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Testing methodologies for the nonlinear analysis of causal relationships in neurovascular coupling

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Abstract

We investigated the use and implementation of a nonlinear methodology for establishing which changes in neurophysiological signals cause changes in the blood oxygenation level-dependent (BOLD) contrast measured in functional magnetic resonance imaging. Unlike previous analytical approaches, which used linear correlation to establish covariations between neural activity and BOLD, we propose a directed information-theoretic measure, the transfer entropy, which can elucidate even highly nonlinear causal relationships between neural activity and BOLD signal. In this study we investigated the practicality of such an analysis given the limited data samples that can be collected experimentally due to the low temporal resolution of BOLD signals. We implemented several algorithms for the estimation of transfer entropy and we tested their effectiveness using simulated local field potentials (LFPs) and BOLD data constructed to match the main statistical properties of real LFP and BOLD signals measured simultaneously in monkey primary visual cortex. We found that using the advanced methods of entropy estimation implemented and described here, a transfer entropy analysis of neurovascular coupling based on experimentally attainable data sets is feasible.
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1. Introduction

The blood oxygenation level-dependent (BOLD) contrast recorded in functional magnetic resonance imaging (fMRI) experiments [1–3] is currently the most widely used signal to study the cognitive and sensory functions of the human brain. The BOLD signal, however, reflects neural activity only indirectly, and the relationship between neural activity and BOLD signal is only partly understood and remains debated [4–9]. Making further progress in the understanding of how changes in neural activity cause changes in BOLD signal is central to the progress of cognitive neuroscience.

Previous studies investigating the neurovascular coupling have mostly concentrated on establishing covariations between electrophysiological or electroencephalographic (EEG) recordings and BOLD fMRI or other related metabolic variables [4,6,7,9–13]. Such covariations were typically established using linear correlation analysis or linear regression between BOLD and electrophysiological signals [4,6,7,10–13]. While correlation analysis is suitable to establish neurophysiological correlates of BOLD signal changes, this methodology is not entirely suitable to elucidate what aspects of neural activity *cause* an observed BOLD signal change. The fundamental difference between correlation and causation can be illustrated by considering two signals X and Y driven (with a different delay) by a common input Z. In such case, there would be a temporal ordering between X and Y (e.g., an upstroke in signal X is followed by an upstroke in Y) and a high value of correlation between X and Y at a particular lag, but there is no causation between X and Y. In particular, there would be no gain in predictability of Y by also taking into account the history of X since the history of X cannot provide any information that was not already conveyed by the history of Y.

An effective approach to establish causal relationships is to use the causality principle formulated by Granger [14].

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Causality between signals can be defined in terms of the enhancement in predictability of future values of one signal (the effect) based on the history of the other signal (the cause), beyond the predictability achieved by considering only its own history. Using this principle, techniques from information theory (such as transfer entropy [15]) can provide quantitative measures of the amount of causation between neurophysiological and BOLD signals which are applicable even in the presence of strong nonlinearities in the considered signals and in neurovascular coupling. However, the application of information-theoretic causation measures to brain recordings is technically challenging because of the difficulties in computing information-theoretic quantities from limited samples of neuronal data [16]. This problem applies to the analysis of any neuroscience data set, but is particularly severe for the analysis of neurovascular coupling because the sampling frequency of BOLD fMRI signals is much lower than that of electrophysiological signals, and this severely limits the amount of joint data points in the time series of BOLD and electrophysiological signals.

In this article, we investigate the feasibility of causal analyses of neurovascular coupling by constructing a number of different algorithms for accurate and data-efficient estimation of information-theoretic causation measures, and we test their performance with simulated data with statistical properties designed to match that of concurrently recorded local field potentials (LFPs) and BOLD concurrently recorded from the primate visual cortex of an anaesthetized macaque.

The article is organized as follows. We first define and explain the information-theoretic measures of causation; we then construct the simulated LFP-BOLD time series; we introduce a number of different algorithms to estimate information-theoretic causation quantities; and we finally test how they can reduce bias and variance of the estimation and thus lead to a robust evaluation. The conclusion is that several algorithms allow an accurate measure and statistical test of significance of causation with data sets of size similar to that collected empirically during a recording session. This suggests that the algorithms presented here can be useful to determine new causal links between different aspects of neural activity and BOLD changes.

2. Information-theoretic measures of causal relationships

Causality methods compute directional measures of interactions between dynamical systems from their associated time series. This methodology has been established by the pioneering work of Wiener and Granger [14]. The definition of causality between two scalar valued time series X and Y observed from systems X and Y leans heavily on the idea that the cause occurs before the effect. If the knowledge of past values of X allows a better forecast of the value of Y better than the forecast obtained merely based on the knowledge of past values of Y, then the signal X is said to be a Granger cause of Y [14].

The amount of causal impact can be quantified as the net gain in predictability due to the added knowledge of the past of X. The keys to this measure are thus a way to predict time series and a measure of the prediction error, or uncertainty, in Y, given one or both histories. The original formulation of Granger used a linear regression for prediction and a mean square error as measure of prediction. This method will of course work well if the time series and their dependence are linear and when prediction errors are approximately Gaussian, but they will not be adequate if one of these assumptions is violated. To extend measures of causality beyond these assumptions, an information-theoretic causal measure called transfer entropy [15] has been developed.

To formally define transfer entropy (abbreviated to TE in the following) between neurophysiological signals and BOLD responses, let us start by denoting as *BOLD* the time series of the recorded BOLD signal from a given location and as *Ephys* the time series of a simultaneously acquired electrophysiological signal (e.g., the LFP power in a particular frequency band) down-sampled to the sampling rate of the BOLD time series. The formal definition of TE has the form of a difference of uncertainties (conditional entropies):

$$T_{Ephys\rightarrow BOLD} = H(BOLD_{\text{present}}\,|\,BOLD_{\text{past}}) - H(BOLD_{\text{present}}\,|\,BOLD_{\text{past}}, Ephys_{\text{past}}), \quad (1)$$

where the conditional entropies are then given by:

$$H(BOLD_{\text{present}}\,|\,BOLD_{\text{past}}) = \sum_{BOLD_{\text{past}}} p(BOLD_{\text{past}}) \sum_{BOLD_{\text{present}}} p(BOLD_{\text{present}}\,|\,BOLD_{\text{past}}) \times log_2 p(BOLD_{\text{present}}\,|\,BOLD_{\text{past}}) \quad (2)$$

and

$$H(BOLD_{\text{present}}\,|\,BOLD_{\text{past}}, Ephys_{\text{past}}) = \sum_{BOLD_{\text{past}}, Ephys_{\text{past}}} p(BOLD_{\text{past}}, Ephys_{\text{past}}) \times \sum_{BOLD_{\text{present}}} p(BOLD_{\text{present}}\,|\,BOLD_{\text{past}}, Ephys_{\text{past}}) \times log_2 p(BOLD_{\text{present}}\,|\,BOLD_{\text{past}}, Ephys_{\text{past}}). \quad (3)$$

Here, $p(BOLD_{\text{present}}|BOLD_{\text{past}})$ is the probability distribution of BOLD signal values at any given ("present") time conditional to the observation of a certain sequence of past values of the BOLD signal; and $p(BOLD_{\text{present}}|BOLD_{\text{past}}, Ephys_{\text{past}})$ is the distribution of present BOLD values conditional to the past history of both *BOLD* and *Ephys* signals; $p(BOLD_{\text{past}})$ is the distribution of sequences of past values of *BOLD*, and $p(BOLD_{\text{past}}, Ephys_{\text{past}})$ is the joint distribution of sequences of past values of *BOLD* and *Ephys*. Eq. (1) can be understood by noting that entropy is a measure

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