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Functional connectivity change as shared signal dynamics

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HIGHLIGHTS

- Interpretability limits of functional connectivity measures identified with modeling.
- Most connectivity measures can change with no brain region interaction change.
- Decomposition of correlation reveals covariance as an important check on results.
- Empirical tests demonstrate that covariance and correlation often differ in practice.
- Even when results are identical between methods covariance provides an important check.

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ABSTRACT

Background: An increasing number of neuroscientific studies gain insights by focusing on differences in functional connectivity—between groups, individuals, temporal windows, or task conditions. We found using simulations that additional insights into such differences can be gained by forgoing variance normalization, a procedure used by most functional connectivity measures. Simulations indicated that these functional connectivity measures are sensitive to increases in independent fluctuations (unshared signal) in time series, consistently reducing functional connectivity estimates (e.g., correlations) even though such changes are unrelated to corresponding fluctuations (shared signal) between those time series. This is inconsistent with the common notion of functional connectivity as the amount of inter-region interaction.
New method: Simulations revealed that a version of correlation without variance normalization – covariance – was able to isolate differences in shared signal, increasing interpretability of observed functional connectivity change. Simulations also revealed cases problematic for non-normalized methods, leading to a "covariance conjunction" method combining the benefits of both normalized and non-normalized approaches.
Results: We found that covariance and covariance conjunction methods can detect functional connectivity changes across a variety of tasks and rest in both clinical and non-clinical functional MRI datasets.
Comparison with existing method(s): We verified using a variety of tasks and rest in both clinical and non-clinical functional MRI datasets that it matters in practice whether correlation, covariance, or covariance conjunction methods are used.
Conclusions: These results demonstrate the practical and theoretical utility of isolating changes in shared signal, improving the ability to interpret observed functional connectivity change.

1. Introduction

Extensive neuroscientific research has identified consistent patterns of brain activity associated with a variety of behavioral processes. In trying to understand the systems-level mechanisms

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underlying these activation patterns, researchers have increasingly relied on functional connectivity—the statistical dependence among brain activity time series. Functional connectivity has been used across a wide variety of systems and a wide variety of neuroscientific approaches, such as functional MRI (fMRI), electroencephalography (EEG), and multi-unit recording (Nolte et al., 2004; Smith et al., 2011b; Buschman et al., 2012). Much of this research has focused on identifying the basic systems-level architecture of the brain via the detection of functional connections during resting state (Biswal et al., 2010; Brookes et al., 2011; Power et al., 2011; Yeo et al., 2011; Craddock et al., 2013). In order to link functional connectivity to cognition and behavior, however, researchers are increasingly focusing on functional connectivity differences. Such differences can be between groups (e.g., patients versus healthy controls), individuals (e.g., correlating with IQ), temporal windows (i.e., functional connectivity dynamics), or task conditions. We focus here on measuring and interpreting such functional connectivity differences.

Despite the common statistical definition of functional connectivity stated above, functional connectivity results are typically interpreted in terms of neural interactions. This is likely due to the distinction between what is of underlying theoretical interest – true neural interactions – and methodological reality. Therefore, we suggest that one can make progress here by reducing the gap between methods and the phenomena of theoretical interest. In other words, we suggest that any functional connectivity measure that more closely reflects true neural interactions is a better functional connectivity measure.

Here we developed a simulation framework to systematically characterize relationships between functional connectivity measures and ground truth interactions. We designed the framework (1) to involve signals (neurons/regions) influencing one another, and (2) to be as simple as possible to facilitate interpretation and to make as few assumptions about the true nature of brain region interactions as possible. Briefly, the framework involves simply summing Gaussian random time series consisting of shared signal (time series copied between source and target), unshared signal (time series that are not copied between source and target), and noise. The simulations allowed us to identify measures that better reflect neural interactions, highlighting the appropriateness of some functional connectivity measures over others when neural interaction changes are of primary interest.

The most common statistical measures used to estimate functional connectivity across a wide variety of neuroscientific approaches are Pearson correlation and related methods (e.g., coherence, partial correlation). These and many other common statistical measures utilize the concept of "percent variance explained" – dividing an estimate of shared variance by overall variance (i.e., variance normalization) – to produce standardized estimates of association. While these measures are frequently useful in other contexts, it was recently suggested that they are inappropriate for estimating functional connectivity differences (Friston, 2011)[1]. If true, this would have major implications for the study of brain network function, as an increasing number of studies use Pearson correlation and related measures when studying functional connectivity differences across groups, individuals, or conditions (Zalesky et al., 2012a, 2012b).

As an illustration of a limitation of Pearson correlation, it has been shown that increased noise in neuronal recordings decreases correlations between neuronal time series, even when the underlying neuronal interactions are unchanged (Behseta et al., 2009). The sensitivity of correlations to unshared signal (rather than noise per se) may be especially problematic, however, as this would reduce the interpretability of any detected functional connectivity difference. For instance, a significant change in inter-region correlation could be driven solely by increased neural processing by only one of the two tested brain regions. Thus, we use the term "unshared signal" to emphasize that these effects could be driven by functionally important neural processes. The same conclusions also apply to the more general concept of "unshared variance", which encompasses both signal and noise.

We used simulations to ground our systematic exploration of shared and unshared signal changes. These simulations revealed a functional connectivity method (covariance) immune to systematic bias from unshared signal. However, simulations also revealed that this method is sensitive to possible increases in overall variance/power that may be unrelated to true brain interaction change. We therefore developed a conjunctive method, in which a functional connectivity change is only considered significant if it is detected using both a variance normalized measure (e.g., correlation) and covariance. We then applied this method to empirical data, determining that it not only provides increased interpretability of results but also often provides results distinct from current methods in practice. These findings validate a new theoretical and methodological framework for characterizing functional connectivity differences, improving interpretability of brain network dynamics.

Due to the complex and potentially counterintuitive nature of the results, we encourage readers to run the simple simulations themselves, available here: https://github.com/ColeLab/simplesims/. Seeing and running the code may facilitate development of an improved intuition for the nature of these functional connectivity measures. Modifications of the code, including testing of other functional connectivity measures and different conditions, are encouraged as well.

2. Materials and methods

2.1. Functional connectivity estimation

Estimates of time series association were calculated using either MATLAB (version R2012a) or R (version 2.15.1). Covariance was the simplest measure we used, and was calculated as

$$\mathrm{cov} = XY = \sum_{i=1}^{n} \frac{\left(X_i - \bar{X}\right)\left(Y_i - \bar{Y}\right)}{n-1}$$

where X and Y are brain activity time series, n is the number of time points, and $\bar{X}$ and $\bar{Y}$ are the time series means.

Pearson correlation was calculated as

$$r = \frac{\mathrm{cov}_{XY}}{S_X S_Y} = \frac{\sum_{i=1}^{n}\left(X_i - \bar{X}\right)\left(Y_i - \bar{Y}\right)}{\sqrt{\sum_{i=1}^{n}\left(X_i - \bar{X}\right)^2}\sqrt{\sum_{i=1}^{n}\left(Y_i - \bar{Y}\right)^2}}$$

where S is the time series standard deviation. Most analyses also involved the Fisher's z-transform of the resulting Pearson correlation, which increases the dynamic range of correlation values beyond ±1.0. This is critical when investigating changes in functional connectivity, as forgoing the Fisher's z-transform would result in artificial restrictions in dynamics. The Fisher's z-transform:

$$Fz = a\tan h(r)$$

[1] Friston emphasized the inadequacy of Pearson correlations in terms of estimating indirect influences, undirected influences, and their tendency for changing due to changes in noise. We focus here on the last criticism, and touch upon the other criticisms in Section 4.