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Experimental Validation of Dynamic Granger Causality for Inferring Stimulus-evoked Sub-100ms Timing Differences from fMRI

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Abstract

Decoding the sequential flow of events in the human brain non-invasively is critical for gaining a mechanistic understanding of brain function. In this study, we propose a method based on dynamic Granger causality analysis to measure timing differences in brain responses from fMRI. We experimentally validate this method by detecting sub-100ms timing differences in fMRI responses obtained from bilateral visual cortex using fast sampling, ultra-high field and an event-related visual hemifield paradigm with known timing difference between the hemifields. Classical Granger causality was previously shown to be able to detect sub-100 ms timing differences in the visual cortex. Since classical Granger causality does not differentiate between spontaneous and stimulus-evoked responses, dynamic Granger causality has been proposed as an alternative,

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thereby necessitating its experimental validation. In addition to detecting timing differences as low as 28 ms during dynamic Granger causality, the significance of the inference from our method increased with increasing delay both in simulations and experimental data. Therefore, it provides a methodology for understanding mental chronometry from fMRI in a data-driven way.

Index Terms

Dynamic Granger causality; Effective connectivity; Brain Networks; Mental Chronometry

I. Introduction

Correct inference of temporal differences in neural activities play a critical role in fully understanding the neural connectivities underlying brain processes. Functional MRI (fMRI) is an indirect measure of neuronal activity based on the blood oxygenation level-dependent (BOLD) hemodynamic response. Typically the hemodynamic response takes 5–8 seconds to reach its peak and 15–30 seconds to return to baseline. On the other hand, neural latencies are typically of the order of tens to hundreds of milliseconds. Therefore, accurate inference of the timing difference of neuronal activities using fMRI is challenging. However, using innovative experimental designs, previous studies have shown that fMRI is sensitive to latency differences of the order of hundreds of milliseconds in the human brain, notwithstanding its poor temporal resolution and hemodynamic smoothing [1,2]. Recently, a study performed by Katwal et al. [3], suggested that recent advances in ultrahigh field image acquisition, fast temporal sampling, and techniques for increasing the available signal-to-noise ratio (SNR) may improve the ability to detect shorter timing differences. Using these strategies, Katwal et al. attempted to detect small timing differences in BOLD signals by introducing known timing differences between left and right visual cortices. They showed that Granger Causality (GC) works well for detecting small temporal precedence in BOLD responses in the visual cortex [3]. GC is a widely-applied method for mapping effective connectivity over the brain, which is based on a statistical measure of how one time series predicts the future values of another [4–7]. However, conventional GC is sensitive to both spontaneous and stimulus evoked responses [8]. Previous studies have proposed that by estimating time-varying coefficients using a dynamic Granger causality (dGC) model, temporal precedence due to stimulus-evoked responses can be inferred and separated from that due to spontaneous activity using both EEG [9,10] and BOLD fMRI data [11–13]. It is noteworthy that Astolfi et al [10] clearly demonstrated the utility of different formulations of the dynamic Granger causality model for tracking dynamically changing signal precedence using simulations. Therefore, the focus of the current paper is to validate dynamic Granger causality as a method for inferring neuronal timing differences from fMRI when the former are smaller than the sampling period of the latter. Specifically, we demonstrate the ability of the dGC model to infer sub-100 milliseconds of timing differences between BOLD fMRI time series from left and right visual cortices using both simulation and experimental data.

II. Methods

A. Experimental Data acquisition

Gradient-echo EPI data (TR=250 ms, TE=25 ms, flip angle=30°, FOV=128 mm×128 mm and voxel size=1 mm×1 mm×2 mm) were acquired from a 7T Philips Achieva scanner from 5 healthy subjects in two coronal slices (with no slice gap) around the calcarine fissure. An event-related visual hemifield paradigm with known timing difference between the hemifields was used. Accordingly, the visual stimulus was presented separately to the left and the right hemifields with a variable delay in the onset times of the stimulus in the right, as compared to the left hemifield. Each visual stimulus comprised a 2-s flashing of checkerboard followed by a 16-s fixation cross for total trial duration of 18 s. Each run included 17 trials and the total run time was 306 seconds. For each subject, five runs were executed by introducing known delays (including 0, 28, 56, 84, 112 ms) between right and left hemifield stimulus, with the left hemifield stimulus leading the right hemifield stimulus. It is well known that the signal in the left sight view maps on to the right primary visual cortex and vice versa. Therefore, ideally, the extracted time series in the left primary visual cortex should be a delayed version of the time series in the right primary visual cortex, and this delayed similarity should be increasingly obvious as the timing differences increase. Fig. 1 shows the stimulus paradigm described above. A standard preprocessing pipeline including motion correction, linear trend removal, normalization and high-pass filtering was adopted. Spatial smoothing was not performed, in order to preserve the high spatial resolution (Please refer to Katwal et al [3] for further details). Regions of interest (ROIs) in the left and right visual cortices were obtained using voxels selected by a novel graph-based visualization of self-organizing maps as shown in Fig. 2 [3,14]. Katwal et al [3] showed that voxels and associated prototype time series identified via self-organizing maps best represented activity across different delays/subjects and hence were better suited for inferring timing differences between the two visual hemifields as compared to those obtained via standard general linear models or independent component analysis. Also as in Katwal et al [3], it was manually made sure that the ROIs did not contain voxels outside V1 and that approximately equal number of voxels were picked both left and right hemispheres contained. The selected prototype time series from left and right hemispheres were averaged and the resulting mean time series were denoted as X and Y, respectively. These time series were used for the current analyses.

B. Generation of Simulated Data

In order to theoretically evaluate the performance of dGC for inferring the time differences, a dataset was artificially generated to simulate the fMRI signals in left and right primary visual cortex with known time differences. Firstly, the “neural” time series of right primary visual cortex with sampling period of 1 ms was generated. The length of this time series was 306000-points corresponding a duration of 306000 ms, and contained 17 trials as in experimental data. Each trial consisted of 2000 points with values of one corresponding to visual stimulation followed by 16000 points with values of zero corresponding to rest. Likewise, “neural” time series corresponding to left primary visual cortex was generated by delaying the time series of right primary visual cortex by 0, 28, 56, 84, 112 points respectively, corresponding to 0–112 ms delays between time series in order to mimic

experimental data. Subsequently, corresponding simulated HRF-convolved fMRI time series was generated by the convolution of “neural” time series with Statistical Parametric Mapping (SPM)’s canonical HRF. Finally the simulated fMRI time series were obtained by down-sampling the simulated HRF-convolved fMRI time series with a factor of 250 (corresponding to the TR used in experimental data) and 5 Db white Gaussian noise was added to mimic thermal noise in the data. Totally 500 simulated fMRI signals were generated for each delay in order to sample the noise distribution adequately. The analyses described below were carried out for both the simulated and experimental data.

C. Dynamic Granger Causality Analysis

As mentioned above, conventional GC is incapable of separating temporal precedence due to spontaneous and stimulus-evoked brain activity. One possible approach for inferring temporal precedence only from stimulus-evoked brain activity is to show that Granger causal estimates covary with the experimental paradigm. Such modulation can confirm temporal precedence due to stimulus-evoked activity and rule out temporal precedence from spontaneous activity. However, conventional GC can only provide one connectivity measure for the entire experiment, because it assumes that the model coefficients are stationary and invariant across time as shown below. Let two fMRI time series from two cortical regions be represented as $[x(t) \ y(t)]$. The fMRI time series can be input into a bivariate autoregressive model [4] as follows:

$$\begin{bmatrix} x(t) \\ y(t) \end{bmatrix} = \begin{bmatrix} 0 & a_{12}(0) \\ a_{21}(0) & 0 \end{bmatrix} \times \begin{bmatrix} x(t) \\ y(t) \end{bmatrix} + \sum_{n=1}^p \begin{bmatrix} a_{11}(n) & a_{12}(n) \\ a_{21}(n) & a_{22}(n) \end{bmatrix} \times \begin{bmatrix} x(t-n) \\ y(t-n) \end{bmatrix} + \begin{bmatrix} e_1(t) \\ e_2(t) \end{bmatrix} \quad (1)$$

Where p is the order of the model [19], a are the model coefficients and e is the model error. We chose a model order of 1 since the timing differences between bilateral visual cortices we were trying to detect is less than 1 TR. Note that $a(0)$ represent the instantaneous influences between time series while $a(1)$ represent the causal influences between time series. The effect of instantaneous correlation on causality can be minimized by modeling both instantaneous and causal terms in a single model as shown before [16]. The model coefficients were allowed to vary as a function of time in order to make the bivariate autoregressive model (i.e. Eq.1) dynamic as given below.

$$\begin{bmatrix} x(t) \\ y(t) \end{bmatrix} = \begin{bmatrix} 0 & a_{12}(0, t) \\ a_{21}(0, t) & 0 \end{bmatrix} \times \begin{bmatrix} x(t) \\ y(t) \end{bmatrix} + \sum_{n=1}^p \begin{bmatrix} a_{11}(n, t) & a_{12}(n, t) \\ a_{21}(n, t) & a_{22}(n, t) \end{bmatrix} \times \begin{bmatrix} x(t-n) \\ y(t-n) \end{bmatrix} + \begin{bmatrix} e_1(t) \\ e_2(t) \end{bmatrix} \quad (2)$$

Considering the model coefficients $a_{ij}(n,t)$ as a state vector of a Kalman filter, they were adaptively estimated using the algorithm proposed by Arnold et al. [17]. Unlike ordinary least squares used to estimate static autoregressive models (i.e. without time-varying coefficients) which use all the data to fit the model at once, the Kalman filter framework allows for recursive estimation of parameters so that the system will not become under-determined. Dynamic Granger causality (dGC), which is a function of time, was then obtained as follows:

$$dGC_{X \rightarrow Y}(t) = \sum_{n=1}^p |a_{21}(n, t)| \quad (3)$$

$$dGC_{Y \rightarrow X}(t) = \sum_{n=1}^p |a_{12}(n, t)| \quad (4)$$

A similar metric has been previously used in the static case [18]. The dGC model was used to get $X \rightarrow Y$ and $Y \rightarrow X$ connectivity time series for all subjects and delays using a model order of one. The forgetting factor for the Kalman filter was estimated based on minimization of relative error variance [13]. Subsequently, we calculated dynamic Granger causality difference (dGCD) time series as follows:

$$dGCD(t) = dGC_{X \rightarrow Y}(t) - dGC_{Y \rightarrow X}(t) \quad (5)$$

dGCD time series is to infer the difference in timing between X and Y. The reason of using Granger causality difference instead of original individual GC for the following analysis is that it can solve the inference problems mentioned in Roebroeck et al [5]. If dGCD is larger than zero, it means that the precedence is from X to Y at the specific time point and vice versa if dGCD is negative.

D. Covariance of Connectivity with Experimental Paradigm

A time series representing the experimental paradigm ("Paradigm" in Eq.6 below) was generated by the convolution of the stimulus boxcar function with Statistical Parametric Mapping (SPM)'s canonical HRF. Fig. 3 shows the stimulus function and the time series representing the experimental paradigm. In order to evaluate how dGCD covaried with the experimental paradigm, a linear regression model (LR) was used, considering the dGCD time series as the response variable and the experimental paradigm as the predictor variable [11,12] as shown in Eq.6, where β_1 is a coefficient and $e(t)$ is the model error.

$$dGCD(t) = \beta_1 \times \text{Paradigm}(t) + e(t) \quad (6)$$

The t -value obtained from the LR is a statistic indicating the significance of the coefficient β_1 and hence represents the strength of co-variance between dGCD time series and the experimental paradigm. For each delay, we obtained 500 t -values for simulation data and 5 t -

values corresponding to experimental data from five subjects, respectively. Subsequently, a one-side z -test was performed to examine whether the sample represented by the t -values had a mean significantly larger than zero. Since we have only one dependent variable in the LR model, we could use either β or t value. In more general case, if we have more than two dependent variables, using t value in the z -test is more suitable. The null hypothesis of z -test was that the sample belonged to a normal distribution with zero mean, and standard deviation of σ . For all z -tests, we set σ equal to the standard deviation of the t -values obtained by 0 ms delay. We used z -test (not to be confused with the commonly used z -score calculation) because we had the assumption that the t values for all the five delays should have same variance, equal to that obtained by a 0 ms delay. By using z -test, we can fix the variances and thus made a more fair comparison of p -values. Finally, we performed a linear regression considering the t -values as a function of the timing difference between the hemi fields in order to test whether the t -values significantly increased with increasing delay.

E. Comparison with cross-correlation function

The conventionally used metric for estimating delays between time series is the cross-correlation function which computes Pearson's correlation coefficient between two time series at various delays and infer the delay corresponding to the highest correlation coefficient as the time delay between the time series. Correlation analysis is the accepted gold standard for relative delay estimation when the "delay" is expressed in terms of the sampling period of the time series. However, in our case, we are trying to estimate a delay which is less than the sampling period. This delay is at the neural level, but we are trying to infer it from fMRI which is a smoothed and downsampled version of the neural signal. Therefore, the efficacy of correlation analysis for inferring neural delays from fMRI must be re-evaluated. The strength of such inference will likely increase with increasing delay. Therefore, we compared the efficacy of dGCD with that of the conventionally used cross-correlation function for inferring neural latencies. The minimum latency that can be inferred using the cross-correlation method is equal to the sampling period. The TR of the fMRI time series we used was 250 ms. Since we were interested in inferring sub-100 ms delays, we upsampled the data 25 times such that the resampled data had a sampling period of 10 ms. The upsampling method used here is called "spline interpolation", which is a fast, efficient and stable method and has been extensively used for interpolation in the past [20–22]. For each delay and subject, we obtained the cross-correlation function between the upsampled data from bilateral visual cortices. The delay corresponding to the maximum cross-correlation value was found in each case. A one-side z -test was performed to test whether the timing differences obtained from the cross-correlation function were significantly greater than zero, similar to the procedure adopted in the case of dGCD.

The up-sampling procedure described above is not a strictly analogous comparison with dGCD wherein we used the time series in its native temporal resolution. Therefore we further hypothesized that cross-correlation between X and Y at a time-shift of 1 TR should be significant for all delays except 0 ms. However, it was found that the cross-correlation between X and Y for 0 ms had a large bias. Therefore, we subtracted this bias from cross-correlation obtained from other delays and then used the z -test for each delay (in both simulated and experimental data), similar to the procedure adopted to test dGCD. Further,

we tested whether cross-correlation increases as a function of increasing delay between left and right hemi fields. We obtained the cross-correlation value between X and Y at 1-TR shift for each delay between the visual hemi fields. Subsequently we performed a linear regression regarding cross-correlation value at 1-TR shift as a function of the timing difference between the hemi fields. If the hypothesis holds true, the gradient should be significantly different from 0.

III. Results

A. Simulated Data

The dGC and cross-correlation analyses without up-sampling were applied on simulated data. Tables 1 and Table 2 show the simulation results using the two methods. Table 1 shows the statistics (i.e. z -value, mean, 95% confidence interval for mean, p -value) of a one-sided z -test used to test whether the 500 t -value sample obtained from simulated fMRI signals using the dGC model was significantly greater than zero. It indicated that dGCD significantly covaried with the experimental paradigm for all the delays except 0. Notable that since it is a one-sided test, all the right hand sides of 95% confidence intervals for mean are $+\infty$. Table 2 shows statistics of a one-sided z -test used to test whether the cross-correlation sample (obtained from 500 simulated fMRI time series) between X and Y at a time-shift of 1TR for non-zero delays is significantly greater than the mean value obtained with 0 ms delay. The results show that no significant correlation was detected for any delay using the cross-correlation analyses.

B. Experimental Data

Fig. 4 shows the t -values of the LR fit between the experimental paradigm and dGCD time series. Table 3 shows the statistics of a one-sided z -test used to test whether the t -value sample was significantly greater than zero. It is notable that no causality was detected for a delay of zero, while dGCD significantly covaried with the experimental paradigm for all other delays. Also, the significance of causality generally increased with increasing delay as evidenced by the significant positive relationship between t -values and the timing difference between visual hemi fields in the linear regression model ($p=0.004$). This indicates that dGCD derived from fMRI data was sensitive to even 28 ms latency and that the sensitivity increased with increasing delay time.

Fig. 5 shows the delays inferred from the cross-correlation function using up-sampled data on the y -axis and the true delays on the x -axis. The statistics of the one-sided z -test used to test whether the delays inferred from the cross-correlation function were significantly different from zero are shown in Table.4. It is apparent that the cross-correlation function with up-sampled data infers a delay when there is no true delay and does not infer a delay when there is one.

Fig. 6 shows the cross-correlation values between X and Y at a time-shift of 1 TR for all delays between X and Y. The cross-correlation between X and Y for 0 ms had a large bias, which can be problematic in experimental studies. Even after subtracting this bias from cross-correlation values at a time-shift of 1 TR obtained from other delays (28–112 ms), the

one-sided z -test was not significant for any delay. The corresponding statistics for the z -test are shown in Table.5. This demonstrates the inability of the cross-correlation framework to infer neuronal delays from fMRI data. The p -value for the linear regression was not significant ($p=0.31$), indicating that there is no significant increase of cross-correlation value with increasing timing difference.

IV. Discussions

There has been intense debate in the past 2 years regarding methods which are suitable to infer directional connectivity information from fMRI [23–27]. Simulations by Smith et al [28] showed that Patel's τ [29] was more suitable than lag-based methods such as Granger causality for detecting directional connectivity. However, studies conducted by different groups have shown that under certain conditions, such as fast sampling and hemodynamic variability being within a range typically observed in healthy individuals, Granger causality can faithfully capture directionality information from fMRI based on neuronal latencies [30–32,35]. The most recent and compelling experimental evidence in favor of Granger causality corresponds to the study by Katwal et al. which showed that using Granger causality for relative timing measurement and self-organizing maps for voxel selection, timing differences as low as 28 ms can be inferred from fMRI time series in bilateral visual cortices, which had experimentally controlled timing differences induced by time-lagged hemi-field stimulation [3]. This makes the data obtained from the Katwal et al.'s study ideal for testing and validating potential approaches for inferring latencies from fMRI.

However, it is notable that we are not aiming at improving the results from Katwal et al. in terms of the ability to detect neuronal lag. One outstanding issue with conventional GC is that it is sensitive to both spontaneous and stimulus evoked responses [8]. Our method is designed to be sensitive to only the stimulus-evoked response, and hence, may be more appropriate for task-based studies. Previous studies using both EEG [9,10] and BOLD fMRI data [11–13] have proposed that by estimating time-varying coefficients using a dynamic Granger causality model (dGC), temporal precedence due to stimulus-evoked BOLD responses can be separated from that due to spontaneous activity. Therefore, in this study, we have reused the data from the study conducted by Katwal et al. [3] to demonstrate and validate the use of dynamic Granger causality to infer tens of milliseconds of stimulus-evoked timing differences from BOLD fMRI. In order to be consistent with the study by Katwal et al., we used dynamic Granger causality difference between bilateral visual cortices as our metric.

We tested three primary hypotheses. First, whether the covariance of dynamic Granger causality difference with the experimental paradigm was non-significant for a delay of 0 ms. This was indeed the case as shown in the simulation and experimental results of Tables 1 and Table.3, respectively, wherein the null result would indicate that there was no underlying timing difference. Second, the amount of covariance of dynamic Granger causality difference with the experimental paradigm must increase with increasing latency. The increasing t -value of the LR in Fig. 4 (and decreasing p -value in Table 1 for simulated data and Table.3 for experimental data) as well as a significant linear relationship (as ascertained through a regression model) between t -values and timing differences supports this

hypothesis. Consequently, the t -value can be interpreted as proportional to the amount of latency between the time series, though the dGC method is not designed to explicitly estimate the latency. Third, we hypothesized that even for a 28 ms delay, we would find significant ($p < 0.05$) covariance between dynamic Granger causality difference and the experimental paradigm. This was proven right as shown from the simulation results shown in Table.1 and experimental results shown in Table.3. Results obtained from the conventionally used cross-correlation function demonstrated its inability to infer neuronal latencies from both simulated and experimental fMRI data. However, this must not be construed as a generalization to inference of delays from cross-correlation analyses of time series in other contexts wherein the delays maybe comparable to or greater than the sampling period.

The potential utility of the proposed method is primarily for investigating task-based directional connectivity between brain regions. Since the covariance of the experimental paradigm with dynamic effective connectivity can be inferred, much like the inference of the covariance of the experimental paradigm with the BOLD signal in traditional LR-based activation analysis, the rich set of tools and experimental designs available for traditional activation analysis can be readily used for connectivity analysis. Another potential application of the proposed method, which is not the primary focus of the current paper, is the investigation of ongoing spontaneous activity on evoked responses. It has been demonstrated that ongoing activity profoundly impacts trial-to-trial variability in task-evoked responses as well as behavior [39]. However, it is yet unclear how intrinsic directional connectivity during ongoing (spontaneous) activity impacts connectivity evoked by subsequent external stimulus and whether such relationships are salient for trial-to-trial variability in behavior. This question assumes greater importance in the context of the Bayesian hypothesis of brain function which proposes that intrinsic activity provides top-down predictions of sensory input while extrinsic activity causes bottom-up prediction errors based on incoming sensory information, and the brain compares both to minimize the surprise (or variational free-energy) due to prediction errors [40,41]. Future studies may test the validity of these notions by using the proposed dynamic connectivity approach which enables the segregation of intrinsic and evoked directional connectivities in the brain.

Finally, we provide a few cautionary notes for interpreting the results presented in this report. First, given the confounding effect of the variability of the hemodynamic response [33,34] on Granger causal estimates obtained from BOLD fMRI [35,36], it is noteworthy that hemodynamic variability was probably not a factor influencing the results of both the Katwal et al.'s study [3] as well as the current study since left and right visual cortices are likely to have the same hemodynamics as they are fed by a common hemodynamic source. Also the monotonic increase in GC measures with the experimentally-controlled delays denotes a task-related effect and rules out hemodynamics as the cause of our results. However, if the proposed dGC technique is applied to other situations where this may not be the case, we recommend that the dGC model be applied on deconvolved fMRI data [37,38]. Second, the performance of the dGC model was aided by the high SNR obtained from the 7T magnet as well as high temporal resolution provided by a TR of 250 ms. More studies are required to ascertain the applicability of these results at lower field strengths and longer TRs. Third, our results should be interpreted within the framework of inferring neuronal

delays as one of the indirect measures of directional connectivity. Neuronal delays are an established electrophysiological signature of directional connectivity; however the activity of region A may directionally influence (or predict) the activity of region B regardless of an explicit delay between the activities obtained from both the regions. Fourth, cross-correlation is a gold standard for estimating delays between time series. However, we did not find it to be useful for inferring neural delays from fMRI data, which is a special case where the delays are lesser than the sampling period. Therefore, the performance of cross-correlation in our context must not be generalized to other situations where the delays may be comparable or greater than the sampling period in which case cross-correlation may work well.

V. Conclusion

In this study, dynamic Granger causality analysis was performed to detect sub-100ms timing differences in BOLD responses from the visual cortex. While Katwal et al. [3] demonstrated this possibility using conventional Granger causality, our proposed dynamic Granger causality metric relies on experimental modulation of causality with time. Consequently, the proposed model was able to infer only stimulus-evoked (and not spontaneous) neural timing differences. In summary, our experimental validation of dynamic Granger causality to detect sub-100ms (as small as 28 ms) timing differences provides a reliable data-driven method for effective connectivity analysis of task-based fMRI data.

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References

1. Menon R, Kim SG. Spatial and temporal limits in cognitive neuroimaging with fMRI. *Trends Cogn Sci*. Jun.1999 3:207–216. [PubMed: 10354573]
2. Menon R, Luknowsky D, Gati J. Mental chronometry using latency-resolved functional MR. *Proc Natl Acad Sci U S A*. Sep.1998 95:10902–10907. [PubMed: 9724802]
3. Katwal S, Gore J, Gatenby J, Rogers B. Measuring relative timings of brain activities using FMRI. *Neuro Image*. Feb; 2013 66(1):436–448. [PubMed: 23110880]
4. Granger C. Investigating causal relations by econometric models and cross-spectral methods. *Econometrica*. Jul.1969 37:424–438.
5. Roebroeck A, Formisano E, Goebel R. Mapping directed influence over the brain using Granger causality and fMRI. *Neuroimage*. Mar; 2005 25(1):230–242. [PubMed: 15734358]
6. Deshpande G, LaConte S, James G, Peltier S, Hu X. Multivariate Granger causality analysis of brain networks. *Human Brain Mapping*. Apr; 2009 30(4):1361–1373. [PubMed: 18537116]
7. Dhamala M, Rangarajan G, Ding M. Estimating Granger causality from fourier and wavelet transforms of time series data. *Physical Review Letters*. Jan.2008 100(1):018701. [PubMed: 18232831]
8. Ryali S, Supekar K, Chen T, Menon V. Multivariate dynamical systems models for estimating causal interactions in fMRI. *Neuro Image*. Jan; 2011 54(2):807–23. [PubMed: 20884354]
9. Hesse W, Moller E, Arnold M, Schack B. The use of time-variant EEG Granger causality for inspecting directed interdependencies of neural assemblies. *Journal of Neuroscience Methods*. Jan; 2003 124(1):27–44. [PubMed: 12648763]

10. Astolfi, Ls, Cincotti, F., Mattia, D., De Vico Fallani, F., Tocci, A., Colosimo, A., ... Babiloni, F. Tracking the time-varying cortical connectivity patterns by adaptive multivariate estimators. *IEEE Transactions on Biomedical Engineering*. Mar.2008 55:902–913. [PubMed: 18334381]
11. Lacey S, Hagtvedt H, Patrick V, Anderson A, Stilla R, Deshpande G, ... Sathian K. Art for reward's sake: Visual art recruits the ventral striatum. *Neuro Image*. Mar.2011 55:420–433. [PubMed: 21111833]
12. Kapogiannis D, Deshpande G, Krueger F, Thornburg M, Grafman J. Brain Networks Shaping Religious Belief. *Brain Connectivity*. 2013 in press.
13. Havlicek M, Jan J, Brazdil M, Calhoun V. Dynamic Granger causality based on Kalman filter for evaluation of functional network connectivity in fMRI data. *Neuro Image*. Oct.2010 53:65–77. [PubMed: 20561919]
14. Katwal S, Gore J, Rogers B. Unsupervised spatiotemporal analysis of fMRI data using graph-based visualizations of self-organizing maps. *IEEE Transactions in Biomedical Engineering*. Sep.2013 60:2472–2483.
15. Akaike H. A new look at the statistical model identification. *IEEE Transactions on Automatic Control*. Dec.1974 9:716–723.
16. Deshpande G, Sathian K, Hu X. Assessing and Compensating for Zero-lag Correlation Effects in Time-lagged Granger Causality Analysis of fMRI. *IEEE Transactions on Biomedical Engineering*. Jun.2010 57:1446–1456. [PubMed: 20659822]
17. Arnold M, Miltner W, Witte H, Bauer R, Braun C. Adaptive AR Modeling of Nonstationary Time Series by Means of Kalman Filtering. *IEEE Transactions on Biomedical Engineering*. May.1998 45:553–562. [PubMed: 9581053]
18. Kaminski M, Ding M, Truccolo W, Bressler S. Evaluating causal relations in neural systems: Granger causality, directed transfer function and statistical assessment of significance. *Biological Cybernetics*. Aug.2001 85:145–157. [PubMed: 11508777]
19. Schwarz G. Estimating the dimension of a model. *Annals of Statistics*. 1978; 6:461–464.
20. Schoenberg I. Spline functions and the problem of graduation. *Proceedings of the National Academy of Sciences of the United States of America*. Oct.1964 6:947–950.
21. Thévenaz P, Blu T, Unser M. Interpolation revisited [medical images application]. *IEEE Transactions on Medical Imaging*. Jul.2000 19:739–758. [PubMed: 11055789]
22. Lehmann T, Gönner C, Spitzer K. Survey: Interpolation methods in medical image processing. *IEEE Transactions on Medical Imaging*. Nov.1999 18:1049–1075. [PubMed: 10661324]
23. Friston K. Causal modelling and brain connectivity in functional magnetic resonance imaging. *PLoS Biology*. Feb.2009 7:e33. [PubMed: 19226186]
24. Deshpande G, Sathian K, Hu X, Buckhalt K. A rigorous approach for testing the constructionist hypotheses of brain function. *Behavioral and Brain Sciences*. Jun.2012 35:148–149. [PubMed: 22617657]
25. Deshpande G, Hu X. Investigating effective brain connectivity from FMRI data: past findings and current issues with reference to granger causality analysis. *Brain Connectivity*. Oct.2012 2:235–245. [PubMed: 23016794]
26. Roebroeck A, Formisano E, Goebel R. The identification of interacting networks in the brain using fMRI: Model selection, causality and deconvolution. *Neuro Image*. Sep.2011 58:296–302. [PubMed: 19786106]
27. Bressler S, Seth A. Wiener-Granger Causality: A well established methodology. *Neuro Image*. Sep. 2011 58:323–329. [PubMed: 20202481]
28. Smith S, Miller K, Salimi-Khorshidi G, Webster M, Beckmann C, Nichols T, ... Woolrich M. Network modelling methods for FMRI. *Neuro Image*. Jan.2011 54:875–891. [PubMed: 20817103]
29. Patel R, Bowman F, Rilling J. A Bayesian approach to determining connectivity of the human brain. *Human Brain Mapping*. Mar.2006 27:267–276. [PubMed: 16092131]
30. Seth A, Chorley P, Barnett L. Granger causality analysis of fMRI BOLD signals is invariant to hemodynamic convolution but not downsampling. *Neuro Image*. Jan.2013 65:540–555. [PubMed: 23036449]
31. Wen X, Rangarajan G, Ding M. Is Granger causality a viable technique for analyzing fMRI data? *PLoS ONE*. Jul.2013 8:e67428. [PubMed: 23861763]

32. Schippers M, Renken R, Keysers C. The effect of intra- and inter-subject variability of hemodynamic responses on group level Granger causality analyses. *Neuro Image*. Jul.2011 57:22–36. [PubMed: 21316469]
33. Aguirre G, Zarahn E, D’Esposito M. The variability of human, BOLD hemodynamic responses. *Neuro Image*. Nov.1998 8:360–369. [PubMed: 9811554]
34. Handwerker D, Ollinger J, D’Esposito M. Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses. *Neuro Image*. Apr.2004 21:1639–1651. [PubMed: 15050587]
35. David O, Guillemain I, Saillet S, Reyt S, Deransart C, Segebarth C, Depaulis A. Identifying Neural Drivers with Functional MRI: An Electrophysiological Validation. *PLoS Biology*. Dec.2008 6:2683–2697. [PubMed: 19108604]
36. Deshpande G, Sathian K, Hu X. Effect of hemodynamic variability on Granger causality analysis of fMRI. *Neuro Image*. Sep.2010 52:884–896. [PubMed: 20004248]
37. Havlicek M, Friston K, Jan J, Brazdil M, Calhoun V. Dynamic modeling of neuronal responses in fMRI using cubature Kalman filtering. *Neuro Image*. Jun.2011 56:2109–2128. [PubMed: 21396454]
38. Wu G, Liao W, Stramaglia S, Ding J, Chen H, Marinazzo D. A blind deconvolution approach to recover effective connectivity brain networks from resting state fMRI data. *Med Image Anal*. Apr. 2013 17:365–374. [PubMed: 23422254]
39. Sadaghiani S, Hesselmann G, Friston K, Kleinschmidt A. The relation of ongoing brain activity, evoked neural responses, and cognition. *Front Syst Neurosci*. Jun.2010 :4.
40. Friston K. The free-energy principle: a rough guide to the brain? *Trends Cogn Sci*. Jul.2009 13:293–301. [PubMed: 19559644]
41. Friston K. The free-energy principle: a unified brain theory? *Nat Rev Neurosci*. Feb.2010 11:127–138. [PubMed: 20068583]

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Fig. 1.

The stimulus paradigm. Adapted from Katwal et al 2012 with permission.

Fig. 2. Selected voxels using SOM method, where right hemisphere (red) and left hemisphere (blue) were manually divided. Adapted from Katwal et al 2012 with permission

Fig. 3.
Stimulus boxcar function and experimental paradigm

Fig. 4. t-values for the LR fit between dGCD and experimental paradigm versus delay times. The dotted line represents the linear regression of t-values with respect to delay which was statistically significant ($p=0.004$)

Fig. 5. Delays inferred from the cross-correlation function on the y-axis and the true delays on the x-axis.

Fig. 6.

Cross-correlations between X and Y at a time-shift of 1TR versus delay times. The dotted line represents the linear regression of cross-correlation values with respect to delay which was statistically insignificant ($p=0.31$). The solid line represents the mean value of cross-correlation obtained from 0 ms delay between X and Y and hence represents the bias.

TABLE I

Statistics of a one-sided z-test used to test whether the t-value sample (obtained from 500 simulated fMRI time series) has a mean significantly greater than zero at each delay between the visual hemifields.

Delay (ms)	z-value	Mean of t-values	95% confidence interval for mean	p-value
0	0.9982	0.1393	$(-0.0902, +\infty)$	0.1591
28	2.3457	0.3274	$(0.0978, +\infty)$	0.0095
56	3.1301	0.4368	$(0.2073, +\infty)$	8.74×10^{-04}
84	4.5836	0.6397	$(0.4101, +\infty)$	2.28×10^{-06}
112	6.5839	0.9188	$(0.6893, +\infty)$	2.29×10^{-11}

TABLE II

Statistics of a one-sided z-test used to test whether the cross-correlation value sample (obtained from 500 simulated fMRI time series) between X and Y at a time-shift of 1TR for non-zero delays is significantly greater than the mean value obtained with 0 ms delay.

Delay (ms)	z-value	Mean of cross correlation values at 1TR-shift	95% confidence interval for mean	p-value
28	-3.8151	0.0357	(0.0356,+ ∞)	0.9999
56	-3.5292	0.0357	(0.0356,+ ∞)	0.9998
84	-6.1076	0.0356	(0.0356,+ ∞)	1
112	-7.3318	0.0356	(0.0356,+ ∞)	1

TABLE III

Statistics of a one-sided z-test used to test whether the t-value sample (obtained from the LR fit between the experimental paradigm and dGCD time series) has a mean significantly greater than zero at each delay between the visual hemifields.

Delay (ms)	z-value	Mean of t-values	95% confidence interval for mean	p-value
0	1.2157	1.2396	$(-0.4375, +\infty)$	0.1120
28	2.7104	2.7636	$(1.0865, +\infty)$	0.0034
56	2.1944	2.2375	$(0.5604, +\infty)$	0.0141
84	4.8846	4.9804	$(3.3033, +\infty)$	5.18×10^{-07}
112	6.8455	6.9798	$(5.3026, +\infty)$	3.81×10^{-12}

TABLE IV

Statistics of a one-sided z-test used to test whether the delays inferred from the cross-correlation function using upsampled data were significantly different from zero

Delay (ms)	z-value	Mean of delays inferred from cross correlation function	95% confidence interval for mean	p-value
0	2.4112	50	(15.8916,+ ∞)	0.0079
28	-2.5077	-52	(-86.1084,+ ∞)	0.9939
56	-0.4822	-10	(-44.1084,+ ∞)	0.6852
84	-8.5839	-178	(-212.1084,+ ∞)	1
112	-0.9645	-20	(-54.1084,+ ∞)	0.8326

TABLE V

Statistics of a one-sided z-test used to test whether the cross-correlation between X and Y at a time-shift of 1TR obtained from non-zero delays is significantly greater than the mean value (i.e. 0.6732) obtained with 0 ms delay.

Delay (ms)	z-value	Mean of cross correlation values at 1TR-shift	95% confidence interval for mean	p-value
28	-0.6714	0.6009	(0.4238,+ ∞)	0.7491
56	-0.2347	0.6479	(0.4709,+ ∞)	0.5929
84	-0.1388	0.6583	(0.4812,+ ∞)	0.5552
112	1.0196	0.7829	(0.6059,+ ∞)	0.1540