Liu TT. Modeling the hemodynamic response to brain activation. *Neuroimage*. 2004 Jan; 23:S220–S233. [PubMed: 15501093]
- Buxton RB, Wong EC, Frank LR. Dynamics of blood flow and oxygenation changes during brain activation: the balloon model. *Magn Reson Med*. 1998; 39:855–864. [PubMed: 9621908]
- Calhoun VD, Adali T, Pearlson GD, Pekar JJ. Spatial and temporal independent component analysis of functional MRI data containing a pair of task-related waveforms. *Human Brain Mapping*. 2001 May; 13(1):43–53. [PubMed: 11284046]
- Calhoun VD, Potluru VK, Phlypo R, Silva RF, Pearlmutter BA, Caprihan A, ... Adali T. Independent component analysis for brain fMRI does indeed select for maximal independence. *PLoS ONE*. 2013; 8(8):1–8.
- Chang C, Glover GH. Effects of model-based physiological noise correction on default mode network anti-correlations and correlations. *Neuroimage*. 2009 Oct; 47(4):1448–1459. [PubMed: 19446646]
- Chang C, Glover GH. Time-frequency dynamics of resting-state brain connectivity measured with fMRI. *Neuroimage*. 2010 Mar; 50(1):81–98. [PubMed: 20006716]
- Childs H, Brugger E, Whitlock B, Meredith J, Ahern S, Pugmire D, ... Navrátil P. VisIt: An end-user tool for visualizing and analyzing very large data. *High Performance Visualization—Enabling Extreme-Scale Scientific Insight*. 2012 Oct.; 357–372.
- Christakos G. On certain classes of spatiotemporal random fields with applications to space-time data processing. *Systems, Man and Cybernetics, IEEE Transactions on*. 1991; 21(4):861–875.
- Comon P. Independent component analysis, A new concept? *Signal Process*. 1994 Apr; 36(3):287–314.
- Cox R. AFNI: Software for the analysis and visualization of functional magnetic resonance neuroimages. *Comp Biomed Res*. 1996; 29:162–173. (Available at <http://afni.nimh.nih.gov>).
- Daubechies I, Roussos E, Takerkart S, Benharrosh M, Golden C, D'Ardenne K, ... Haxby J. Independent component analysis for brain fMRI does not select for independence. *P Natl Acad Sci USA*. 2009 Jun; 106(26):10415–10422.
- Ding Z, Newton AT, Xu R, Anderson AW, Morgan VL, Gore JC. Spatio-temporal correlation tensors reveal functional structure in human brain. *PLoS ONE*. 2013 Dec; 8(12):e82107. [PubMed: 24339997]
- Enßlin TA, Frommert M. Reconstruction of signals with unknown spectra in information field theory with parameter uncertainty. *Phys Rev D*. 2011; 83:105014.
- Enßlin TA, Frommert M, Kitaura FS. Information field theory for cosmological perturbation reconstruction and nonlinear signal analysis. *Phys Rev D*. 2009 Nov; 80(10):105005.
- Enßlin TA, Weig C. Inference with minimal Gibbs free energy in information field theory. *Phys Rev E*. 2010 Nov; 82(5):051112.
- Fiecas M, Ombao H, van Lunen D, Baumgartner R, Coimbra A, Feng D. Quantifying temporal correlations: A test-retest evaluation of functional connectivity in resting-state fMRI. *NeuroImage*. 2013; 65:231–241. [PubMed: 23032492]

- Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*. 2007; 8(9):700–711. [PubMed: 17704812]
- Frank LR, Galinsky VL. Information pathways in a disordered lattice. *Phys Rev E*. 2014 Mar. 89:032142.
- Frank LR, Galinsky VL. 2015 Detecting spatio-temporal modes in multivariate data by entropy field decomposition. *Phys Rev E*. submitted
- Frank LR, Galinsky VL, Wurman JM. Signatures of tornadogenesis in mobile doppler radar data detected by entropy field decomposition. *J Atmos Sci*. 2015 (submitted).
- Fransson P, Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: evidence from a partial correlation network analysis. *Neuroimage*. 2008; 42:1178–1184. [PubMed: 18598773]
- Frommert M, Enßlin TA. Ironing out primordial temperature fluctuations with polarization: optimal detection of cosmic structure imprints. *Mon Not R Astron Soc*. 2009; 395(4):1837–1844.
- Frommert M, Enßlin TA. The axis of evil - a polarization perspective. *Mon Not R Astron Soc*. 2010 Apr; 403(4):1739–1748.
- Galinsky VL, Frank LR. Simultaneous multi-scale diffusion estimation and tractography guided by entropy spectrum pathways. *IEEE Trans Med Imag*. 2015 May; 34(5):1177–1193.
- Ghil M, Allen MR, Dettinger MD, Ide K, Kondrashov D, Mann ME, ... Yiou P. Advanced spectral methods for climatic time series. *Reviews of Geophysics*. 2002; 40(1)
- Glover GH, Li TQ, Ress D. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magn Reson Med*. 2000 Jul; 44(1):162–167. [PubMed: 10893535]
- Greicius M, Krasnow B, Reiss A, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci*. 2003; 100:253–258. [PubMed: 12506194]
- Heine L, Soddu A, Gómez F, Vanhaudenhuyse A, Tshibanda L, Thonnard M, ... Demertzi A. Resting state networks and consciousness: Alterations of multiple resting state network connectivity in physiological, pharmacological, and pathological consciousness states. *Frontiers in Psychology*. 2012; 3:1–12. [PubMed: 22279440]
- Hyvarinen A, Oja E. Independent component analysis: algorithms and applications. *Neural Networks*. 2000; 13(4–5):411–430. [PubMed: 10946390]
- Jaynes E. Information theory and statistical mechanics. *Phys Rev*. 1957a; 106(4):620–630.
- Jaynes E. Information theory and statistical mechanics. II. *Phys Rev*. 1957b; 108(2):171.
- Jenkinson M, Bannister JM, Brady P, Smith S. Improved optimisation for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*. 2002; 17(2):825–841. [PubMed: 12377157]
- Jenkinson M, Beckmann C, Behrens T, Woolrich M, Smith S. FSL. *NeuroImage*. 2012; 62:782–790. (Available at <http://fsl.fmrib.ox.ac.uk>). [PubMed: 21979382]
- Karahano lu FI, Caballero-Gaudes C, Lazeyras F, Van De Ville D. Total activation: fMRI deconvolution through spatio-temporal regularization. *NeuroImage*. 2013 Jun. 73:121–134. [PubMed: 23384519]
- Karahano lu FI, Van De Ville D. Transient brain activity disentangles fMRI resting-state dynamics in terms of spatially and temporally overlapping networks. *Nature Communications*. 2015 Jul. 6:7751.
- Kolchinsky A, Van Den Heuvel MP, Griffa A, Hagmann P, Rocha L, Sporns O, Goni J. Multi-scale integration and predictability in resting state brain activity. *Frontiers in Neuroinformatics*. 2014 Jul. 8:1–15. [PubMed: 24501593]
- Lamus C, Haemelaenen MS, Temereanca S, Brown EN, Purdon PL. A spatiotemporal dynamic distributed solution to the MEG inverse problem. *NeuroImage*. 2012; 63(2):894–909. [PubMed: 22155043]
- Lee MH, Hacker CD, Snyder AZ, Corbetta M, Zhang D, Shimony JS. Clustering of resting state networks. *PLoS ONE*. 2012; 7(7):1–12.
- Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neuro-physiological investigation of the basis of the fMRI signal. *Nature*. 2001 Jul; 412(6843):150–157. [PubMed: 11449264]

- Lowe M, Mock B, Sorenson J. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. *Neuroimage*. 1998; 7:119–132. [PubMed: 9558644]
- McKeown MJ, Makeig S, Brown GG, Jung TP, Kindermann SS, Bell AJ, Sejnowski TJ. Analysis of fMRI data by blind separation into independent spatial components. *Science*. 1998; 6(3):160–188.
- Min W, Wynter L. Real-time road traffic prediction with spatio-temporal correlations. *Transportation Research Part C-Emerging Technologies*. 2011 Aug; 19(4):606–616.
- Plaut G, Vautard R. Spells of low-frequency oscillations and weather regimes in the Northern Hemisphere. *Journal of the Atmospheric Sciences*. 1994; 51(2):210–236.
- Plis S, George J, Jun S, Paré-Blagoev J, Ranken D, Wood C, Schmidt D. Modeling spatiotemporal covariance for magnetoencephalography or electroencephalography source analysis. *Physical Review E*. 2007 Jan.75(1):011928.
- Shehzad Z, Kelly AMC, Reiss PT, Gee DG, Gotimer K, Uddin LQ, ... Milham MP. The resting brain: Unconstrained yet reliable. *Cerebral Cortex*. 2009; 19(10):2209–2229. Retrieved from <http://cercor.oxfordjournals.org/content/19/10/2209.abstract>. DOI: 10.1093/cercor/bhn256 [PubMed: 19221144]
- Smith SM, Beckmann CF, Andersson J, Auerbach EJ, Bijsterbosch J, Douaud G. ... Consortium, f. t. W.-M. H. Resting-state fMRI in the Human Connectome Project. *Neuroimage*. 2013 Oct; 80(C): 144–168. [PubMed: 23702415]
- Tian L, Kong Y, Ren J, Varoquaux G, Zang Y, Smith SM. Spatial vs. temporal features in ica of resting-state FMRI - a quantitative and qualitative investigation in the context of response inhibition. *PLoS ONE*. 2013; 8(6):1–12.
- Tononi G, Sporns O, Edelman GM. A measure for brain complexity - relating functional segregation and integration in the nervous-system. *Proc Natl Acad Sci*. 1994; 91(11):5033–5037. [PubMed: 8197179]
- Uhl C, Friedrich R, Haken H. Reconstruction of spatio-temporal signals of complex systems. *Zeitschrift für Physik B Condensed Matter*. 1993; 92(2):211–219.
- Uhl C, Friedrich R, Haken H. Analysis of Spatiotemporal Signals of Complex-Systems. *Physical Review E*. 1995 May; 51(5):3890–3900.
- Varoquaux G, Sadaghiani S, Pinel P, Kleinschmidt A, Poline JB, Thirion B. A group model for stable multi-subject ICA on fMRI datasets. *Neuroimage*. 2010; 51:288–299. [PubMed: 20153834]
- Wallace JM, Smith C, Bretherton CS. Singular value decomposition of win-tertime sea surface temperature and 500-mb height anomalies. *Journal of Climate*. 1992; 5(6):561–576.
- Wang J-H, Zuo X-N, Gohel S, Milham MP, Biswal BB, He Y. Graph Theoretical Analysis of Functional Brain Networks: Test-Retest Evaluation on Short- and Long-Term Resting-State Functional MRI Data. *PLoS ONE*. 2011; 6(7)
- Wong CW, Olafsson V, Tal O, Liu TT. The amplitude of the resting-state fMRI global signal is related to EEG vigilance measures. *Neuroimage*. 2013; 83:983–990. [PubMed: 23899724]
- Yeo BTT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, ... Buckner RL. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*. 2011 Sep; 106(3):1125–1165. (Available at <https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation-Yeo2011>). [PubMed: 21653723]
- Zuo XN, Di Martino A, Kelly C, Shehzad ZE, Gee DG, Klein DF, ... Milham MP. The oscillating brain: Complex and reliable. *NeuroImage*. 2010; 49(2):1432–1445. [PubMed: 19782143]
- Zuo XN, Kelly C, Adelstein JS, Klein DF, Castellanos FX, Milham MP. Reliable intrinsic connectivity networks: Test-retest evaluation using ICA and dual regression approach. *NeuroImage*. 2010 Feb; 49(3):2163–2177. [PubMed: 19896537]

Figure 1.

Comparison of EFD with ICA in task-based FMRI simulation. (Top) Simulated signals with additive Gaussian noise so that $SNR = 2.5$. The spatial dimensions are 64×64 voxels and there are 160 time points. (Middle) Estimated modes using EFD. (Bottom) Estimated modes using ICA. All voxels in region *A* have the same time course (4 cycles) and all voxels in region *B* have the same time course (5 cycles).

Figure 2.

Task-based FMRI simulation. (Top) Simulated signals with additive Gaussian noise so that $SNR = 5$. The spatial dimensions are $(64 \times 64 \text{ voxels})$ and there are 160 time points.

(Bottom) Estimated modes using EFD. All voxels in region 1 have the same time course (4 cycles) and all voxels in region 2 have the same time course (8 cycles). The waveform in region 2 is multiplied by a Fermi filter so that it gradually turns on and then off.

Figure 3.

Toy example with seven non-periodic and spatially overlapped regions. Red, green, blue, and white spheres are oscillating at a single distinct frequency, whereas magenta, yellow and cyan ellipsoids are oscillating with non-periodic time courses created by filtering the sinusoidal amplitude variations with a Fermi filter that smoothly but rapidly turns the activation on, then off. The width of the Fermi filter is 30% of the length of the time series with a transition width of 2 time points. The filter begins 30% of the way into the time series.

Figure 4.

Spatial (top) and temporal (bottom) pattern of extracted modes for temporally non-periodic ellipsoids that overlap with each other and with a periodically oscillating central sphere. The time sequences on the bottom panel show the original signals in the overlap region of each ellipsoid (solid line) and the extracted signal (black dashed line). The original signal from the isolated regions (without mixing with the signal from the neighboring overlapping areas) are also included with dotted lines. As the whole volume is submerged in Gaussian noise with $\sigma = 0.1$ the signal for all spheres corresponds to SNR of about 6.9.

Figure 5.

Spatial (a) and temporal (b) pattern of the extracted mode for the central overlapping sphere. This sphere overlaps with three neighboring ellipsoids (cyan, magenta and yellow), all four different signals contribute to the overall signal at the center area of the white sphere. The time sequence on panel (b) shows the original signals at the center of the white sphere (solid line) and the extracted signal (dashed line). The original signal from the isolated white sphere (without mixing with the signal from all four neighboring overlapping regions) is also shown by the dotted lines. In panel (c) restored signals for all four modes that give input to the original signal at the central area are plotted (signals from magenta, yellow, cyan ellipsoids, and gray sphere). Panel (d) shows this original noisy signal (solid line) and the sum of all four restored signals (dashed line).

Figure 6.

Comparison of EFD with ICA on the detection of the Default Mode Network (DMN) in the NYU TRT data Subject 1. Activations are thresholded at .9 for both EFD and ICA.

Figure 7.

Comparison of EFD with ICA on the detection of the Default Mode Network (DMN) in the NYU TRT data Subject 2. Activations are thresholded at .9 for both EFD and ICA.

Figure 8.

Comparison of EFD with ICA on the detection of the Default Mode Network (DMN) in the NYU TRT data Subject 3. Activations are thresholded at .9 for both EFD and ICA.

Figure 9.

Comparison of EFD with ICA on the detection of the Default Mode Network (DMN) in the NYU TRT data Subject 4. Activations are thresholded at .9 for both EFD and ICA.

Figure 10.

Comparison of detection of the Default Mode Network with EFD and ICA in the UCSD caffeine data. EFD threshold is .8 of the maximum values, ICA threshold = .5 of its maximum value.

Figure 11.

Comparison of detection of the Executive network with EFD and ICA in the UCSD caffeine data. EFD threshold is .8 of the maximum values, ICA threshold = .5 of its maximum value.

Figure 12.

Comparison of detection of the Saliency network with EFD and ICA in the UCSD caffeine data. EFD threshold is .8 of the maximum values, ICA threshold = .5 of its maximum value.

Figure 13.

Comparison of detection of the Visual network with EFD and ICA in the UCSD caffeine data. EFD threshold is .8 of the maximum values, ICA threshold = .5 of its maximum value.

Figure 14. Average networks across 10 subjects detected with EFD in the UCSD caffeine data. Networks 1–4 as described by Yeo (Yeo et al., 2011).

Figure 15.

Average networks across 10 subjects detected with EFD in the UCSD caffeine data. Networks 5–7 as described by Yeo (Yeo et al., 2011).

Figure 16.

Example time series from three different modes in the CFMRI study demonstrating the complicated nature of the detected waveforms. There are 155 samples spaced at equal time intervals of 1.8s.

Figure 17.

Subject 1 networks. The power from each mode was registered to the standard MNI template MNI152_T1_2mm and then multiplied by the MNI 9 region template (MNI-maxprob-thr25-2mm). The histogram of values in each of the 9 regions (numbered on the x-axis) is shown on the left of each mode. The interdependencies of the different networks is more easily seen by showing the correlation of the histogram, which is shown on the right of each histogram.

Figure 18.

Results of the EFD functional tractography analysis for the Default Mode Network for 3 subjects from rsfMRI collected in a single normal human subject on a standard 3T clinical scanner at the UCSD Center for FMRI. Tracts have been registered to the standard MNI template brain (MNI152_T1_2mm_brain). The tracts are colored according to the standard scheme used in DTI tractography (red = right/left, green = anterior/posterior, blue = inferior/superior).

Figure 19. Largest (i.e., principal) space-time eigenmode of the functional space-time tractography (Figure 18) in the Default Mode Network of Subjects 6, 8, and 10 of the CFMRI data.