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The global signal in fMRI: Nuisance or Information?

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ABSTRACT

The global signal is widely used as a regressor or normalization factor for removing the effects of global variations in the analysis of functional magnetic resonance imaging (fMRI) studies. However, there is considerable controversy over its use because of the potential bias that can be introduced when it is applied to the analysis of both task-related and resting-state fMRI studies. In this paper we take a closer look at the global signal, examining in detail the various sources that can contribute to the signal. For the most part, the global signal has been treated as a nuisance term, but there is growing evidence that it may also contain valuable information. We also examine the various ways that the global signal has been used in the analysis of fMRI data, including global signal regression, global signal subtraction, and global signal normalization. Furthermore, we describe new ways for understanding the effects of global signal regression and its relation to the other approaches.

1. Introduction

The development of methods to mitigate the effects of noise has played a key role in the development of functional magnetic resonance imaging (fMRI). One approach that has gained widespread adoption is the removal of a global signal component, either as a preprocessing step or through its inclusion as a nuisance regressor in general linear model analyses. This approach is commonly referred to as global signal regression (GSR). However, the use of GSR has sparked a great deal of controversy, especially in the analysis of resting-state fMRI studies where some investigators routinely remove the effects of the global signal while others argue strongly against its use (Murphy et al., 2009; Fox et al., 2009; Saad et al., 2012; Burgess et al., 2016; Murphy and Fox, 2017).

At first glance, it is rather surprising that such a simple signal should spark so much debate. After all the computation of the global signal is straightforward – it is simply the mean of the voxel time-series within the brain. What could be controversial about projecting out the effects of this global signal? We believe that there are several factors that have led to the continuing controversy. First, because the global signal is a “catch-all” signal that reflects the contributions of a variety of noise components, it is not always clear what exactly GSR is removing. Second, while GSR is a fairly straightforward mathematical operation, it still involves the regression of a mean time course (with hundreds of time points or more) from each voxel time series in the brain (ranging from tens to hundreds of thousands of voxels), where the exact numbers of time points and voxels depends on the duration and the temporal and spatial resolutions of the acquisition. Due to the large size of the signal space, it can be difficult to understand the effects of GSR not only on the signals themselves but also on the relation (e.g. correlation) between signals from different regions. Furthermore, it has not been clear how well the arguments made with relatively low-dimensional simulations apply to the high-dimensional datasets obtained in experiments. Finally, with the growing evidence supporting a link between neural activity and the global signal, there has been some concern that GSR may also be removing information that is of interest.

Our goal in this paper is to provide a deeper understanding of the characteristics of the global signal and its role in the analysis of fMRI studies. We will begin by examining the components of the global signal, focusing primarily on the contributions due to low-frequency drifts, motion, physiological activity, and neural fluctuations. We will then review the use of the global signal in the analysis of both task-related and resting-state fMRI studies. Although our focus will be on GSR, we will also examine related methods such as global signal subtraction and global signal normalization. We will conclude with a look at emerging methods for understanding both the global signal and GSR.

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2. What is the global signal?

In this section, we review the basic properties of the global signal. Although the basic definition of the global signal is rather straightforward, we will see that there is considerable variability in the implementation of this definition. We will also build up an intuitive picture of the global signal as a time-varying measure of spatial homogeneity.

2.1. Computation of the global signal

The concept of the global signal was first introduced into the fMRI literature by Zarahn et al. (1997), who defined the global signal as the mean time course computed over all voxels within the brain. While the global signal can be calculated from the raw image time series, it is usually computed after some degree of preprocessing. However, the extent of the pre-processing can vary greatly across studies. In some studies, the global signal is computed after the application of a minimal set of preprocessing operations, typically consisting of some combination of image registration, slice-timing correction, and spatial smoothing (Power et al., 2014; Satterthwaite et al., 2013; Fox et al., 2005). For these studies, the global signal has been found to be most strongly correlated with signals from gray matter regions, with lower and more variable correlations observed for signals from white matter and ventricular regions (Power et al., 2014, 2016). In other studies, the global signal is calculated after minimal preprocessing and the removal of additional nuisance regressors, such as low-frequency trends, motion-related regressors, and white matter and cerebrospinal fluid signals (Erdogan et al., 2016; He and Liu, 2012; Zarahn et al., 1997). When external measures of cardiac and respiratory activity are available, additional physiological noise regressors can be removed from the data prior to the computation of the global signal (Wong et al., 2012, 2013).

Examples of the global signal from a representative scan previously analyzed in Wong et al. (2013) are shown in Fig. 1. Four different variations of the global signal are presented, corresponding to different sets of nuisance regressors, ranging from an empty set for the minimal preprocessing case (shown in blue) to a full complement of regressors, consisting of low-frequency, motion-related, physiological, and white matter and cerebrospinal fluid nuisance terms (shown in cyan). As the set of regressors is expanded, there is a clear decrease in the overall amplitude of the signal. This trend can also be seen in Fig. 2, where we have plotted the global signal amplitudes from 30 scans using each of the four preprocessing variations applied to data from Wong et al. (2013). Note that for the purpose of this paper and consistent with the terminology used in Wong et al. (2013), the term GS **amplitude** will refer to the standard deviation of the GS computed across all time frames within a scan. There is a wide range of amplitudes in the minimally processed data, and this range decreases as the set of nuisance regressors is expanded. By normalizing the amplitudes in each set by their respective values in the minimally processed case (i.e. the GS amplitude obtained with each pre-processing approach was divided by the amplitude obtained with minimal pre-processing), we can gain a sense of the average percent variance explained by each set of regressors. On average, the low-frequency and motion regressors explain 48% of the variance of the global signal. The addition of physiological noise regressors explains an additional 31% of the variance. Further addition of white matter and cerebrospinal fluid regressors explains another 14% of the variance. On average, only 7% of the variance of the minimally processed global signals remains after the contributions of the complete set of nuisance regressors have been removed.

What determines which form of the global signal should be used? When the primary goal is to remove global effects from the data, then the minimally processed version is typically used and the global signal is included as an additional nuisance regressor term in a general linear model (GLM) analysis of the data (Power et al., 2014). In this case there is no need to remove the other nuisance regressors from the global signal, since the GLM analysis projects out the signal component that lies in the signal subspace spanned by all of the nuisance regressors (including the global signal). On the other hand, when the primary goal is to further our understanding of the neural components of the global signal, then it is desirable to project out nuisance components that are thought to be unrelated to neural activity (Wong et al., 2013). However, as we shall discuss in more detail below, the determination of whether or not a nuisance component is unrelated to neural activity is not necessarily straightforward.

2.2. Normalization options

Another source of variabilty in the computation of the global signal arises from different choices in the normalization of the blood oxygenation level dependent (BOLD) fMRI signal. As the raw fMRI

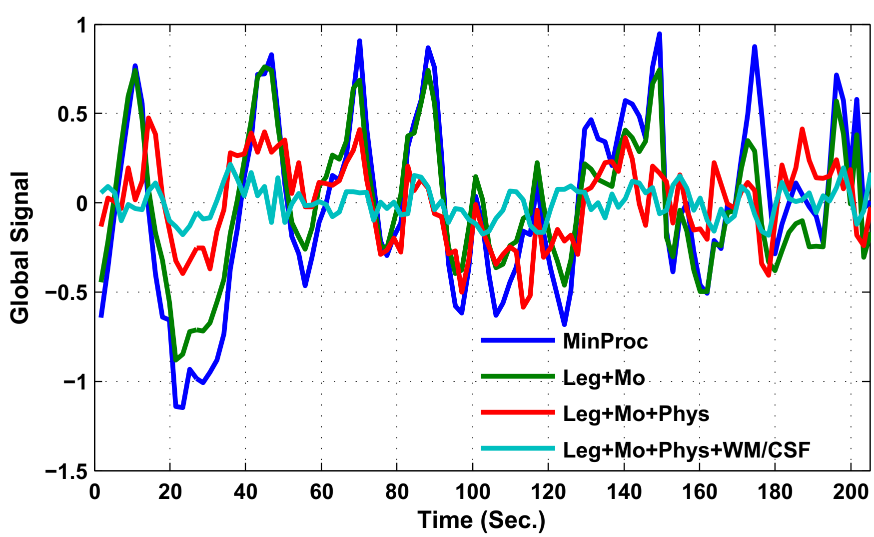

Fig. 1. Examples of global signal time series computed after (1) minimal preprocessing (MinProc, blue), (2) MinProc plus removal of low-frequency (Leg: Legendre polynomial) and motion-related (Mo) nuisance terms (Leg+Mo; green), (3) MinProc plus removal of low-frequency, motion-related, and physiological (Phys) nuisance terms (Leg+Mo+Phys; red), and (3) MinProc plus removal of low-frequency, motion-related, physiological, and white matter and cerebral spinal fluid (WM/CSF) nuisance terms (Leg+Mo+Phys+WM/CSF; cyan). WM and CSF regions were defined using partial volume thresholds of 0.99 for each tissue type and morphological erosion of two voxels in each direction to minimize partial voluming with gray matter. Additional details about the processing are provided in Wong et al. (2013).