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Mixed signals: On separating brain signal from noise

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Abstract

Accurate description of human brain function requires the separation of true neural signal from noise. Recent work examining spatial and temporal properties of whole-brain fMRI signals demonstrates how artifacts from a variety of sources can persist after rigorous processing, and highlights the lack of consensus on how to address this challenge.

Keywords

artifact removal; functional connectivity; global signal regression; resting state fMRI

Text

When conducting studies of functional connectivity with resting state fMRI (Text Box), researchers typically go to great lengths to remove signals from the data that are not caused by neural activity. In early studies, the global signal (Text Box), considered to represent physiological noise caused by respiratory and cardiac events, was typically removed from the time series of each voxel through linear regression prior to subsequent analyses [1]. However, this practice of “global signal regression”, or GSR, came under later scrutiny for a number of reasons, one of which was the demonstration from electrophysiological recording studies in macaques that the global signal also includes neural components [2]. This and subsequent studies suggested that while artifacts (noise) may be represented in the global signal, neural activity (signal) is represented as well. This realization prompted the field to probe more closely whether the practice of GSR amounted to throwing the baby out with the bathwater.

Text Box

Resting state fMRI

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fMRI data collected in the absence of task performance. First introduced as a method for examining functional brain connectivity in 1995 [10]. Participants are typically instructed to rest and think of nothing in particular during data acquisition.

Global signal

In an fMRI dataset, the average value of all gray matter (brain) signals. Global signal is sometimes removed from an fMRI dataset prior to functional connectivity analysis, though this step is controversial [3]

Independent Component Analysis (ICA)

ICA is a model-free, data-driven approach whereby four-dimensional fMRI data is decomposed into a set of independent one-dimensional time series and associated three-dimensional spatial maps, which describe the temporal and spatial characteristics of the underlying signals or components. ICA is often used as a tool for removing motion and other artifacts from fMRI data in a process referred to as denoising [5].

Wavelet despiking

Wavelet despiking is an unsupervised, data-driven, wavelet-based method for modeling and removing motion artifacts from fMRI data. The method detects non-stationary events across different frequencies as chains of scale-invariant wavelet coefficients and removes them from the fMRI time series [8].

While controversies surrounding GSR and its consequences persist [3], empirical properties of global signals are relatively under-studied. Thus, the question “What exactly are we removing when we perform GSR?” is still open. Power and colleagues attempt to address this gap by analyzing six large, heterogeneous resting state fMRI datasets with an eye towards detecting relationships between the global signal and commonly observed artifacts. Strengths of this study include the examination of data collected at various sites, scanners, and MRI sequences from over 700 participants representing clinical and non-clinical populations across a wide age range. The authors systematically examine the spatial distribution of the global signal and note several key points: 1) global signal is most strongly represented in the gray matter, 3) subjects showing less variance in the global signal exhibit less head motion, 2) when more uniform patterns of global signal are observed, this typically can be attributed to scanner-related and coil artifacts, and 3) subjects with high levels of variance in global signal show high variance in heart rate and respiration. They conclude that a great deal of the variance in the global signal can be explained by respiratory variables, participant head motion, and scanner hardware-related artifacts.

These findings in and of themselves should not be surprising to researchers in the field. More surprising and disheartening is the finding that several widely-used fMRI processing methods fail to remove these global artifacts. Regression of motion parameters, regression of nuisance signals related to white matter, and incorporation of analytic pipelines explicitly modeling physiology all failed to adequately remove global artifacts. The authors argue that the multiple sources contributing to artifactual signals have yet to be unambiguously identified, and conclude by calling for the field to work towards developing novel denoising

strategies that isolate and remove global artifacts while preserving true neural global signals [4].

So where does this leave us? While providing no clear path forward, the authors do initiate a much-needed discourse on a topic of great relevance to cognitive and clinical neuroscience. However, their conclusions may be unnecessarily pessimistic. For example, the authors take the position that independent component analysis (ICA, Text Box) is unlikely to identify global signals, which have little spatial specificity. However, ICA has been shown to successfully remove motion-related noise from resting state fMRI data [5]. Head motion is a particularly problematic artifact in resting state fMRI, as demonstrated in earlier work drawing attention to the potential effects of head motion on functional connectivity estimates [6]. As Power and colleagues demonstrate that a large portion of global signal variance is related to head motion, it stands to reason that ICA denoising can remove a large portion of these artifactual signals. ICA approaches have the added benefit of leaving intact the integrity of the fMRI time series, so as to not destroy the autocorrelation structure of data and preserve the temporal time series characteristics. Recent analyses demonstrate that ICA denoising abolishes distance-dependence motion effects (eg. motion artifacts present in the data after ICA impact all functional connections between brain regions in consistent manner, independent of spatial distance between brain regions) [7]. Other denoising methods with these advantages have been proposed and successfully implemented, including wavelet despiking (Text Box) which is further able to accommodate the substantial spatial and temporal heterogeneity of motion artifacts [8]. ICA and wavelet approaches, when carefully applied, can thus at least partially ameliorate the confounding effects of head motion and other artifacts, and produce time series that can be further subjected to analyses aimed at characterizing temporal aspects of brain signals including dynamics.

Power and colleagues argue that the motivation for the current work is that “there is almost no information in the literature on the composition of the global signal in typical data, much less how well global signal can be broken into constituent signals worth preserving or discarding.” The real work now will be to discover the true nature of the global signal so that the neural signal from the noise can be separated with greater confidence. Towards this end, the best way forward is with simulated data, where the ground truth can be known. In one of the earlier papers bringing the GSR controversy to light, Saad and colleagues used models to demonstrate how GSR could artificially introduce correlations between brain regions and wildly distort group differences in interregional correlations [9]. Unlike with empirical fMRI data, simulated data from “model brains” are ideal for testing hypotheses surrounding the effects of certain types of artifactual signals on time series. With synthetic data, the investigator can set the parameters giving rise to the signal, and inject varying types of noise to systematically examine the influence on the time series. If the goal is to separate brain signal from noise to uncover the true nature of inter-regional interactions in the brain, moving towards these types of models will likely provide greater insight than trying to decipher the mixed signals we get from empirical data.

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