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Resting-state fMRI confounds and cleanup

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ABSTRACT

The goal of resting-state functional magnetic resonance imaging (fMRI) is to investigate the brain's functional connections by using the temporal similarity between blood oxygenation level dependent (BOLD) signals in different regions of the brain "at rest" as an indicator of synchronous neural activity. Since this measure relies on the temporal correlation of fMRI signal changes between different parts of the brain, any non-neural activity-related process that affects the signals will influence the measure of functional connectivity, yielding spurious results. To understand the sources of these resting-state fMRI confounds, this article describes the origins of the BOLD signal in terms of MR physics and cerebral physiology. Potential confounds arising from motion, cardiac and respiratory cycles, arterial CO_2 concentration, blood pressure/cerebral autoregulation, and vasomotion are discussed. Two classes of techniques to remove confounds from resting-state BOLD time series are reviewed: 1) those utilising external recordings of physiology and 2) data-based cleanup methods that only use the resting-state fMRI data itself. Further methods that remove noise from functional connectivity measures at a group level are also discussed. For successful interpretation of resting-state fMRI comparisons and results, noise cleanup is an often over-looked but essential step in the analysis pipeline.

Introduction

Recently, resting-state fMRI has become an extremely popular area of research for neuroimagers as evidenced by the exponential growth in related publications per year (Birn, 2012). The goal of resting-state fMRI is to use the common variance of the fMRI blood oxygenation level dependent (BOLD) signals in different regions of the brain as an indicator of synchronous neural activity. The assumption is that the temporal similarity between the BOLD signals in each region demonstrates that they are in constant communication with one another and thus form a functional network. The popularity of the technique stems not only from the relative ease of data acquisition (the participants are not required to perform a task) but from the fact that resting-state networks are a phenomenon that fMRI, as a relatively young technique (~20 years), was the first to discover. Using resting-state fMRI, it is possible to simultaneously examine the relationship between multiple resting-state networks and independently measured behavioural traits, fuelling its popularity amongst neuroscientists and clinicians alike. The demonstration of resting-state networks has helped fMRI live up to its initial promise as a tool for investigating brain dynamics.

fMRI appears to be the ideal neuroimaging technique for the investigation of resting-state network characteristics. The spatial resolution is superior to other methodologies such as EEG and MEG, allowing for localization and separation of the various resting-state networks simultaneously. The relative lack of temporal resolution in the BOLD signal is not problematic since spontaneous neural fluctuations can be found in the low frequency range (Leopold et al., 2003). Furthermore, other work has demonstrated significant correlations between variations in the power of electrophysiological activity in higher frequency bands (e.g. alpha and beta) and resting-state fMRI signals (Laufs et al., 2003). However, despite the broad use of resting-state fMRI as a technique to investigate low-frequency BOLD fluctuations, the mechanisms that give rise to synchronous, spontaneous neural activity across brain regions remain largely unknown (Leopold and Maier, 2012). (These issues are addressed elsewhere in this *NeuroImage* special edition by Scholvinck).

Resting-state BOLD networks were first demonstrated by Biswal and colleagues in 1995 when spontaneous BOLD fluctuations in the left and right motor cortex were shown to be correlated in the absence of a task (Biswal et al., 1995). An early detailed analysis of the frequency spectrum of resting-state fMRI data demonstrated that low frequency fluctuations (defined as <0.1 Hz) contributed to more than 90% of the correlation coefficient between regions of the same resting-state network (Cordes et al., 2001). Furthermore, it was demonstrated the these low-frequency fluctuations have similar properties to task-related BOLD signals (Biswal et al., 1997; Cordes et al., 2001; Lowe et al., 1998; Peltier and Noll, 2002). Using the spontaneous oscillations measured with fMRI, many resting-state networks have been discovered that

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correspond well to functional networks activated by a variety of tasks (Smith et al., 2009). One of the most notable and studied networks is the default mode network (DMN) which has been shown to deactivate during cognitive tasks (McKiernan et al., 2003; Raichle et al., 2001). Although it was first demonstrated using PET (Raichle et al., 2001), resting-state fMRI has become the primary tool to investigate the DMN ever since it was shown to be functionally connected at rest (Greicius et al., 2003).

One weakness of resting-state fMRI lies in an important difference between the analysis of spontaneous fluctuations and more traditional studies of task-evoked BOLD responses. In the latter, the timing and intensity of the task are known a priori and the responses of many trials are combined together to eliminate noise and to increase statistical significance (Bandettini et al., 1993; Friston et al., 1995). However, in resting-state fMRI, functional connectivity is determined by measuring the temporal similarity of the BOLD time series in voxels using some metric, commonly the correlation coefficient. For example, in the original Biswal paper (Biswal et al., 1995), the correlation coefficient between the BOLD time series of a voxel in the motor cortex and every other voxel in the brain was calculated. Voxels whose correlation coefficient passed a statistical threshold were deemed to be functionally connected, thus revealing common spontaneous fluctuations between left and right motor cortices. Since the two time series are measured simultaneously, any non-neural activity-related process that affects one or both time series will affect the measure of functional connectivity, thus yielding a spurious result. These resting-state fMRI confounds cannot only increase the apparent functional connectivity by introducing spurious similarities between the time series', but also reduce the connectivity metric if differential confounds between regions are introduced. This can be particularly problematic if the temporal similarity metric is to be used to compare connectivity between groups that display physiological or behavioural differences whilst at "rest" in the scanner (Bright and Murphy, 2013; Murphy et al., 2011; Power et al., 2012; Van Dijk et al., 2012).

To understand the source of these resting-state fMRI confounds, thus providing us with avenues for removing them, we must first understand the origins of the BOLD signal itself.

Origin of the BOLD signal

A brief description of the origin of the BOLD signal, which is reviewed more comprehensively by introductory textbooks (Buxton, 2002; Jezzard et al., 2001), follows.

fMRI is mainly performed using gradient echo imaging techniques. The magnitude of the measured signal of a gradient echo sequence (S) depends on the initial magnetisation (M_0), the T_2^* decay time and the time at which the image is acquired, denoted TE, the echo time (see Fig. 1A).

M_0 depends directly on the number of excited spins in a voxel. T_2^* is the inverse of the relaxation rate (R_2^*) of the magnetisation caused by local susceptibility-induced magnetic field gradients. Changes in T_2^* are the basis for the blood oxygenation level dependent (BOLD) signal that is of interest in fMRI. TE, the echo time, is chosen by the experimenter to maximise the BOLD contrast which is TE-dependent: usually around 30 ms for a magnetic field strength of 3 T. The BOLD contrast arises from the fact that oxyhaemoglobin is diamagnetic whereas deoxyhaemoglobin is paramagnetic. An increase in deoxyhaemoglobin concentration ([dHb]) causes faster dephasing of excited spins, shortening T_2^*, leading to a smaller BOLD signal measured at the echo time, TE.

Neural activity is primarily an aerobic process: the production of ATP in this way means that the cerebral metabolic rate of oxygen consumption ($CMRO_2$) closely parallels neural activity (Attwell and Laughlin, 2001). In a healthy brain, arterial blood oxygen saturation is close to 100%, that is, all haemoglobin molecules are fully loaded with oxygen. Once this blood reaches an area of neural activity in which $CMRO_2$ has increased, the increased oxygen concentration gradient across the vessel wall causes more oxygen to unload from the passing haemoglobin. This implies that increased neural activity will lead to increased deoxyhaemoglobin concentration, [dHb], in local venous blood vessels, shortening T_2^* and thus reducing the BOLD signal.

However, the earliest studies of neural activity using fMRI demonstrated the reverse: BOLD signal increases with increased neural activity (Bandettini et al., 1992; Ogawa et al., 1992). This indicates that [dHb] is reduced. This dichotomy is caused by neurovascular coupling (described more comprehensively elsewhere by Liu in this *NeuroImage* special edition). Through multiple mechanisms, neural activity causes an increase in perfusion/cerebral blood flow (CBF) through localised vasodilation (increased cerebral blood volume (CBV)) when more oxygen is in demand. The resulting increase in CBF, whilst coupled to the increased metabolism, is roughly a factor of two larger than the increase in $CMRO_2$ (Davis et al., 1998; Hoge et al., 1999). Therefore, oxyhaemoglobin is oversupplied to the activated region leading to a reduction in deoxyhaemoglobin concentration [dHb] and, thus, an increase in the BOLD signal.

From this description of the BOLD contrast, it is clear that BOLD, rather than being a direct measure of neural activity, is a complex function of metabolism ($CMRO_2$), CBF and CBV (see Fig. 1B). Changes in the BOLD signal accurately reflect neural activity if and only if the intermediary vascular steps are not significantly altered. Phenomena that affect the complex balance between the 3 parameters $CMRO_2$, CBF and CBV in the frequency range of resting-state fluctuations will cause changes in resting-state BOLD signals that may be spuriously correlated across regions. Similarly, phenomena that globally affect aspects of the signal other than T_2^* (i.e. longitudinal magnetisation $-M_0$) will cause correlated changes in BOLD signal that may be entirely unrelated to physiology. Both magnetisation and physiological processes that change over time and that are reflected in resting BOLD signals are considered to be resting-state fMRI confounds.

Resting-state fMRI confounds

Isolating true neural activity-related BOLD signals of interest is an ongoing challenge since resting-state fMRI confounds can arise from many processes in the MRI environment. Apart from signal changes that occur due to scanner hardware instabilities (e.g. spiking), fMRI confounds arise from phenomena related to the participant that are outside the control of the experimenter. Although hardware related confounds can be fixed (at least in theory), participant-related fMRI confounds, whilst perhaps reduced through various strategies, will always remain and therefore must be understood to be removed. The following are descriptions of common resting-state fMRI confounds that can affect the BOLD signal by changing M_0, T_2^* or both in a time varying way.

Motion

Motion artefacts are problematic for all types of fMRI including resting-state fMRI. When the participant moves in the magnetic field, three effects on M_0 can compromise data quality. First, movement of the head causes the content of each voxel to change. Since M_0 is directly proportional to the number of spins in the voxel, any alteration in voxel content will manifest itself as a change in the BOLD signal. This is particularly problematic at tissue interfaces such as grey/white matter boundaries, around large vessels and at the edges of the brain. Second, movement of the head will alter the uniformity of the magnetic field that has been shimmed for one particular head position. This changes locations of distortions and signal dropout boundaries along with directly affecting M_0 itself. Finally, movement of the head within the scanner during a scan will change steady state magnetisation by changing the time between excitations in the parts of tissue that have moved from one slice to the next. This transiently influences the magnetisation M_0 until steady state is reached and is often referred