

# Solving the brain synchrony eigenvalue problem: conservation of temporal dynamics (fMRI) over subjects doing the same task

S. J. Hanson · A. D. Gagliardi · C. Hanson

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**Abstract** Brain measures often show highly structured temporal dynamics that synchronize when observers are doing the same task. The standard method for analysis of brain imaging signals (e.g. fMRI) uses the GLM for each voxel indexed against a specified experimental design but does not explicitly involve temporal dynamics. Consequently, the design variables that determine the functional brain areas are those correlated with the design variation rather than the common or conserved brain areas across subjects with the same temporal dynamics given the same stimulus conditions. This raises an important theoretical question: Are temporal dynamics conserved across individuals experiencing the same stimulus task? This general question can be framed in a dynamical systems context and further be posed as an eigenvalue problem about the conservation of synchrony across all brains simultaneously. We show that solving the problem results in a non-arbitrary measure of temporal dynamics across brains that scales over any number of subjects, stabilizes with increasing sample size, and varies systematically across tasks and stimulus conditions.

**Keywords** Neuroimaging · Time series · Eigenvalue · Event perception · Synchrony · Temporal dynamics · Inter-subject-correlation

## 1 Introduction

Brain measures such as EEG/MEG or fMRI can be shown to possess significant temporal structure in response to task demands. These temporal dynamics have been studied at different levels of neural organization in the brain and behavior, on various time scales with various stimulus type and duration in both human and animal systems (Kelso 1995; Friston et al. 2003; Buzsaki 2006; Hanson and Timberlake 1983). In the present research we analyze the temporal structure in fMRI and show that temporal dynamics are conserved across subjects doing the same type of behavioral task. Current practice in fMRI focuses on the individual voxel level and treats it as a single variable in a general linear model (GLM). If regressors (e.g. autoregressive) are constructed that have dependencies over time or have some temporal structure, the GLM will, of course, be able to identify tissue possessing temporal sensitivity. However, the variation in a typical block or event related design relies on categorical variations in the constructed variables, usually without any temporal reference. In effect, the GLM forces a decomposition of the sources contributing to stimulus variation thereby accounting for the variation in the response variables, in the case of fMRI, voxels in the image space. Corrections to control for false discovery rate are typically introduced as spatial procedures that either explicitly re-estimate Type II errors or decrease the effective number of variables (e.g., by smoothing), but are not temporal in nature. Consequently, current practice in the analysis of fMRI signals has required a model of the presumed structure and effects of a given stimulus context (as in a design specification) that might evoke a specific brain response, rather than measuring the actual evoked response that was experienced by subjects over time.

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S. J. Hanson (✉) · A. D. Gagliardi · C. Hanson  
Psychology Department,  
Rutgers Mind/Brain Analysis (RUMBA) Labs,  
Rutgers University,  
Newark, NJ, USA  
e-mail: jose@tractatus.rutgers.edu

One possible strategy to directly study the evoked response in the brain is to do a kind of system identification that measures common or conserved responses between what we expect to be nearly identical systems. To the extent that a response pattern between sets of systems is conserved, it is possible to identify structure that is independent of any given stimulus properties (and unfortunately, at the same time losing information about the stimulus generation itself). Recently this approach has become popular both in measuring so-called “resting state” dynamics (Gusnard and Raichle 2001) and in a seminal study that introduced a surprisingly simple method for measuring conserved responses (Hasson et al. 2004) while subjects passively watched a 1/2 hour segment of the same commercial movie. Because of the continuous and uncontrolled nature of such a stimulus, standard analysis could not be easily adapted to identify the conserved neural response inferred from fMRI between pairs of subjects. Instead, Hasson et al. correlated (Pearson Product Moment Correlation—PPMC) fMRI timeseries (as phaselocked as possible) between pairs of subjects producing a dynamical signature of the “effect” of the time dependent waveform (the movie). Interestingly, this can be seen as analogous to creating a phase space between sets of variables in a dynamical system. As the two variables vary in time, in this case the fMRI time dependent signals, they can be characterized by examining their dependency by parameterizing time, in effect, removing the temporal variable. For a given dynamical system, these dependencies or trajectories in the phase plot are often organized by “attractors”, or coordinate points (stable points) in the space toward which the dynamical system tends in equilibrium, independent of where the system starts (“initial conditions”) or how it might be perturbed. Although noise in signals like fMRI will tend to mask even low order dynamics, strong correlations between variables can indicate that the underlying system has non-arbitrary properties related to stimulus variation in time. For brain imaging signals, it thus seems possible to examine these variations between voxels and to explore such dynamics in the way that Hasson et al. (2004) had suggested. In order to get a firmer theoretical grip on this type of procedure and to put it in the proper framework, we next consider the conventional generation process of the BOLD signal from neural dynamics.

### 1.1 Brain dynamics

How might these brain imaging dynamics arise and be synchronized? Consider a simple coupled linear dynamical system that might govern two neurons ( $N$  and  $M$ ) or for our purposes here a cluster or populations of neurons that can be approximated as mean field (e.g.  $\langle N \rangle$ ,  $\langle M \rangle$ ) strengths where the change in activity of one population is inversely

proportional to its own activity (thus decaying exponentially to its baseline without further input where  $C_N$  and  $C_M$  are fixed constants) and a function of its own strength modulated by the strength of the other population:

$$\begin{aligned} dN/dt &= h(N, M) - N + C_N \\ dM/dt &= g(N, M) - M + C_M \end{aligned} \quad (1)$$

Convolving these neural populations with the BOLD response function,  $B(x;t,s)$ , which is a function of time ( $t$ ) and spatial ( $s$ ) diffusion also makes the assumptions of time invariance of the neural impulse (which itself is delayed by milliseconds from stimulus onset) and of system linearity (sums of stimulus events and therefore neural spiking produce sums in BOLD responses—which is actually unlikely to be true, Glover 1999; nonetheless for a first order approximation for this analysis we will assume it to be true; but see next section).

$$\begin{aligned} d[B(t, s) \otimes N(t)]/dt &= h[B(t, s) \otimes N(t), B(t, s) \otimes M(t)] \\ &\quad - B(t, s) \otimes N(t) + \widehat{C}_N \\ d[B(t, s) \otimes M(t)]/dt &= g[B(t, s) \otimes N(t), B(t, s) \otimes M(t)] \\ &\quad - B(t, s) \otimes M(t) + \widehat{C}_M \end{aligned} \quad (2)$$

Consequently, with these strong linearity assumptions the convolution can preserve a spatio-temporal diffused and instantaneous response (assuming the timing of the event was recorded and labeled) of neural spiking and therefore of the underlying stimulus waveform. If either the neural response or the BOLD response to the neural response includes a noise term the convolution of the two functions will blend the noise terms as well (as shown in Eq. (2)), making inversion of the BOLD signal to the stimulus or neural waveform very difficult or impossible.

Assuming the neural spiking is entrained by the stimulus and triggers neural resonance at various periods due to coupling and feedback through functions such as  $h$  and  $g$ , correlations could occur at multiple scales. These oscillations can be, of course, at multiple frequencies and therefore be the basis for the type of time series associations we observe in conserved fMRI responses across subjects. Notwithstanding the noise level in fMRI and the probable nonlinearity of the system, the synchronization would only be modulated as long as the phase of both time series are well within the period of the resonate frequency of the system.

One common way to indicate the kind of dependency in phase space of a homogenous linear dynamical system is to find the eigenvalues associated with the matrix of constant coefficients of the linear system. Depending on the nature of the eigenvalues (distinct real or complex values) of the

linear system, the solution will contain stable points, saddle points, or periodic solutions. Although the use of eigenvalues with a given dynamical system can categorize the complexity of that system, due to our ignorance concerning the actual dynamics of the BOLD signal, they can only provide an inspiration below for measuring the underlying complexity of the temporal dynamics from the brains of subjects doing the same task.

Many in the field have examined various measures of voxel complexity over time (e.g. Hurst exponents, Bullmore et al. 2001; Shimizu et al. 2004). Although such analyses indicate the presence of high order dynamical structure in voxel variation, they are neither sufficient to identify anatomical function nor necessary to determine if such dynamics are phase locked to any specific stimulus variation. However, if such correlations arise independently between voxels from a group of subjects experiencing the same stimulus events, then it is unlikely that the implicated anatomical areas are arbitrary relative to those stimulus variations. This type of conservation is not a function of simple spatial aggregation or averaging since it depends on the dynamical time correlation. For neuroimaging data, it is important, therefore, to discuss the BOLD signal's potential for the kind of temporal resolution which is known to capture a given perceptual or cognitive function, since conservation will be dependent on temporal resolution perhaps even at multiple time scales.

### 1.2 Time resolution of the BOLD signal: is it just too slow?

In some ways time resolution in the BOLD signal has been a paradox. On the one hand, the sluggish character of the hemodynamic response (HDR) peaks anywhere from 4 to 6 s after a stimulus onset, depending on the tissue being measured. The fastest onset of a measurable change from the stimulus onset for the HDR is probably only about two seconds. On the other hand, with a sufficient number of trials, it may be possible to see measurable evoked HDRs at sub-second resolution (e.g., see Menon et al. 1998) similar in kind to that which can be obtained from phase-locked averaging of EEG signals. Event related designs with staggered event points are another way of obtaining sub-second resolution as long as a sufficient number of sample points are taken. The ability to obtain a temporal resolution greater than that of HDR response may seem paradoxical if the HDR signal was Gaussian and linear. However, the BOLD response is highly nonlinear and its distribution possesses a long tail (Hanson and Bly 2001; Chen et al. 2003). It is highly likely, therefore, that the fMRI signal has a significant autocorrelation, a feature which is often associated with a high temporal complexity, and one that potentially can be used to obtain a higher temporal resolution than that indicated by the sluggish HDR

diffusion process. In fact, an examination of the underlying complexity of the BOLD time series using various measures (e.g. Hurst exponents,  $AR(p)$  and other similar estimates; also see Bullmore et al. 2001), even without a task, one finds “long memory” temporal dependencies in the time series (indicated by Hurst values  $>0.5$ , often near 0.7). These dependencies across various sets of regions may reflect underlying anatomical or functional networks that persist in recurrent or reciprocal neural activation. In any case, it seems clear that there are significant dependencies at various temporal scales (milliseconds, seconds, minutes) in the BOLD signal during “rest” that could be differentially modulated by stimulus contexts. Nonetheless, the substantial noise level in fMRI, and its weak correlation with the stimulus waveform, make it difficult to measure such dynamics using stimulus regressors in any precise way. Consequently, it becomes necessary to take a more indirect approach to measuring temporal dynamics that can provide signal sharpening while minimizing noise, based on the conserved temporal dynamics across individuals experiencing the same stimulus conditions.

### 1.3 Measuring the temporal dynamics across brains: conserving synchrony

Assuming that temporal dynamics are more or less stationary (once corrected for temporal drift and various physiologic artifacts such as breathing, heart rate etc.), it should be possible to measure temporal dynamics as a function of stimulus conditions that are held constant over some measurement interval. The challenge here is not unlike that faced when noise in the fMRI measurement must be controlled for, despite an unknown underlying distribution. The GLM uses a “black box” contrast in which it is assumed that signals that are not modulated by the different stimulus conditions (e.g., noise) will be removed during the linear contrast. Thus, the GLM assumes an additive nature of the underlying factors (which include noise) and estimates the mean effect between stimulus conditions by treating the unknown noise structure as though it were identical between conditions and brains. Thus, to the extent that noise is correlated with a given stimulus condition, the estimated mean effect will incorporate the correlated noise from the contrast and be smoothed into the effects image. Unfortunately, the standard linear model provides no way of completely removing correlated noise without also directly modeling the noise itself in the estimator. Thus, the GLM is effectively limited in revealing parametric dependencies of different stimulus conditions by its inability to accurately model the nonlinearity of the HDR and the complexity of the noise in the BOLD signal. However, if similar stimuli produce similar temporal responses across different brains, it should be possible to

estimate the underlying temporal dynamics from the conserved temporal patterns, and reduce the influence of noise, as long as the signal and noise are marginally different. This type of “signal sharpening” should increase with the number of brains in the sample, improving asymptotically as the underlying noise is incrementally removed (the exact size of the sample is unknown, but see below).

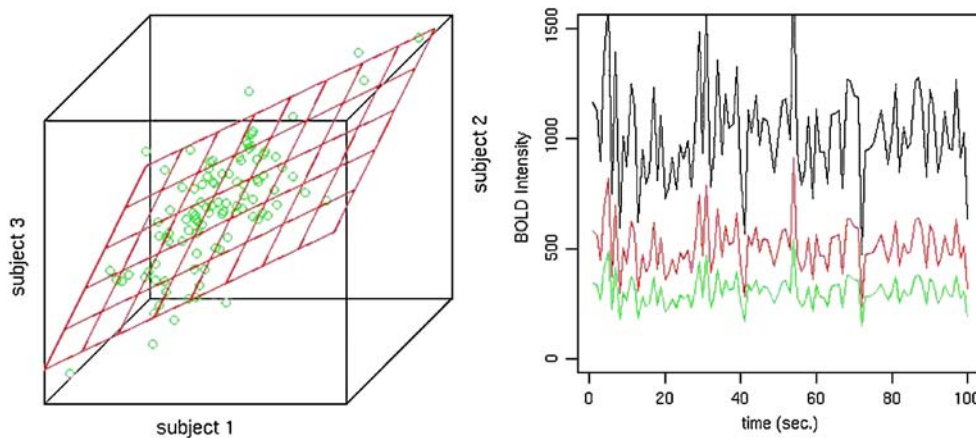
Intuitively, temporal dynamics within a single brain can be identified by considering the aligned synchrony that is common between subjects as can be seen in the time series plot of three brain/voxels shown in Fig. 1. This phase space shows that common or conserved temporal dynamics are equivalent to a projection of the time points into a lower order manifold (plane) that is shown here in 2-D as the first eigenvector of a corresponding association matrix. As the three subjects’ projections cluster near the principle component in this space, a high temporal synchrony is revealed. Mathematically, we can express potential synchrony across all brains in a population (per voxel) as an eigenvalue problem and ask whether, given  $b$  brains (per voxel) across  $T$  (over  $t$ ) time points, is there some non-zero measure of synchrony,  $\sigma$ , that is conserved across all brains such that voxel time patterns are a linear combination of one another? This eigenvalue problem can be framed within a brain by brain covariance/correlation in which  $\sigma$  represents the strength of the temporal synchrony between subjects’ brains at each voxel and eigenvectors indicate the agreement and directionality in subject space. In this way,  $\sigma$  and the eigenvectors can be used as a measure of overall subject synchrony and could also be used as a measure of individual differences among subjects (to the extent that coefficients contrast between subjects). Although a brain by brain ( $b \times b$  in the equation below) covariance/correlation involves an assumption about linearity concerning the temporal dynamics, the actual pattern of these dynamics could be highly nonlin-

ear. Equation (3) states the eigenvalue problem including the relevant matrices.

$$\begin{aligned}
 A_b^b S_b &= \sigma_b S_b \\
 A_b^b &= COV(V_b^t) \\
 V_b^t &= \begin{bmatrix} V_{b11} V_{b21} V_{b31} \\ V_{b12} V_{b22} V_{b32} \\ V_{b13} V_{b23} V_{b33} \\ \dots\dots\dots \\ V_{b1T} V_{b2T} V_{b3T} \end{bmatrix}
 \end{aligned}
 \tag{3}$$

The solution to Eq. (3) is equivalent to finding the eigenvectors,  $S$ , that are associated with the largest eigenvalues,  $\sigma$  per voxel over all brains and time points. The largest eigenvector is directly related to Roy’s Largest Root Statistic (Pillai 1965), and with appropriate degrees of freedom, can be tested directly as an F statistic. Note because the extraction is using ALL brains at once, there are no order effects as there is in the PPMC/ISC method (Hasson et al. 2004). Further note, that if  $N=2$  this is exactly the Hasson algorithm as we show below. By calculating a family-wise error over the entire voxel eigenvalue set a corrected statistical significance can be achieved. It is also trivial to prove that the eigenvalue between two brains must be monotonically related to a product moment correlation. It is also obvious that the synchrony between two brains (Hasson et al. 2004) is a special case of the eigenvalue problem we have just outlined. Furthermore all utilizations of the Hasson et al. brain-PAIRWISE method (a recent example is Hejnar et al. 2007, but there are many others) are also subject the limitations and interpretation problems we discuss below. We will demonstrate this point by comparing our eigenvalue approach for ALL brains at the same time with a brain pair-wise pearson product moment correlation (PPMC or what they called Inter-subject correlation—ISC) for the case of two brains exposed to the same continuous stimulus

**Fig. 1** Constructed example showing three subjects time series (right panel), and their phase space showing (in green) the times series values from the right panel as they project to the eigenvector 2D plane (red grid). The closer the time series points to the plane indicates high synchronization between time series



(a short action sequence video). Before examining some of the properties of the eigenvalue synchrony measure (EVS), we will describe some types of stimuli and methods that might be used with this novel approach to detecting conservation of temporal dynamics in brain imaging measures. Note that any group-wise analysis using other temporal extraction algorithms (Maximum Likelihood factor analysis or any other variance/covariance factoring methods) will of course accomplish the same kind of conservation given they are sensitive to the underlying temporal dynamics. In contrast, factoring methods such as ICA in the groupwise case (for a groupwise ICA method, see for example, Beckman and Smith 2005), would instead tend to extract hypothetical statistically independent processes that exist in different areas of the brain across all subjects. Consequently, ICA over brains (per voxel) would tend to find a smaller set of conserved areas, if any, since they are required to be both conserved and orthogonal. Principal Components Analysis (PCA) or Independent Components Analysis (ICA) can also be used to compress the number of variables based on temporal variations, but often in a more exploratory context, and do not need to be related to the design variables and can be used for analysis of resting state patterns and for separating signal from noise (albeit in an unsupervised way, often requiring a keen eye to determine which is which)

#### 1.4 Summary of EV method

Because this is a novel method, it's important to emphasize the novel aspects of the approach. (1) This method works across ALL subjects (brains) simultaneously. (2) The largest eigenvalue is extracted over all brains for each voxel (see Fig. 4 below for exact flow of computation and pseudo-code). (3) This measure of dynamical conservation is known as the Roy's largest Root (or properly normed as Wilkes Lambda—see below) for all brains, which is a measure that scales over sample size (brains) and time points simultaneously. (4) This is a novel method that finds the synchronization of fMRI time series and generalizes other approaches to this problem and provides a statistically principled way to scale over subjects and time points unlike other methods that possess sequential bias, are ad hoc, and use less efficient permutation tests for statistical significance (e.g. Hasson et al 2004). Note that the key aspect to the new method is not the particular statistic (RLR) that we have used to determine the significance of the temporal synchrony, but rather the ability to exploit more brains in the synchrony estimate (RLR or "r") thus potentially increasing the power of the approach dramatically.

In the next section we will apply the eigenvalue synchrony (EVS) method to fMRI data sets acquired from subjects watching short movies (minutes) and asked to push

a button when they detect a change point in the action sequence. This will allow us to benchmark the method and contrast it with the PPMC pairwise method.

#### 1.5 Continuous stimuli paradigms: event cognition

Although any type of stimulus paradigm, including a block design, could be used to find conservation of temporal dynamics between subjects, a continuous stream of events should create optimal conditions for observing the similarity of temporal dynamics across subjects. We decided to create our own video sequences, rather than use commercially available movies, in order to systematically control differences across sequences which would allow us to map differences in response to specific changes in the stimuli. Whereas commercially available movies can vary in the number of camera views, actors, objects, as well as plot complexity, we constructed three types of simple video sequences with increasingly more complex goal structures. One type of sequence (schema-rich) consisted of a single actor performing a simple, familiar task (e.g., making a cup of coffee) that took no more than a few minutes (four to eight minutes) to complete. We characterized this type of video as schema-rich because it involved a well-defined task with a simple goal structure that was composed of highly predictable actions. Previous work shows that to comprehend the meaning of action streams, people naturally and spontaneously parse activity into distinct units of meaning (e.g., eating dinner, going to the movies, etc). Moreover, observers who are asked to categorize action sequences in real time produce consistent judgments about action cluster start and end points (more details of video construction can be found in Hanson and Hirst 1989; Hanson and Hanson 1996; Heider and Simmel 1944; Zacks and Tversky 2001; Bartels and Zeki 2005; Hanson et al. 2007). Thus, although parsing video action sequences into a constituent structure is a relatively complex visual task, it is one that is naturally and easily performed by most people both inside and outside of the laboratory.

The second type of action sequence (we define as "schema-poor") we used was an animated set of geometric shapes moving around each other. This stimulus was modeled on one constructed originally by Heider and Simmel (1944) who showed in their seminal study that subjects will anthropomorphize about moving geometric shapes, creating a story involving goals and emotions, even when the motion and nature of the stimuli are arbitrary. In our animated video we produced a short sequence lasting about 4 min in which a circle moved around a geometric "house" consisting of a set shapes in fixed locations. This sequence was less well-defined than the schema-rich sequence, allowing for various plausible accounts rather than one simple and obvious goal based structure.

The final type of stimulus (schema-free) depicted a “jittering” rectangle that periodically expanded and contracted but would increase in length by three standard deviations at certain time points that corresponded to the subject’s parsing of the schema-rich sequence. Because the subject was unaware of the connection between the jittering and his/her own responses, the sequence seemed to be meaningless and unpredictable. This allowed us to control for the subject’s responses and frequency of responding with independent of movie content. To the extent that this sequence required vigilance to detect significant signal change against background noise, it closely resembled an oddball task. Note in all tasks including schema-free, subjects were required to parse the stimulus by pressing a button indicating change point in the sequence, hence allowing us to assess the vigilance and performance.

## 2 Materials and methods

We used a 3T Siemens Allegra head only MRI scanner (Erlangen, Germany). We acquired structural images with a 3D magnetization prepared rapid acquisition gradient recalled echo (MP-RAGE) T1-weighted scanning sequence with 2 mm isotropic resolution. Our functional data consisted of a T2\*-weighted asymmetric spin-echo, echo planar sequence with flip angle of 90 and a 30 ms time to echo (TE) involving 32 4 mm slices with each slice consisting of  $3.75 \times 3.75$  mm cells in  $64 \times 64$  grid. Our time to repetition (TR) for each volume lasted 1.5 s. We registered the images to Talairach space and applied 12 mm full width at half maximum (FWHM) smoothing.

We constructed maps representing the amount of synchrony between subjects in the viewing of a video by extracting the eigenvector from each voxel individually over all subjects.

Specifically we calculated the covariance for each voxel independently based on a brains  $\times$  time points data matrix producing a brains $\times$ brains ( $b \times b$  in equation below) covariance matrix and a singular value decomposition (SVD) per voxel on the scaled brain by brain covariance matrix:

$$\det[A_b^b - \lambda I] = 0 \quad (4)$$

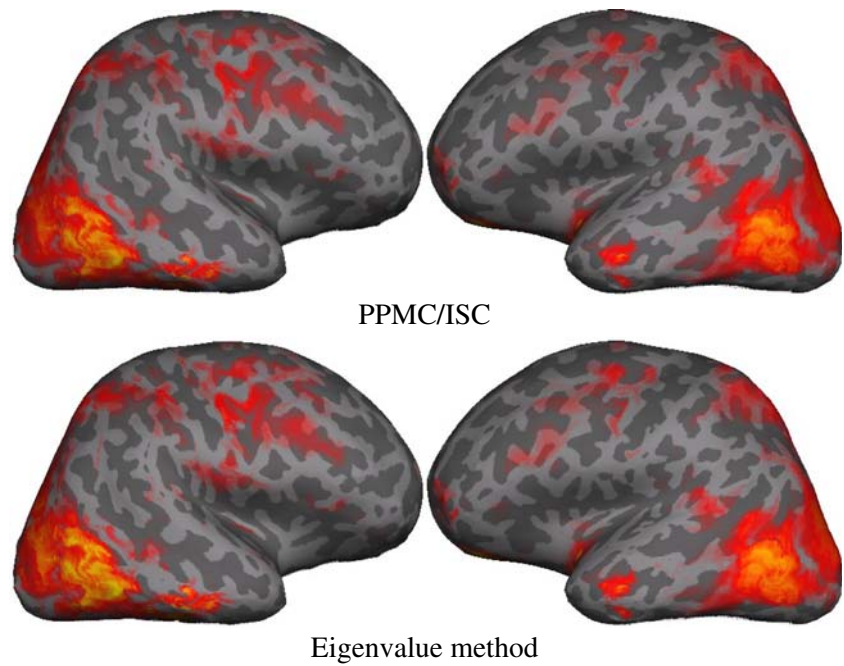
The corresponding largest eigenvalue for each subject/voxel time series was used with the coefficients for each eigenvector. When coefficients were all the same sign (positive or negative) then these subject-voxels were labeled as “aligned” or “conserved”. We constructed a heat map which shows the constructed  $F$  value (Roy’s Largest Root; Pillai 1965) from the largest eigenvalue (using  $\text{RLR} = F(df1, df2) = \text{LEV} * (df2/df1)$ , where  $df1 = \text{maximum} < \text{number}$

of subjects, time points  $-1 >$  and  $df2 = (\text{time points}) \text{ per voxel}$ . If the eigenvector coefficients were not aligned, conservation was not achieved by our definition and these voxels were not mapped. Family-wise voxel correction was done by using a Bonferroni correction to the alpha level ( $\alpha_{\text{corrected}} = \alpha / \text{aligned eigenvalue voxels}$ ).

### 2.1 Conservation over brains: sample size and statistical parametric maps

We first apply the method to two brains and compared the eigenvalue synchrony (EVS) method with a Pearson product moment correlation (or ISC; Hasson et al. 2004). Shown in Fig. 2 (top) are the set of brain maps which were derived with PPMC using a per voxel threshold  $p < 0.05$  ( $r > 0.14$ ,  $df = 102$ ). On the bottom of Fig. 2 are the brain maps calculated by using Roy’s Largest Root also thresholded per voxel at  $p < 0.05$  ( $\text{RLR} > 1.257$ ). Note that the maps are identical in location and shape of activation patterns. This is not surprising given that the eigenvalue per voxel must be, at the very least, monotonically related to the correlation measure per voxel. However, both sets of maps are displaying the non-corrected family-wise values and are unlikely to be significant once properly thresholded (this is a fundamental problem with the PPMC method, since averaging over properly thresholded and hence empty brain maps will not in general increase the sensitivity of the measure per voxel). We can increase the sensitivity of the eigenvalue method by sampling more brains within the given time points. In a pairwise PPMC, the only way to increase sensitivity would be to measure more time points. Although measuring more time points eventually will produce maps with significant p-values, increasing the temporal sample size will result in little variance being accounted for beyond that which can be attributed to time dynamics. The other obvious problem with using pairwise PPMC is that aggregating or even simply averaging over pairwise sets of brains produces a distribution that is not Gaussian, or inverse-gamma (as for Pearson  $R$ ), as is assumed for a typical PPMC test statistic. Of course, it is possible, and probably advisable in this case, to do some bootstrap estimate in order to provide a valid test statistic, even if inefficient. Nonetheless, attempting a PPMC/ISC method will require a large number of time points which, unfortunately, can entail still other problems. For example, it is not difficult to find a long commercial movie to use as a stimulus (as with the Hasson et al. 2004), but the longer time sample itself could contain a mixture of time dynamics at different resolutions and of different functions, possibly obfuscating simpler, short term dynamics that might be more task specific. For the eigenvalue method this poses no problem inasmuch as the number of time points will trade off with the number of brains in the sample, increasing

**Fig. 2** Comparison of Pearson product moment correlation (on the *top*) and eigenvalue conservation method (on the *bottom*) using two brains without family-wise correction



sensitivity to temporal dynamics associated with short time cycles and/or specific brain areas.

## 2.2 Parametric statistical maps: stability and significance

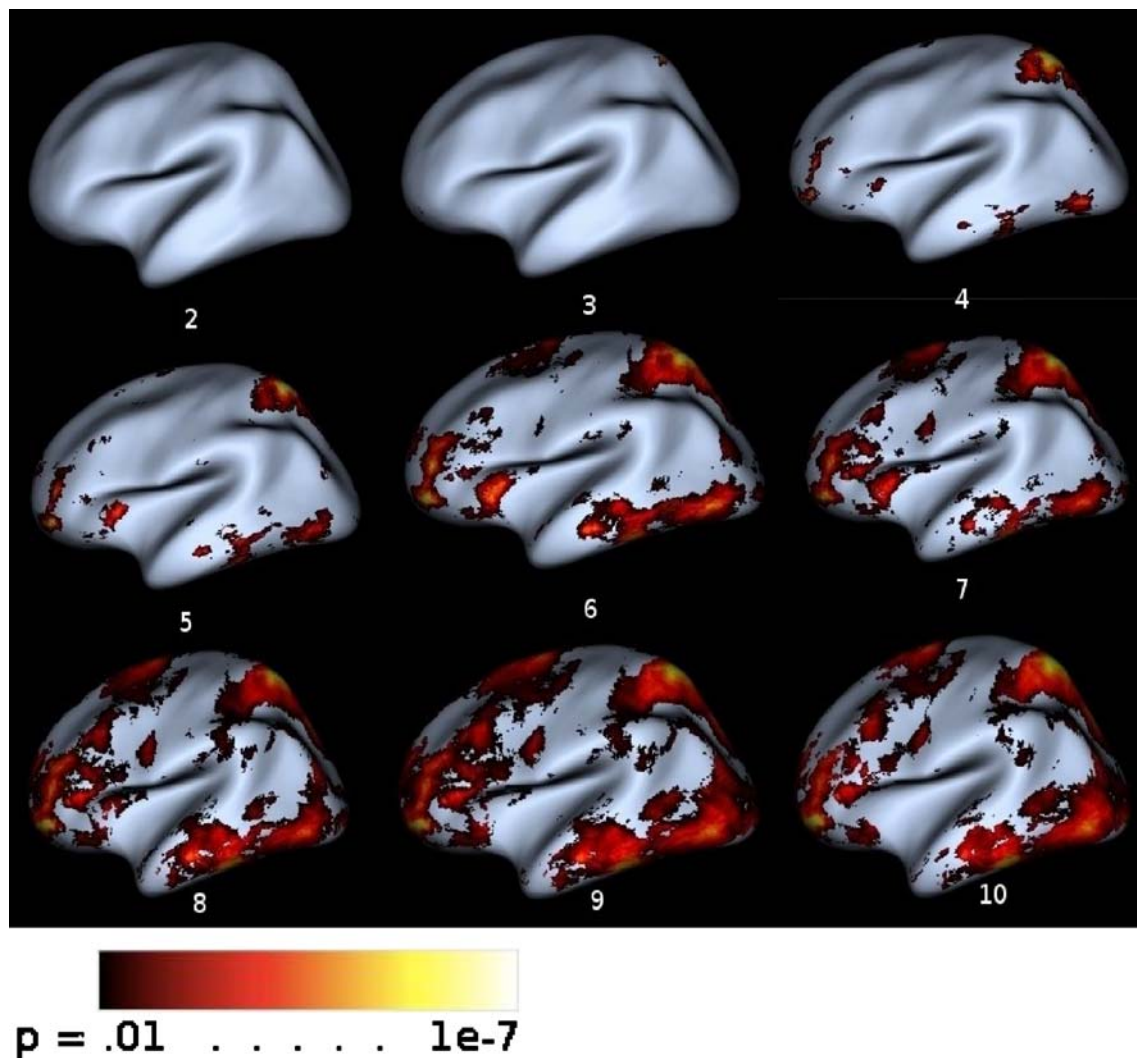
Synchrony measures will often involve data from the whole brain as most kinds of cognitive tasks can be associated with temporal dynamics that occur throughout the brain. Whole brain estimation requires a family-wise correction (e.g. Bonferroni) in order to properly assess localization and significance of the resultant parametric map. This also provides an index of the stability as the sample size increases. We applied the eigenvalue method to one of our standard tasks, increasing the number of brains from two to ten brains while applying a corrected threshold (see Fig. 3). Interestingly, with two brains, no significant synchrony could be detected reliably within the TR sample size ( $n=104$ ,  $p<0.01$ ). This is unfortunate for the PPMC (inter-subject correlation method) since there is no significant correlation at these short time scales, indicating that although there is synchrony present in these smaller time scales, the PAIR-WISE method is insensitive to them<sup>1</sup>. In fact, synchrony did not appear until six or seven brains were included and did not stabilize until about 10 brains (although we have run the analysis over 22 brains and seen similar stability with an  $N=10$  to 12). This is a serious

<sup>1</sup> Note that if one averages Pair-estimates before thresholding, the synchrony estimate is limited by the  $N=2$  sample size, any weak or non-significant correlation values can not be re-estimated up or down by post averaging  $N=2$  cases. Fundamentally, the power of the sample must derive from the size of the synchrony estimate that is dependent on both the size of the time series and the number of brains.

drawback for pairwise methods such as PPMC/ISC (Hasson et al. 2004) since averaging over the  $N=2$  case, where the brain is empty will of course lead to an empty average brain no matter how many pairs are correlated. This is consistent with past work using PPMC (Hasson et al. 2004), in which longer stimulus durations (about 30 min) and larger time samples (thousands of time points) were used. Although this work found that a large sample size resulted in significant per voxel synchrony, the overall BOLD activity correlations are typically less than 0.15, barely 2% of the overall variance of the time series. Averaging across subjects will increase the correlation, but arguably defeats the purpose of detecting task related temporal dynamics in as much as averaging over subjects prior to correlation preserves only the coarsest of time scale. In contrast, to increase power in the eigenvalue method (EVS) one need only increase the number of brains that are included in the analysis. This aspect increases the potential sensitivity of the eigenvalue method to the underlying task dependent dynamics. Before considering other stimulus variations in goal complexity, it is important to consider the application of the EVS method to simulated data, in order to understand its sensitivity to variables like phase and time resolution of the assumed dynamics.

## 2.3 Simulations of conservation under fixed assumptions

The first eigenvector extracted from the BOLD activity across ALL subjects depends on the correlation matrix between the voxel activity of those subjects (see Fig. 4 for exact pseudo-code and flow of algorithm). The eigenvalue from two brains equals one plus the absolute value of the



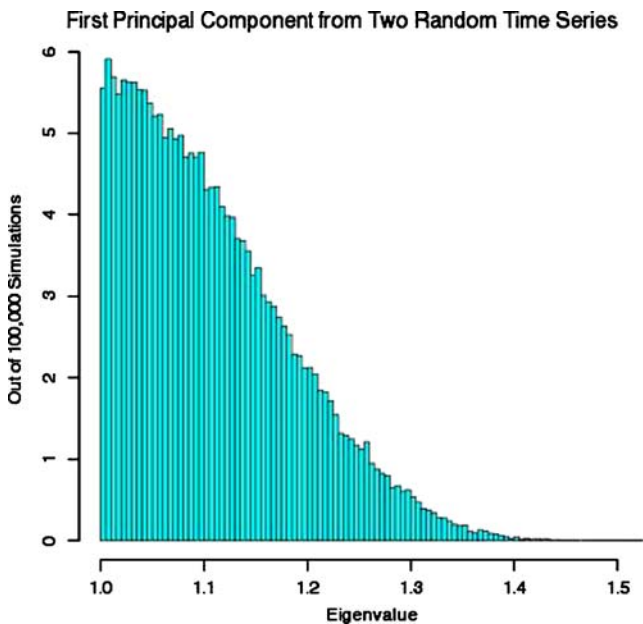
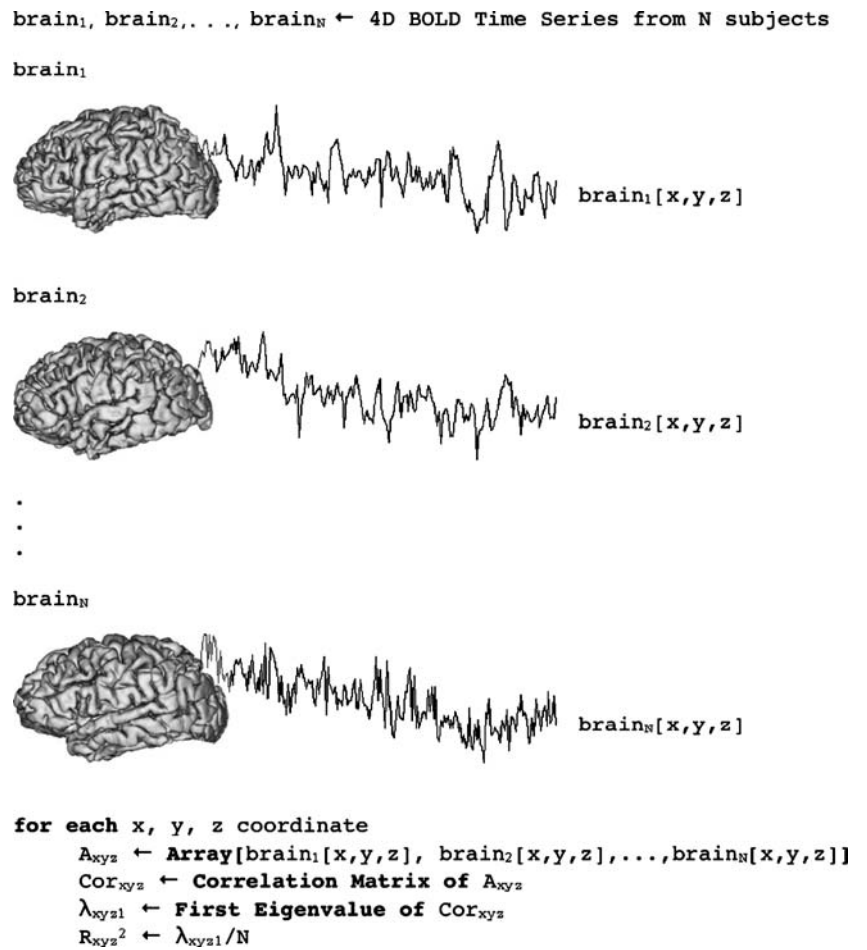
**Fig. 3** Effect on sampling size on statistical parametric map, showing from *top left* to *bottom right* row, Roy's Largest Root Statistic ( $F$  value) thresholded at  $p < 0.01$  for 2, 3, 4, 5, 6, 7, 8, 9 and 10 subjects.

correlation coefficient  $(1 + |r|)$ . For example, if we generate time series consisting of frequencies of 1.414, 0.305, 0.066, and 0.014 Hz, with randomized phase, and a sampling rate of 5 Hz (simulating a TR of 2.0 s) with Gaussian noise with a standard deviation of two (where each frequency has an amplitude of 1), the correlation between any two such time series will follow a normal distribution with a mean of zero and a standard deviation of about 0.135. A sample distribution of 100,000 corresponding eigenvalues from the first eigenvector of two such random time series is shown in Fig. 5. For comparison, when the same frequencies are phase locked between the two time series, we see a distribution like that in Fig. 6. As predicted based on the empirical BOLD data from participants watching the same videos, the eigenvalues rise as a direct function of phase locking the underlying frequencies ( $t > 24$ ,  $p < 2.2e-16$ ). The phase locked example in Fig. 6 involves four frequencies,

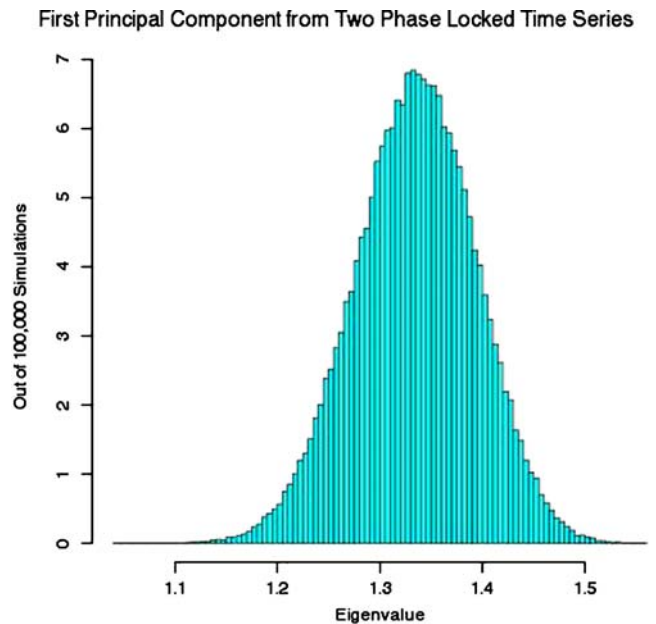
Note sample stability of the 0.01 activity in this case starts around 6 brains and shows little or no variation after eight brains

all perfectly synchronized, with random noise added ( $SD=2$ ). If we take the first eigenvector from two time series, one constructed from four frequencies as above, the other constructed from 3, 2, or 1 of those frequencies, the eigenvalues become progressively less significant. Figure 7 shows a boxplot for each distribution of eigenvalues when 0, 1, 2, 3, or all 4 frequencies are locked, with the remaining frequencies' phases randomized. The relationship between the number of locked frequencies and the eigenvalue of the first eigenvector is highly significant ( $p < 2.2e-16$ ), indicating that as the phase or common frequencies are different that there is a gradual reduction in the strength of the synchrony measure, showing how temporal synchronization could arise at many different time resolutions and phase shifts. Although clearly the simulations show how important the initial phase overlap is for the EVS measure. These simulations give us a good

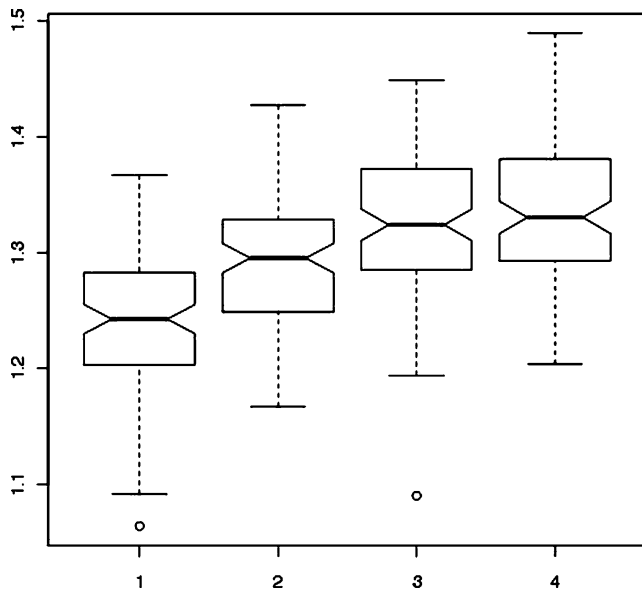
**Fig. 4** EVS computational flow showing how brain maps are constructed. First the brain array of all N brains per voxel are bound in a 4-D data structure over time points (TRs) and the correlation matrix is calculated over time for brains against brains, and the first eigenvalue is calculated for each voxel. These are then transformed to Roy's largest Root statistic



**Fig. 5** Frequency distribution of the first eigenvalue of two random time series constructed to test EVS method



**Fig. 6** A frequency distribution of the first eigenvalue for two phase locked time series constructed to test EVS method

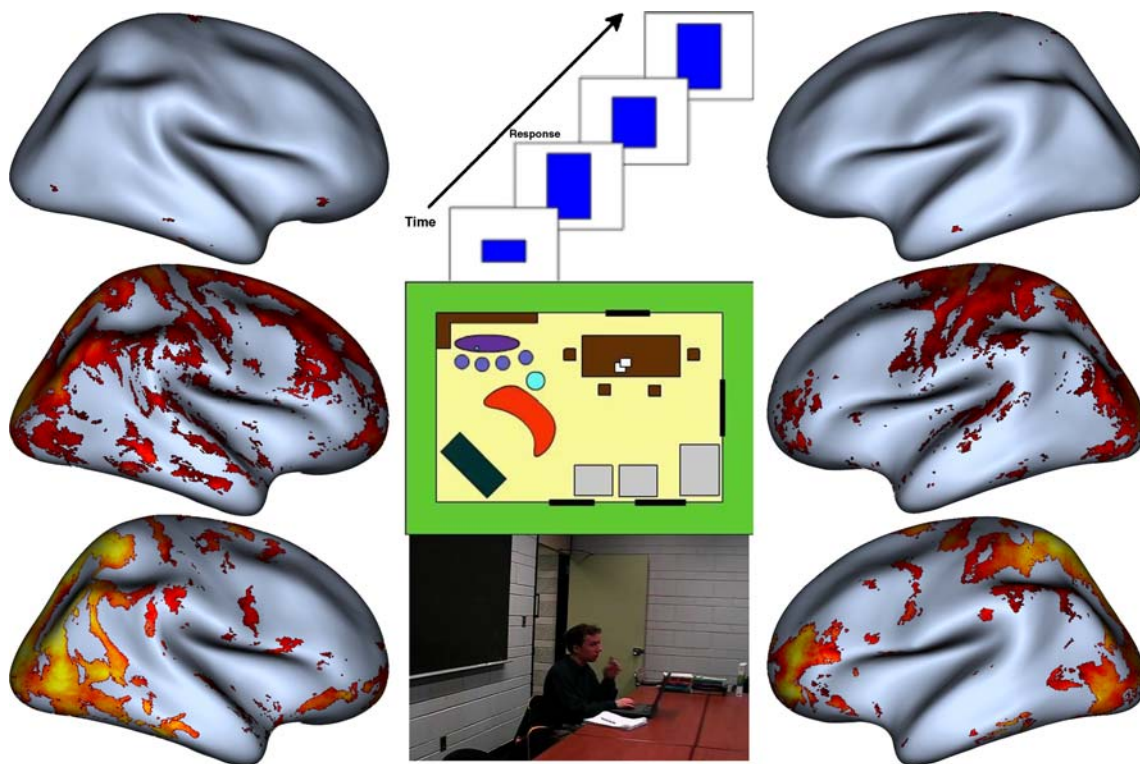


**Fig. 7** Boxplot for distributions of eigenvalues (*Y*-axis) with successive mismatch in shared frequencies of time series. Note gradual drop in synchrony value as the number of shared frequencies are removed

basis to look at actual BOLD data from subjects while their expectancies are manipulated with respect to the stimulus content.

### 3 Conservation of stimulus expectancies

The eigenvalue conservation method was applied to 6 subjects watching the same video from each of the three sequence types described earlier. We show the results in Fig. 8, in which the synchrony measure for each condition is displayed with a typical frame from each type of video. For the schema-free video (top panel), we found virtually no synchrony. On the other hand we found significant synchrony for the schema-poor stimulus (middle panel) (RLR>1.9,  $p<0.05$ ), particularly in the: cuneus, lingual gyrus, superior temporal sulcus (areas associated with visual object and motion pathways). Finally, for the schema-rich videos (bottom panel) we found high amounts of correlation (RLR=2.4,  $p<0.01$ ), particularly in the: superior parietal lobule, inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, middle occipital gyrus,



**Fig. 8** Eigenvalue method results as a function of complexity and goal directed aspects of the action sequence. *Top panel* shows synchrony with oddball task, in fact showing no or little correlation, in *middle panel* is the response to cartoon stimulus with arbitrary

motion showing moderate synchrony, finally in *panel 3*, is a high correlation to the familiar action sequence videos. Left and right hemispheres are shown on each side of the figure

superior occipital gyrus, precuneus, cuneus, middle temporal gyrus; areas associated with visual processing of objects and motion as well as areas associated with planning, response selection, and decision making.

A simple but nonetheless critical control for all such conservation methods is showing that there is difference when  $n$  brains are watching the same video as opposed to when  $n$  brains are watching different videos. This comparison would establish whether the synchrony seen is due to some general visual processing and comprehension processes or to some specific content. Is the same or similar video needed to produce brain synchrony in time? Are there different levels of synchrony that organize on different time scales? Does the specific content matter or is it sufficient to have two different videos of an actor engaging with a specific object with specific actions? When we compared the results of six brains watching the same video versus six brains watching different videos, we found differences both in the average synchrony voxel-by-voxel, and in the number of supra thresholded voxels. We ran a Student's  $t$ -test on the corresponding eigenvalues and found a significantly higher level of conservation ( $t > 14$ ,  $p < 10e^{-15}$ ) when our participants were watching the same video even though similar areas were conserved across brains in both conditions. So, although simply watching a familiar action sequence engages some type of generic goal-directed visual processing response, it seems clear that the specific content does matter. This finding suggests that there is a continuum of synchrony strength, with greater similarity of stimulus contexts yielding greater synchrony among brains, which was also consistent with our simulation studies reported earlier.

#### 4 Discussion

We have developed a new method for detecting synchrony among brains and conservation across any number of subjects (EVS). This approach allows the construction of parametric brain maps (based on eigenvalue statistics—Roy's Largest Root) which are sensitive to sample size and related to proper family-wise statistical correction. Consequently, our method has significant generality and can be applied to situations where the stimulus presentation and structure is arbitrarily complex (not simply continuous stimulus paradigms or uncontrolled movie stimuli). Moreover, it can be used in experimental contexts where the stimulus is relatively short or event related because the power of the method depends on conservation of time dynamics over subjects, not over the time sample itself.

The eigenvalue approach is a general way to identify temporal dynamics across subjects and subsumes other

associative methods while avoiding the need for large time samples that could possibly diminish sensitivity to the actual temporal dynamics of interest. We have also shown that temporal synchrony among brains does vary with the complexity and goal-directed features of the stimulus and that the areas of synchrony are consistent with areas obtained through a general linear model (GLM) analysis of event related stimuli (Hanson et al. 2007). The high sensitivity of the temporal synchrony to variables like stimulus type, complexity, and expectancies opens up new lines of research in the theory and analysis of brain interactivity and dynamics. We can further generalize this work to exploit voxel interactions by including terms in the fundamental eigenvalue problem that reflect the temporal synchrony of organizing assemblies of neurons and thereby create higher coherence and possibly sharper functional localization.

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