Analyzing MEG Data with Granger Causality: Promises and Pitfalls

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Contents

Abstract

In this chapter we begin by introducing the basic idea of Granger causality and discussing its applications to local field potential data. We then proceed to comment on recent results of applying Granger causality to MEG data. Recognizing that Granger causality is frequently used to examine neural activity recorded during stimulus processing, we point out the adverse effects of the inevitable trial-to-trial variability of stimulus-evoked responses on Granger causality estimation. We end the chapter by discussing the future prospects of using Granger causality in basic and clinical neuroscience research.

Keywords

Granger causality · MEG · Local field potential · Trial-to-trial variability · Stimulus-evoked responses

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1 Introduction

Cognitive functions are achieved through cooperative neural computation. Multi-sensor recording and functional imaging afford us the opportunity to study brain mechanisms of cognition from a network perspective. Analytically, cross correlation and ordinary coherence have been the main statistics for assessing the functional connectivity among the monitored nodes of a neuronal network. In the case of MEG, these nodes could be defined either in sensor space or in source space. These measures have the drawback that they do not provide information on the direction of information flow. As neural interactions are mediated by synaptic transmissions which are inherently directional, and the hypotheses concerning the role of network operations in cognitive paradigms become more elaborate, being able to assess the direction of information flow between neuronal ensembles is becoming increasingly important to better understand the organization and function of complex neural networks. Granger causality has emerged in recent years as a statistically principled way to furnish this capability. The goal of this chapter is to introduce the basic idea of Granger causality and discuss its various applications to local field potential (LFP) and MEG data. Important insights generated by this method are highlighted and a potential issue pointed out.

2 Granger Causality: Basic Idea and Applications to LFP Data

The basic idea of Granger causality can be traced back to Wiener (1956). He proposed that, for two simultaneously measured time series, one series can be called causal to the other if we can better predict the second series by incorporating past knowledge of the first one. This concept was later adopted and formalized by Granger (1969) in the context of linear regression models of stochastic processes. Specifically, if the variance of the prediction error for the second time series at the present time is reduced by including past measurements from the first time series in the linear regression model, then the first time series can be said to have a causal (directional or driving) influence on the second time series. One repeats the process to address the question of driving in the opposite direction by reversing the roles of the two time series. From this definition, it is clear that the flow of time plays an essential role in allowing inferences to be made about directions of causal influences from time series data.

Mathematically, the above idea can be further illustrated as follows. Let the two time series be denoted as $x_1, x_2, \ldots, x_n, \ldots$ and $y_1, y_2, \ldots, y_n, \ldots$. Suppose that one wants to predict the value of x_n from the linear combination of m previous values of the x-series: $a_1 x_{n-1} + a_2 x_{n-2} + \cdots + a_m x_{n-m}$. Because the time series came from a stochastic process, x_n can be written as $x_n = a_1 x_{n-1} + a_2 x_{n-2} + \cdots + a_m x_{n-m} + \varepsilon_n$, where ε_n is the prediction error. This is nothing but a single variable autoregressive (AR) model. The variance of the error series ε_n is a gauge of the prediction accuracy. Now consider the prediction of x_n by including the previous values of both x-series and y-series, namely, $x_n = b_1 x_{n-1} + b_2 x_{n-2} + \cdots + b_m x_{n-m} + c_1 y_{n-1} + c_2 y_{n-2} + \cdots + c_m y_{n-m} + \eta_n$. The variance of the error series η_n is a gauge of the prediction accuracy of the new expanded predictor. If var(η_n)/ var (ε_n) is less than one in some suitable statistical sense, meaning that the prediction of x_n is improved by incorporating the past knowledge of the y-series, then we say the y-series has a causal influence on the x-series. The role of the x- and y-series can be reversed to address the influence from x to y.

A comprehensive statistical framework has been developed to estimate Granger causality from experimental data in both the time and frequency domain (Geweke 1982; Ding et al. 2006). A key question is whether Granger causality, a statistically estimated measure of information flow, reflects physiological information flow mediated by action potential transmission. This question was considered by Bollimunta et al. (2008) in the context of alpha rhythm (8–12 Hz) generation. Alpha oscillations were discovered in the 1920s (Berger 1929). Prior to the 1970s, the thalamus was thought to be the generator of cortical alpha (Andersen and Andersson 1968). More recent studies using in vitro preparations have discovered the role of deep layer pyramidal cells in alpha pacemaking in cortical slice preparations (Silva et al. 1991). We took this finding as the "ground truth" for testing the validity of Granger causality and predicted that if multiple electrodes are placed simultaneously in different layers of the cortical column, because alpha activity measured at middle (layer 4) and superficial layers stems from synaptic transmission of alpha signals from deep layers, one should observe Granger causal influences from deep to middle and superficial layers in the alpha frequency band. Bollimunta et al. (2008) confirmed this prediction by analyzing laminar recordings from V2 and V4 in two awake behaving monkeys and thereby established the basis for interpreting Granger causality in terms of neuronal information flow. See Fig. 1a.

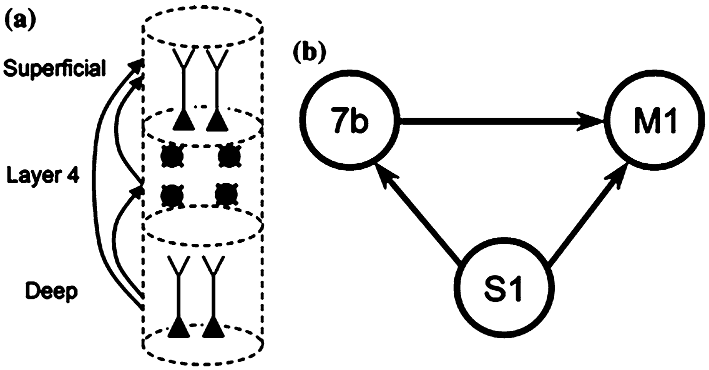

Fig. 1 (**a**) Granger causality graph for laminar alpha generation. (**b**) Granger causality graph for sensorimotor beta network

The crucial role of directional information provided by Granger causality in the formulation of scientific hypotheses was considered in another series of studies in awake behaving monkeys where local field potentials were recorded simultaneously from multiple sites in the sensorimotor system (Brovelli et al. 2004; Chen et al. 2006; Ding et al. 2006). From power spectral and coherence analysis, it was found that during the prestimulus period in which the monkey anticipated the stimulus onset by attending the computer monitor while holding steady a depressed mechanical lever, there are synchronized beta oscillations in three recording sites: primary motor (M1), primary somatosensory (S1), and posterior parietal area 7b. However, based on power and coherence alone, the functional significance of this oscillation network remains difficult to ascertain. The evaluation of Granger causality, yielding the pattern of causal interactions, (1) S → M1 (2) S1 → 7b and (3) 7b → M1, shown in Fig. 1b, overcame the problem. The following three reasons led to the hypothesis that the beta oscillation network may exist to support the steady pressure maintenance of the depressed lever. First, steady pressure maintenance is akin to closed loop control, and, as such, sensory feedback is expected to provide the input needed for cortical assessment of the current state of behavior. It is well known that the maintenance of sustained motor output is severely impaired when somatosensory input is lacking (Rothwell et al. 1982). This notion is consistent with our observation that S1 serves as the dominant source of causal influence to other areas in the network. Second, posterior parietal area 7b is known to be involved in the control of non-visually guided movement, and, as a higher-order association area, it maintains representations pertaining to the current goals of the motor system (Rushworth et al. 1997). This would imply that area 7b receives sensory updates from area S1 and outputs correctional signals to the motor cortex (M1). This conceptualization is consistent with the causality pattern in Fig. 1b. Third, previous data from M1 have already implicated beta range oscillations as a neural correlate of isometric pressure maintenance (Baker et al. 2003). By including S1 and 7b, the relation between M1 and the postcentral areas is further clarified. Clearly, in the formulation of the above hypothesis, the vivid computational picture in Fig. 1b derived from Granger causality played a crucial role.

3 Applications to MEG Data

Granger causality is increasingly applied to MEG data. With very few exceptions, the analysis is done in the source space. Three examples are considered here to illustrate the diversity of paradigms where this technique has been used to generate insights.

Moratti et al. (2011) analyzed MEG data recorded during the viewing of affective pictures with the goal to study the functional network organization associated with the generation of the magnetic homolog of the emotion-induced late positive potential (mLPP). The research question concerns whether the affective modulation of the mLPP is an automatic bottom-up response to motivationally salient stimuli or a response that reflects both bottom-up and top-down effects. To address this question requires the decomposition of neural interactions into their directional components. Reconstructing the source space time series of cortical activity by using the beamformer technique and computing time-domain Granger causality among predefined regions of interest (ROIs), they found that bidirectional influences between frontal and occipitoparietal cortex were stronger for emotional relative to neutral pictures, lending support to the hypothesis that mLPP reflects a combination of both bottom-up and top-down mechanisms.

Ploner et al. (2009) applied frequency-domain Granger causality to investigate functional integration among pain-related cortical regions. They conducted an MEG study using a simple reaction time paradigm in which painful and nonpainful stimuli were randomly applied to the right hand. Primary (S1) and secondary (S2) somatosensory cortices as well as primary motor cortex (M1) were source localized from evoked responses by a spatiotemporal source model (Hämäläinen et al. 1993) and were selected as ROIs. Time courses were computed using a linearly constrained minimum variance beamformer applied to the source locations. The Granger causality analysis revealed that there are causal influences from S1 to S2 during the processing of nonpainful stimuli but such influences are absent in the processing of painful stimuli. These results are taken to be in support of the proposition that there is a partially parallel organization of pain processing in the human brain.

Gow et al. (2008) applied Granger causality to simultaneously record MEG and EEG data to study whether the influence of lexical knowledge on speech perception takes the form of direct top-down influences on perceptual processing or it mainly involves feedforward convergence during decision-making. In their analyses, the minimum-norm estimate (MNE) and the noise-normalized MNE called dynamic statistical parametric mapping (dSPM) (Dale et al. 2000) were applied to estimate the time courses of activation across the cerebral cortex. MNE is an estimate of the actual activation time courses, whereas the dSPM provides a statistical measure that indicates regions where the estimated activity exceeds the estimated noise level. Therefore, dSPM was applied for identifying ROIs, but for analysis within and across ROIs, the MNE values were used. In their ROI identification, the 40 Hz gamma-band phase synchrony was considered as a mechanism for binding neural populations into transient cell assemblies. Thus a network of ROIs was identified based on the 40 Hz phase-locking values across the cortical surface to a reference region. The reference region, consisting primarily of the left posterior superior temporal gyrus (pSTG), was selected as the first area of increased cortical activity after stimulus onset. Within the identified network, the results of Granger causality analysis showed that the left supramarginal gyrus (SMG), known to be associated with wordform representation, influences phonetic processing in the left pSTG during a period of time associated with lexical processing. This finding provided evidence that lexical processes exert top-down influences on lower level phonetic perception.

4 Impact of Stimulus-Evoked Responses on Granger Causality Estimation

The LFP studies reviewed above mainly focus on ongoing neural activity in the absence of a transient sensory stimulus. The three MEG studies reviewed above, however, share a common feature in that they all focus on neural activity in the time period following the presentation of a transient sensory stimulus. Poststimulus neural activity can be written as the superposition of stimulus-evoked responses, which vary from trial to trial in both amplitude and latency, and ongoing activity which is assumed to be zero-mean (Xu et al. 2009). To estimate Granger causality from the ongoing activity, a common approach is to remove the average stimulus-evoked response from single trial data. Past work has shown that this approach leaves traces of stimulus-evoked response in the ongoing activity which can adversely impact Granger causality estimation (Wang et al. 2008). Without being cognizant of such adverse effects, Granger causality analysis can be misconstrued.

Granger causality analysis begins with the fitting of an autoregressive model to data (Ding et al. 2006). The common AR model formulation assumes that the input time series come from a zero-mean stationary stochastic process. To meet the zero-mean requirement, one typically computes the average event-related potential (ERP)/event-related field (ERF) and removes it from single trial data. Inherent in this practice is the assumption that ERP/ERF is invariant across trials. It is now clear that this assumption is overly simplistic and trial-to-trial variability of ERP/ERF is substantial (Wang et al. 2008; Liu et al. 2012). This means that removing the average ERP/ERF from single trial data will leave traces of stimulus-evoked response in the residual, which, as the following conceptual model illustrates, can significantly impact Granger causality analysis. A more thorough analysis of this problem can be found in Wang et al. (2008).

Consider two recording channels where ERP/ERFs are represented by sinusoids in Fig. 2a, b. ERP/ERF 2 (channel 2) (Fig. 2b) is 20 ms behind ERP/ERF 1 (channel 1) (Fig. 2a). The amplitude of the evoked response varies from trial to trial, and these variations are assumed to be correlated between the two recording sites. Physiologically, one may view ERP/ERF 1 as arising from a primary sensory area while ERP/ERF 2 from an association area. To calculate Granger causality between the two channels, we follow the traditional approach by first obtaining the average ERP/ERF and then subtracting the average from each trial to produce the residual data (Fig. 2c, d), which are then subjected to a sliding window analysis. For the 50 ms window between the two solid lines, the strong activity in channel 1 temporally precedes that in channel 2. Since these activities are correlated, by the definition of Granger causality, we will see a causal influence from channel 1 to channel 2. As the window is moved between the dashed lines, the opposite occurs. Specifically, the temporal precedence of strong activity in channel 2 over that in channel 1 will result in a causal influence from channel 2 to channel 1. In general, as the analysis window is moved through the entire trial, one may observe multiple episodes of causal influence reversals, depending on the morphology of

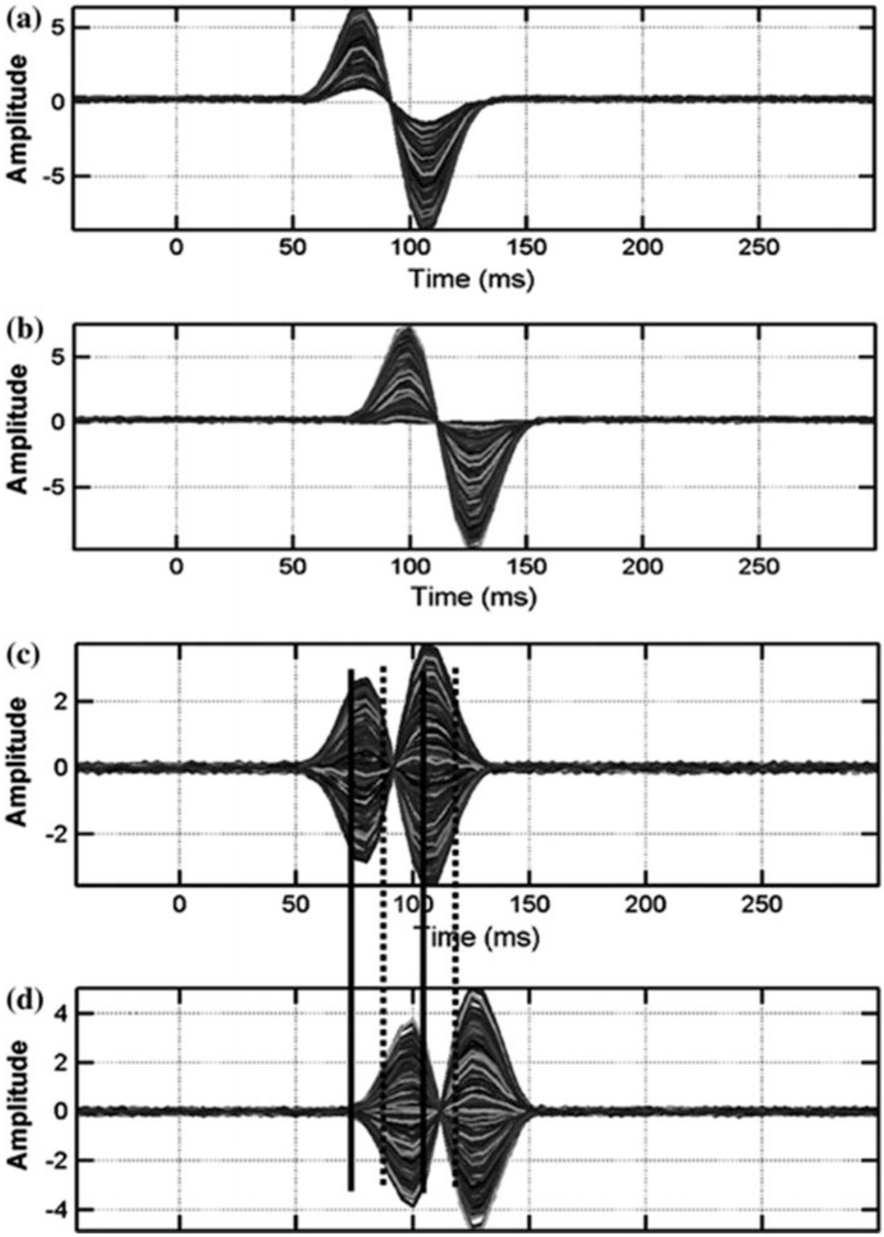

Fig. 2 A conceptual model illustrating the impact of trial-to-trial variability of stimulus-evoked response on Granger causality estimation. (**a** and **b**) Five hundred trials of simulated data from channel 1 and 2, respectively. (**c** and **d**) Residuals after subtracting the ensemble averages. Two analysis windows are delineated by the interval between the two solid lines and that between the two dashed lines. Vertical axis: arbitrary unit. (From Wang et al. (2008))

the ERP/ERFs. Such intricate temporal patterns of Granger causality modulations are clearly artifactual and are the result of three factors. First, the event-related responses from two different channels are of a similar shape and have different temporal onsets. Second, the two event-related responses have correlated trial-to-trial variability. Third, the time-frequency analysis of Granger causality is carried out by employing a small moving window. It is worth noting that an analysis with a long time window extending over the entire evoked response will result in a predominantly unidirectional driving from channel 1 to channel 2.

5 Concluding Remarks

Multivariate neural recordings promise unparalleled insights into how different areas of the brain work together to achieve thought and behavior and how such coordinated brain activity breaks down in disease. While the accumulation of data continues at an astonishing rate, how to effectively analyze these data to extract information about the workings of the brain remains a key challenge. Work over the past decade has established the importance of Granger causality in dissecting the directional interaction patterns in neuronal networks. As a tool for exploratory analysis, Granger causality is shown to be able to generate physiologically meaningful hypotheses, which can then be tested with further analysis and experimentation (Brovelli et al. 2004; Ding et al. 2006), while as a tool for confirmatory analysis, Granger causality can be used to test physiological hypotheses that are formulated according to consideration and knowledge existing outside the Granger causality analysis framework (Bollimunta et al. 2008).

Despite these promises there are also potential pitfalls associated with the application of Granger causality to MEG/EEG data. Discussions above pointed out the negative impact of the trial-to-trial variability of stimulus-evoked response on Granger causality estimation (Wang et al. 2008). One possible remedy for this problem is to remove evoked responses on a single trial basis (see Wang and Ding 2011; Schoffelen et al. 2017). Another problem, which is more of a concern in electrophysiological recordings such as LFP, EEG, and ECOG, has to do with the negative impact of common reference and volume conduction on connectivity measures. The possible remedy in this case is to perform the analysis in source space or after local referencing such as bipolar derivation to remove or attenuate the effect of common reference and volume conduction; (see Bollimunta et al. 2009; Trongnetrpunya et al. 2016).

These concerns notwithstanding, evidence so far suggests that Granger causality has a useful role to play in both basic and clinical neuroscience, complementing other methods. For many problems the framework for initiating and interpreting a Granger causality analysis is already established by the knowledge accumulated by years of research. For example, the neural substrate of a given behavior is often encapsulated in a network flow diagram with arrows connecting different structures emphasizing their respective roles and their interrelations with one another. An example derived from the literature on sensorimotor control is shown

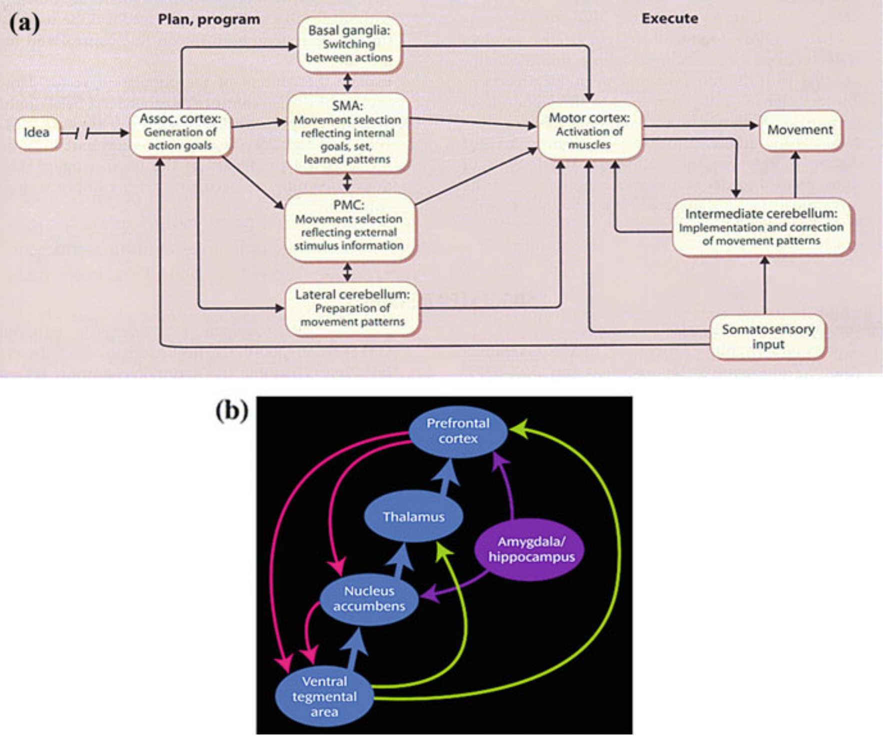

Fig. 3 (**a**) Diagram showing the functional relations among different brain areas involved in sensorimotor integration. (From Gazzaniga et al. (2002)). (**b**) Diagram showing the interactions of the mesocortical and mesolimbic circuits in drug addiction. (From Goldstein and Volkow (2002))

in Fig. 3a (Gazzaniga et al. 2002). Likewise, many neurological and psychiatric disorders involve abnormal cortical and subcortical circuit dynamics. The network mechanisms of these disorders are also expressed in diagrams similar to Fig. 3a. In the case of drug addiction, it has been shown that the nucleus accumbens, amygdala, and hippocampus comprise the mesolimbic system that is important in the reinforcing effects of drugs, whereas the prefrontal cortex, orbitofrontal cortex, and anterior cingulate comprise the mesocortical circuit known to mediate the conscious experience of drug intoxication. These brain areas are hypothesized to interact as illustrated in Fig. 3b (Goldstein and Volkow 2002). These diagrams are compiled from many studies using diverse techniques and could be used to formulate initial hypotheses for a Granger causality analysis and constrain the subsequent interpretation.

As the contributions in this volume demonstrate, MEG, offering superior temporal resolution over fMRI and superior spatial resolution over EEG, can be used to address many basic and clinical neuroscience questions. Because Granger causality can be applied to either sensor or source space, MEG has a significant role to play in quantifying the strength of interaction between different brain areas in normal and diseased circuits. It is expected that, with proper care and precaution, principled applications of Granger causality to MEG data will continue to grow, generating insights into the collective computation in the brain not possible with other methods.

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