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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.

Keywords

Functional Magnetic Resonance Imaging (FMRI); resting-state; functional connectivity; noise correction; physiological noise

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

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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 <0.1Hz) 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 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 is 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 can not 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 Figure 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 30ms for a magnetic field strength of 3T. 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 Figure 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, while 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 gray/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 to as a spin history effect. The change in signal intensity due to spin history effects can often be up to twice the expected BOLD signal change (Muresan et al., 2005).

For resting-state FMRI, motion-related confounds are problematic due to their global nature. These confounds can be further compounded when comparing differences in functional connectivity between groups. Children and patient populations are usually more uncomfortable in the MR environment than young healthy controls, resulting in a greater amount of head motion. Recent studies have demonstrated that functional connectivity conclusions may be erroneous when motion artefacts have a differential effect on resting BOLD signals for between group comparisons (Power et al., In Press; Satterthwaite et al., 2012; Van Dijk et al., 2012). In these studies, subtle motion artefacts (< 0.5mm) rather than larger head movements were the cause for concern. Head motion introduced a specific bias, increasing short range and right-left connections whilst decreasing long-range and anterior-posterior connections.

Cardiac and Respiratory Physiological Noise

Although attempts to limit large movements during FMRI are commonly made using head restraints, it is not possible to limit all movement-related artefacts, even in compliant and motivated participants. Bulk motion related to the cardiac and respiration cycles will lead to similar confounds as motion of the head itself. Movement of the subject's chest can alter the magnetic field in a time dependent manner (Brosch et al., 2002). Respiration causes bulk susceptibility variation in the lungs leading to variations in the static magnetic field within brain tissue (Raj et al., 2001). These magnetic field changes can result in a shift of the MR image in the phase-encoding direction. Small movements of the head due to breathing alter spin history in a spatially dependent manner (Friston et al., 1996). Cardiac pulsation and respiratory cycles cause the brain stem to push up into the surrounding brain tissue causing deformation and cerebrospinal fluid movement which manifest themselves in M_0 changes (Dagli et al., 1999). Pulsations of the vessels caused by cardiac-related pressure changes will generate small movements in and around large blood vessels (Dagli et al., 1999). Evidence indicates that such physiological motion also affects resting-state FMRI time series through the mechanism of steady-state free precession (SSFP) disturbance (Zhao et al., 2000).

Cardiac and respiratory cycles are relatively high frequency (~1 Hz and ~0.3 Hz, respectively) compared to the low-frequency (< 0.1 Hz) BOLD fluctuations under scrutiny in resting-state FMRI. However, due to the long TR of standard resting BOLD EPI (~2–3 secs), cardiac and respiratory noise at the primary frequency are aliased into this low-frequency range (Bhattacharyya and Lowe, 2004; Lowe et al., 1998). Thus, cardiac and respiratory noise will appear as low-frequency fluctuations and may be mistaken for neural activity-related BOLD oscillations.

Furthermore, it has been demonstrated that there is a significant correlation between changes in cardiac and respiratory rates and the BOLD signal (Birn et al., 2006; Shmueli et al., 2007; Wise et al., 2004). These fluctuations in rate are within the frequency range of resting BOLD oscillations (~0.04 Hz for cardiac (Akselrod et al., 1981) and ~0.03Hz for respiration (Wise et al., 2004)) and therefore, will artificially inflate functional connectivity measures or cause spurious connectivity patterns where BOLD connectivity is not present. Rather than arising from movement-related artefacts, low-frequency fluctuations in cardiac and respiratory rate manifest themselves in resting BOLD signals through arterial CO_2 concentration and blood pressure changes that are under sympathetic and parasympathetic nervous system control.

Arterial CO_2 concentration

Carbon dioxide (CO_2) in arterial blood is a potent vasodilator producing a global increase in CBF. CO_2 is produced in tissue as a by-product of glucose metabolism and its vasodilatory properties are thought to be one of the mechanisms mediating neurovascular coupling (Raichle and Stone, 1971). However, arterial tension of CO_2 can change with respiration rate, thereby changing CO_2 concentration in the venous vasculature leading to BOLD signal changes that are unrelated to neural activity.

Using transcranial doppler (TCD) ultrasound, it has been demonstrated that after breathing air enriched with CO_2 to cause hypercapnia (an increase in arterial CO_2 concentration), blood velocity in the middle cerebral artery (MCA) changed by 2–5% per mmHg change in arterial carbon dioxide (Ide et al., 2003; Poulin et al., 1996). CO_2-mediated increases in CBF caused by hypercapnia have been shown to also increase the BOLD signal (Kastrup et al., 1999; Poulin et al., 1996; Rostrup et al., 2000): the increased CBF reduces deoxyhaemoglobin concentration resulting in a longer T_2^*. Similarly, cued changes in participant breathing will affect the BOLD signal. Hypercapnia arising from breath-holds

increases BOLD signal (Murphy et al., 2011) whilst hypocapnia arising from hyperventilation reduces it (Bright et al., 2009; Posse et al., 2001).

Breath-to-breath variations in arterial CO_2 partial pressure during spontaneous breathing lead to changes in respiration rate (Modarreszadeh and Bruce, 1994). Random disturbances in CO_2 concentration, although small, have significant effects on ventilation rates. Increased arterial CO_2 levels activate chemoreceptors that increase subsequent breathing depth and rate (Van den Aardweg and Karemaker, 2002). An arterial baroreflex has been proposed as the cause of fluctuations in both respiratory and cardiac rates (Cohen and Taylor, 2002), suggesting that low-frequency variations in cardiac and respiratory rates are intimately linked.

The response of the vasculature to CO_2, often referred to as *vascular reactivity*, is very sensitive, thus any changes in respiration rate and resulting CO_2 variations will have consequences for resting BOLD signal fluctuations. In resting-state FMRI, we are interested in low-frequency oscillations in metabolism, however, using near-infrared spectroscopy (NIRS), is has been demonstrated that such fluctuations are also accompanied by low-frequency variations in CBF and oxygenation (Obrig et al., 2000). End-tidal CO_2 partial pressure measurements are a surrogate for arterial CO_2 concentration measures and have been shown to fluctuate in the 0–0.05Hz frequency range (Wise et al., 2004). Wise and colleagues demonstrated that a component of the low-frequency BOLD signal fluctuations is mediated by CO_2-induced changes in CBF. Fluctuations in end-tidal CO_2 of ±1.1mmHg lead to BOLD signal fluctuations of ±0.12% in grey matter. Using a measure called RVT (respiration volume per time) that attempts to capture breathing rate and depth as a surrogate for end-tidal CO_2, Birn and colleagues demonstrated that related fluctuations in resting-state FMRI BOLD localised to regions with high blood volume and large blood vessels (Birn et al., 2006). It remains an ongoing mystery as to why these regions overlap well with the default mode network. A possible explanation is that brain areas that are predominantly active “at rest” have evolved to have a higher *CBF* and *CBV*.

Blood Pressure and Cerebral Autoregulation

Cerebral autoregulation is the intrinsic dynamic ability of cerebral vessels to maintain steady-state CBF despite fluctuations in arterial blood pressure (Lagopoulos et al., 2006). Cerebral autoregulation protects the vasculature from excessive blood flow, which may cause haemorrhage leading to ischemia and cell death. The arterial and arteriolar systems are responsible for maintaining stable CBF during times of increased blood pressure and do so by changing *vascular tone* through vasoconstriction and vasodilation processes (Ekstrom-Jodal et al., 1971; Failla et al., 1999). In the healthy brain, CBF is held constant at 40–50 ml/100g/min over the range of arterial blood pressure from 50 to 150 mmHg (Kontos et al., 1978).

Like arterial CO_2 concentration, arterial blood pressure also fluctuates over time. Blood pressure variations are a key source of CBF fluctuations due to the delay in dynamic autoregulation (Diehl et al., 1995; Lang et al., 1999). Blood pressure is under the control of the sympathetic and parasympathic nervous systems that modulate arterial vascular tone (Failla et al., 1999) and heart rate in the low-frequency range (Akselrod et al., 1981; Katura et al., 2006). Low-frequency oscillations in oxyhaemoglobin stem from both heart rate and blood pressure fluctuations, with the former explaining 20% of variance, the latter 5% and a common contribution of approximately 10% on the variance using Optical Topography data (Katura et al., 2006). However, non-linear modeling demonstrates that blood pressure accounts for 60% of the total predictive power of CBF fluctuations whereas CO_2 accounts for only 17% (Mitsis et al., 2004). Therefore, fluctuations in arterial blood pressure are

likely to have a greater influence on vasculature than fluctuations in CO_2 concentration and, thus, on resting-state BOLD signal variations.

Evidence of the influence of blood pressure oscillations on resting-state FMRI fluctuations in humans is sparse. Blood pressure levels in rats have been shown to affect evoked fMRI responses, with transient hypertension increasing BOLD (Wang et al., 2006) and CBF (Qiao et al., 2007) signals. Under hypotension, neural activity-evoked CBV increases in visual cortex are negligible compared to ~10% at normal blood pressure levels (Nagaoka et al., 2006). Increases in the amplitude of low-frequency BOLD fluctuations have been demonstrated with a drop in mean arterial pressure (Biswal and Kannurpatti, 2009). As supporting evidence in humans, BOLD signal correlates of heart rate and pulse height in the low frequency range have been discovered with fluctuations in cardiac rate explaining up to 11% of the variance in the resting-state BOLD signal (Chang et al., 2009; de Munck et al., 2008; Shmueli et al., 2007).

Vasomotion

In addition to the autoregulatory response to blood pressure changes, vascular tone throughout the body exhibits low-frequency oscillations (< 0.1 Hz) in the absence of any stimulus (Aalkjaer et al., 2011). This phenomenon, known as vasomotion, is still poorly understood, particularly in the brain. Controversy exists in the literature over whether vasomotion is an independent process from CO_2 and blood pressure fluctuations. Vasomotion is directly affected by baseline vascular tone (Morita-Tsuzuki et al., 1992), is independent of cardiac and respiratory cycles and is increased when cerebral perfusion is challenged (Biswal and Kannurpatti, 2009; Hudetz et al., 1998), the most potent stimuli being hypotension, hyperventilation and vasoconstriction. Vasomotion fluctuations are absent in ischemic brain territories and dependent on intravascular pressure suggesting that these oscillations stem from a myogenic mechanism, that is, the smooth muscle of the arterioles contracting due to the mechanical stress of increased blood volume (Hudetz et al., 1998). If vasomotion is independent of cardiac, respiratory, arterial CO_2 concentration and blood pressure fluctuations, its low-frequency characteristics will present another confound for resting-state FMRI BOLD oscillations.

Resting-state FMRI cleanup

The BOLD signal is an indirect measure of neural activity. The goal of resting-state FMRI is to use synchronous low-frequency resting-state BOLD fluctuations from disparate regions of the brain as an indicator of synchronous neural activity. As outlined in the previous section, the BOLD signal can be confounded by many processes also low in frequency but not related to neural activity. Thus, interpretation of functional connectivity measures is difficult unless these confounds are removed. Fortunately, due in no small part to the popularity of the field, much effort has been focussed on addressing these issues. Although it is not currently possible to entirely remove all confounds, application of one or more of the noise removal techniques allows for more subtle measures to be made and can serve to increase confidence in resting-state FMRI results and interpretations. One important caveat is that some variations in physiology and other confounding processes may be temporally coupled with variations in the neural activity of interest. Removing such variance will also remove signals of interest. All attempts to cleanup resting-state FMRI data should bear this caveat in mind.

For individual resting-state dataset cleanup, noise removal methods can be roughly placed into two categories: 1) those utilising external recordings of physiology and 2) data-based cleanup methods that only use the resting-state FMRI data itself. Techniques from both categories can be used in conjunction when appropriate. Once functional connectivity

measures are calculated on an individual basis, further cleanup can be performed at the group level.

Time-series Cleanup with Physiological Recordings

As demonstrated in the "Resting-state FMRI confounds" section, many of the noise sources that can affect functional connectivity measures originate from physiological processes. For well over 100 years, scientists have used external recordings of these processes to understand the workings of the human body. Many physiological recordings methods can be translated into the MR environment. By concurrently recording cardiac, respiratory, end-tidal CO_2 and blood pressure traces, estimates of the related BOLD fluctuations can be modelled. The majority of the cleanup techniques that utilise physiological recordings remove these estimates from each voxels' time series using linear regression, thus "cleaning up" the resting-state FMRI data. The influence of each physiological process on the BOLD signal is modelled as a time series and is fit to the data using a linear regression procedure. This fit is then subtracted from the data to remove the associated physiological variance.

Most MRI scanners come with a finger/toe pulse oximeter and a respiratory bellows, making it relatively easy and painless to record cardiac and respiratory traces during resting-state FMRI data acquisitions. Methods to remove the primary effects of cardiac and respiratory cycles have been developed for both k-space (Hu et al., 1995) and image space data (Glover et al., 2000). The former suffers from the problem that correction of single k-space points affects all voxels, potentially introducing spatially correlated noise whilst allowing high spatial frequency confounds to remain. The latter, dubbed RETROICOR (standing for RETROspective Image CORrection) estimates the phase of the cardiac and respiratory cycles at which an imaging slice is acquired. Low-order Fourier series' of the phase data are fit to each voxels' time series using a general linear model and removed. Since the phases of the cardiac and respiration cycles are matched to the timing of each imaging slice, the technique can remove the primary cardiac and respiratory frequencies that are aliased into the low-frequencies of interest (Lowe et al., 1998). Recently, it has been shown that averaged over gray matter, the cardiac and respiratory regressors modelled in RETROICOR account for only a small amount of time course variance, ~5% (Bianciardi et al., 2009; Jo et al., 2010). (It is important to note that the proportion of overall variance attributable to the underlying physiological noise increases with the signal-to-noise ratio (SNR) and so may be smaller or larger depending on voxel size and field strength (Bodurka et al., 2007; Kruger and Glover, 2001; Murphy et al., 2007; Triantafyllou et al., 2005)). The original implementation of RETROICOR did not fit Fourier series' of orders greater than 2. More recently, it has been demonstrated that model fitting with higher orders along with interaction terms improves the fit but may suffer from a loss of some signal of interest (Harvey et al., 2008). One drawback of the RETROICOR technique is that changes in the time interval between cardiac beats are primarily associated with time variation in the diastolic rather than the systolic part of the cardiac cycle. This makes it difficult to determine an exact cardiac phase for each slice accurately (Dagli et al., 1999).

Low-frequency BOLD fluctuations related to variations in cardiac and respiratory rates can also be removed from the data with the same physiological traces. Birn and colleagues developed a measure called RVT (respiration volume per time) that attempts to capture changes in respiration depth and rate which cause periodic fluctuations in arterial CO_2 concentration (Birn et al., 2006). RVT is calculated by generating envelopes of the maximum and minimum respiratory belt positions at the peaks of inspiration and expiration, respectively. The difference of these envelopes is divided by the breath-to-breath period of respiration. Using this as a regressor in a linear model, Birn and colleagues could remove the variance of respiration induced changes from resting-state BOLD signals. Convolution of the RVT regressor with a respiration response function further improved the fit to breathing-

induced changes in BOLD data (Birn et al., 2008). Low-frequency changes in heart rate (HR) can also be removed from resting-state BOLD data using regression (Shmueli et al., 2007), a process further improved by convolution of the HR regressor with a cardiac response function (Chang et al., 2009). Combining both the RVT and HR methods into a single regression step can explain ~16% of resting-state BOLD variance with each explaining ~8% individually (Chang et al., 2009).

End-tidal CO_2 partial pressure is a surrogate measurement for arterial CO_2 concentration. A significant correlation between resting-state BOLD signals and end-tidal CO_2 measured with a capnograph can be found. Wise and colleagues first demonstrated that ~16% of resting-state BOLD variance can be explained in grey matter (Wise et al., 2004) and thus removed. They also found that doppler ultrasound of the middle cerebral artery demonstrated that blood velocity lagged the low-frequency CO_2 fluctuations by 6.3s and that the BOLD signal fluctuations were mediated by CO_2-induced changes in CBF. The RVT correction method was developed to emulate end-tidal CO_2 noise removal in situations where a capnograph is unavailable. As such, both regressors are highly correlated and explain similar spatial and temporal BOLD signal variance (Chang and Glover, 2009b). Figure 2A demonstrates in a cohort of 12 subjects that although end-tidal CO_2 and RVT regressors remove common variance, each also captures separate components of the noise. RVT is not a perfect substitute for end-tidal CO_2 correction. However, if both options are available then both noise correction strategies should be performed.

Near-infrared spectroscopy (NIRS) acquired simultaneously with BOLD FMRI can provide information about blood flow and oxygenation. By using a concurrent NIRS recording at multiple delays to build six regressors in a method called Regressor Interpolation at Progressive Time Delays (RIPTiDe), Frederick and colleagues demonstrated that 10.5% of resting-state BOLD variance could be explained throughout the brain (Frederick et al., 2012). Comparisons with a combination of RETROICOR and RVT corrections that could only explain 6.8% of the variance show that this method may provide a superior correction technique. However, one major drawback of this technique is that care must be taken to ensure that the NIRS regressors do not contain neural activity-related fluctuations of interest. It is unclear how this could be achieved in practice.

A more interventionalist approach to reducing CO_2-mediated resting-state BOLD fluctuations can be taken by controlling arterial gases. By utilising dynamic end-tidal forcing or prospective targeting to limit fluctuations in arterial CO_2 and O_2, related BOLD variance can be reduced (Madjar et al., 2012; Slessarev et al., 2007; Wise et al., 2007). However, it is unclear what effects these interventions will have on resting-state neural activity. Also dynamic, and even slice-specific, shimming of the B_0 magnetic field can reduce the effect of chest motion and fluctuations in CO_2 concentration on the BOLD signal which is especially problematic at higher field strengths (van Gelderen et al., 2007).

It is likely that blood pressure fluctuations will have an equal or greater influence on resting-state BOLD signals than respiration-related variations (see above). If MR-compatible continuous blood pressure devices were available such variance could be removed using similar regression techniques. Fluctuations in arterial blood pressure are controlled by the sympathetic nervous system through changes in arterial vascular tone (Failla et al., 1999). Sympathetic tone may be monitored by estimating arterial stiffness through pulse wave velocity (PWV) measurements. Partially inflated non-invasive blood pressure cuffs placed around the bicep and thigh are used to monitor the heart beat-induced pressure wave. Timing delays between the pressure wave traces divided by the arterial distance between the cuffs provide the measure of arterial stiffness or PWV. Figure 2B demonstrates that significant variance in the global BOLD signal can be explained by variance in PWV measurements.

The almost instantaneous influence of PWV on resting-state BOLD signals is expected if this variance can be attributed to short-term fluctuations in CBF driven by variations in blood pressure. The relationship between PWV and BOLD signals is widespread throughout the brain and can be seen to be localised to more vascular regions in some subjects in Figure 2B. However, the inherent noisy nature of PWV measurements make voxel-wise comparisons difficult. These results demonstrate that blood pressure fluctuations are a confound in resting-state BOLD signals. Once an MR-compatible continuous blood pressure device has been developed, removal of such noise will be possible by following standard regression techniques.

Data-based time series cleanup techniques

There are many reasons why physiological recordings may not be available when analysing resting-state FMRI data; lack of equipment, data corruption and non-compliant/uncomfortable participants, to name but a few. Large databases of freely downloadable resting-state FMRI data exist such as the 1000 Functional Connectomes Project (http://fcon_1000.projects.nitrc.org/), the Autism Brain Imaging Data Exchange (ABIDE - http://fcon_1000.projects.nitrc.org/indi/abide/) and Alzheimer's Disease Neuroimaging Initiative (ADNI - http://www.adni-info.org/). Unfortunately, varying degrees of corresponding physiological recordings accompany this data with the vast majority having none at all. Lack of physiological recordings renders each of the previously described cleanup methods impossible to perform. If, however, researchers find themselves in this situation, many methods exist that attempt to estimate and remove resting-state FMRI confounds using only the resting-state data itself.

The simplest strategy is to bandpass filter the data so that fluctuations outside the frequency range of interest do not affect functional connectivity measures. Most studies of resting-state BOLD fluctuations perform this step as standard (even when physiological data has been recorded), usually filtering out frequencies lower than ~0.01Hz and greater than ~0.1Hz. Removal of primary cardiac (~1Hz) and respiration (~0.3Hz) frequencies was first demonstrated with such a technique dubbed IMPACT – Image-based Physiological Artifacts estimation and Correction Technique (Chuang and Chen, 2001). However, this is only possible when the TR is short enough (<0.5s) since these confounding frequencies are aliased into the lower frequency range at longer, more standard TRs (2s – 3s) (Lowe et al., 1998). Accounting for non-neural noise by using high sampling rates was popular in the early days of resting-state FMRI (Biswal et al., 1995; Cordes et al., 2001; De Luca et al., 2006; Lowe et al., 1998). Kiviniemi and colleagues, taking advantage of this aliasing of physiological noise, demonstrated that low-frequency BOLD signal fluctuations exist that are unrelated to the aliased cardiac and respiratory frequencies (Kiviniemi et al., 2005). One drawback of low-TR sampling is limited spatial coverage. Recent advances in image acquisition techniques have allowed high-frequency temporal sampling at the same time as whole brain coverage (Domsch et al., 2012; Moeller et al., 2010). Sampling faster than the haemodynamic response may be advantageous for resting-state cleanup strategies. However, any frequency filtering strategy cannot remove low-frequency variations related to physiology, such as arterial CO_2 concentration and blood pressure variations, which are in the same frequency range as neural activity-related resting-state BOLD oscillations.

Motion of the participant in the scanner is problematic for all types of FMRI, introducing noise into task-related designs and biasing correlations between regions in resting-state FMRI. Motion correction is a standard preprocessing technique in all FMRI data analyses. Usually six motion regressors are estimated from the data (3 translations, 3 rotations) by determining the amount of movement required to optimally register each brain volume to the previous volume (Friston et al., 1996; Jenkinson et al., 2002). Variance related to the 6 motion regressors can be removed from the BOLD time series' using a multiple linear

regression. Lund and colleagues investigated the effects of residual movement artefacts on intra-subject and inter-subject variability and demonstrated that inclusion of motion parameters in the analyses significantly reduce both types of variance (Lund et al., 2005).

Although inclusion of motion parameters can reduce motion-related FMRI confounds, recent studies have shown that subtle movement artefacts, rather than large head motion artefacts, remain that bias functional connectivity comparisons between groups (Power et al., 2012; Van Dijk et al., 2012). This phenomenon is particularly pronounced when comparing healthy controls to children or patient populations as these groups are more likely to move in the scanner. Power and colleagues proposed a volume censoring technique to deal with this problem dubbed “scrubbing” whereby volumes that were deemed to be affected by excessive motion (using metrics called framewise displacement and DVARS; the first being a measure of instantaneous motion at each time point, the second being a measure of the rate of change of BOLD signal at each time point) are simply ignored in the functional connectivity analyses (Power et al., 2012). There is some debate in the literature about when this scrubbing technique should be applied (Carp, In Press; Power et al., In Press). If scrubbing is performed after temporal filtering of the time series then artefactual motion-related noise from the censored volumes will be smoothed into neighbouring time points (Carp, In Press). It was suggested that instead, “bad” time points should be replaced by interpolating adjacent time points before temporal filtering. However, Power and colleagues argue that the large chunks of data that are replaced may have characteristics of interest that will be lost (Power et al., In Press). Also, variation in degrees-of-freedom lost across subjects using the scrubbing technique must be accounted for. Regression of up to 36 motion-derived parameters along with motion spike regressors to account for movement in individual time points has also been proposed (Satterthwaite et al., 2013). However, the authors note that the procedure does not result in the elimination of motion artefact and so recommend that subject motion be explicitly reported as an outcome measure in resting-state FMRI studies.

Other methods for removing these subtle motion-related confounds require an adjustment to the acquisition of resting-state FMRI data. Bright and Murphy introduced a dual-echo approach in which the time series of the shorter echo is regressed from the longer BOLD echo on a voxelwise basis (Bright and Murphy, 2013). If the TE of the first echo is short enough to minimise BOLD weighting, motion-related and physiological confounds can be successfully removed from resting-state FMRI data. Multi-echo approaches in which M_0 and T_2^* fluctuations can be separated effectively could further enhance this method (Barth et al., 1999; Kundu et al., 2012; Posse et al., 1999; Speck and Hennig, 1998).

The majority of methods from the “Time-series Cleanup with Physiological Recordings” section derive time series from physiological traces and remove the associated variance from BOLD time series using regression methods. Confound regressors can also be derived from the resting-state dataset itself. Global signal regression (GSReg) removes the global mean BOLD signal computed across all voxels in the brain (Desjardins et al., 2001; Greicius et al., 2003; Macey et al., 2004). The assumption is that any process that affects BOLD signals globally must be unrelated to neural activity and, therefore, must be a confound. GSRreg was widely used in early resting-state FMRI studies because it revealed a more consistent and focal pattern of functional connectivity across the brain (Fox et al., 2005; Fox et al., 2009; Greicius et al., 2003). The utility of GSReg as a confound correction technique has been called into question over recent years. Functional connectivity analyses, using the posterior cingulate (PCC) as a seed region, maps the default mode network (DMN). It has been demonstrated that fluctuations in the DMN are anti-correlated with a network that routinely exhibits task-related activations, named the task-positive network (TPN) (Fox et al., 2005). The implication is that these two networks are diametrically opposed at rest with

one showing decreasing activation when the other increases neural activity. However, Murphy and colleagues demonstrated mathematically that the process of GSReg forces the sum of correlation values across the brain to be less than or equal to zero and that this anti-correlated network disappears from the results when GSReg is not performed (Murphy et al., 2009).

Many studies have tried to determine whether these anticorrelations are a true reflection of functional connectivity or an artefact of the GSReg technique (Anderson et al., 2011; Chai et al., 2012; Chang and Glover, 2009a; Fox et al., 2009; Fransson, 2005). The first paper to claim that global signal regression uncovers truly anti-correlated networks argued that their spatial distribution, consistency across subjects, presence when the regressed signal was from a subset of all voxels and their existence before global signal regression demonstrated a biological basis (Fox et al., 2009). Since then, studies have attempted to detect the anti-correlated networks with other imaging methods.

Electrophysiological studies in the cat homologues of the DMN and TPN show that the two networks are anti-correlated at most 20% of the time (Popa et al., 2009). In humans, no negative correlations between the dorsal attention network and the DMN were observed in MEG signal (de Pasquale et al., 2010). Furthermore, it has been demonstrated that local field potentials from a single cortical site in monkeys at rest exhibit widespread positive correlations with BOLD signals across the entire brain (Scholvinck et al., 2010). This indicates that the global BOLD signal is tightly coupled with underlying neural activity and so the assumption that it purely represents a confound is questionable. All the evidence suggests that, at best, GSReg will reduce positive correlations that may or may not be spurious but will introduce negative correlations that can not be trusted. Indeed, by modelling group comparisons, it has been shown GSReg can alter local and long-range correlations, potentially spreading group differences that exist only in one region to regions that show no true functional connectivity differences (Saad et al., 2012). Interpretation of functional connectivity results after GSReg is difficult and, therefore, this resting-state FMRI cleanup method should be avoided.

The problems with global signal regression stem from the fact that the fluctuations of interest, that is, the BOLD fluctuations related to neural activity on which we would like to base our functional connectivity measure, contribute to the global signal confound regressor. To this end, alternative methods have been devised that attempt to circumvent that problem. BOLD signals related to neural activity fluctuations should be predominantly present in gray matter. Nuisance regressors derived from other areas such as CSF, white matter, the sagittal sinus or the edges of the brain that are unlikely to show neural activity-induced BOLD signal fluctuations have been employed with some success (Birn et al., 2009; Bright and Murphy, 2013; Weissenbacher et al., 2009). White matter and CSF signal regression improves the specificity of functional connectivity maps (Weissenbacher et al., 2009). Partial volume with gray matter can cause problems, therefore erosion of the white matter and ventricular CSF masks is advised (Jo et al., 2010). Similarly, a method called CompCor derives confound regressors from the principal components of the BOLD signal in white matter and CSF to avoid generating a time series that is modulated by neural activity (Behzadi et al., 2007). Nuisance regressors can also be constructed from soft tissue far from the brain such as the face and the calvarium which can represent significant noise variance in the BOLD data (Anderson et al., 2011).

Independent component analyses (ICA) is a successful technique for detecting consistent resting-state networks (Bartels and Zeki, 2004; Beckmann et al., 2005; Damoiseaux et al., 2006; Kiviniemi et al., 2003). The ICA method separates resting-state FMRI data into spatial components that are mathematically independent and determines the associated time

series. If noise sources are independent from neural activity-related BOLD fluctuations, ICA is able to isolate one type of signal from the other. However, the results of ICA yield one time course per resting-state network and don't allow the detailed analysis of connectivity between nodes of the same network that seed correlation approaches provide. Various noise correction methods use ICA to isolate physiological noise components to remove them from resting-state data allowing further seed region analyses. CORSICA uses spatial ICA to identify and remove signal fluctuations that match known spatial patterns of physiological noise (Perlbarg et al., 2007). PESTICA, using a similar approach, estimates cardiac and respiratory fluctuations from resting-state data with temporal ICA, generating spatial weight matrices that can be applied to other resting-state data (Beall and Lowe, 2007). Using multi-echo BOLD acquisition, Kundu and colleagues have demonstrated an automated ICA sorting algorithm that can separate BOLD from non-BOLD signals (Kundu et al., 2012).

Group level cleanup

The resting-state FMRI cleanup techniques described in the last two sections are concerned with resting-state confound correction in BOLD signal time series. After removal of these confounds, one would expect functional connectivity measures to be less biased. However, physiological differences between groups may still confound group comparisons. Changes in vascular structure and integrity with age and disease cause many changes in neurovascular coupling: atherosclerosis, increased tortuosity, changes in collateral circulation after recanalization of occluded cerebral vessels, reduction in resting CBF, changes in vascular reactivity, lowered resting $CMRO_2$ (D'Esposito et al., 2003). Each of these age-related changes can affect how a given amount of fluctuation in neural activity is translated into a BOLD signal fluctuation.

Focussing on vascular reactivity, decreased vascular responsiveness to hypercapnia has been observed in aged rats (Tamaki et al., 1995). This suggests that for a given amount of neural fluctuation, the corresponding CBF fluctuations will be reduced in amplitude in older people. Results presented by Biswal and colleagues showing changes in connectivity and fluctuation amplitude with age may be evidence of this (Biswal et al., 2010). Murphy and colleagues have demonstrated that by measuring an individual's vascular reactivity using a breath-hold task, variance in across group measures of functional connectivity can be reduced as evidenced by increased spatial extent and statistical significance of resting-state networks (Murphy et al., 2011).

An example of altered vasculature affecting resting-state FMRI measures can be found in pharmacological studies where the drugs may alter vascular properties such as resting CBF levels and vascular reactivity (Iannetti and Wise, 2007). Caffeine has been shown to reduce resting-state BOLD functional connectivity measures in the visual cortex (Rack-Gomer et al., 2009). However, corresponding reductions in baseline CBF demonstrate that this phenomenon may have a vascular along with a neural component. A recent study into psilocybin examining functional connectivity differences caused by the drug presented more convincing results by accounting for CBF alterations and vascular reactivity differences between drug and placebo sessions (Carhart-Harris et al., 2012).

Other group-level cleanup methods could also be performed. Any physiological quantity that varies across a group and that is thought to affect the BOLD signal change to neural activity could be used. For example, resting heart rate, resting systolic and diastolic blood pressure, resting end-tidal CO_2 levels and even age may be used as covariates at a group level. It is important to bear in mind that there may be a linear relationship between these confounds and the underlying true neural activity levels across the group, for example, the underlying neural activity levels may decrease with age (D'Esposito et al., 2003). Therefore, caution should be used when interpreting results after such group level corrections.

Caveats

Resting-state FMRI confound removal should increase confidence in functional connectivity results, however, we must be aware of two caveats. The first is that cleanup methods may result in a variable loss of degrees-of-freedom that can be offset by adjusting the length of the resting-state scan. This may not be troublesome if all data in a study are processed so that each subject/group suffers an identical reduction in the degrees-of-freedom. The second is more serious. Variations in cardiac rate, respiration, arterial CO_2 concentration or blood pressure may be correlated with the variations in neural activity that we would like the BOLD signal to capture. For example, heart rate variability is an indicator of emotional arousal and autonomic nervous system activity (Macefield, 2009) and breathing variations are often tied to emotional state (Shea, 1996). If neural activity in the resting-state network under investigation is linked to, or synchronous with, any of these physiological processes, removing the physiological confound will also remove these neural activity-related BOLD fluctuations. Since resting-state FMRI is based on spontaneous fluctuations in BOLD and the relationship between the resting-state network and physiological processes may not be known, resting-state FMRI confound removal should always be performed with this caveat in mind.

Conclusions

The BOLD signal arises from a complicated interaction between neural activity and vascular processes. Resting-state FMRI uses the temporal similarity of intrinsic BOLD signal fluctuations across brain regions as an indicator of synchronous neural activity. However, the influence of noise confounds on measures of functional connectivity is too often ignored. The utility of resting-state FMRI lies in examining differences between sessions or groups to determine if there is a relationship between altered functional connectivity and behavioural/clinical symptoms. Unfortunately for the field, many of the sources of resting-state FMRI confounds, as outlined in this paper, also vary between sessions or groups, rendering the results of such studies difficult to interpret. The resting-state FMRI cleanup methods described in this paper go some way to providing useful confound removal. However, many have focussed on cardiac and respiratory processes that are easy to record and have largely ignored other sources such as arterial CO_2 concentration and blood pressure that may provide complementary information. Further refinement of resting-state FMRI noise removal is of paramount importance, always keeping in mind the caveat that the noise may be coupled to the signals of interest. The field of resting-state FMRI would certainly benefit from an increased effort in noise correction techniques, paving the way for more advanced applications to the healthy and diseased brain.

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Highlights

- Resting-state FMRI measures temporal similarity between BOLD signals
- Confounds can arise that affect the BOLD signals leading to spurious results
- Motion, cardiac/respiration, arterial CO_2 concentration & blood pressure are sources
- Techniques to remove resting-state FMRI confounds are reviewed
- Noise correction is an essential step for resting-state FMRI analyses

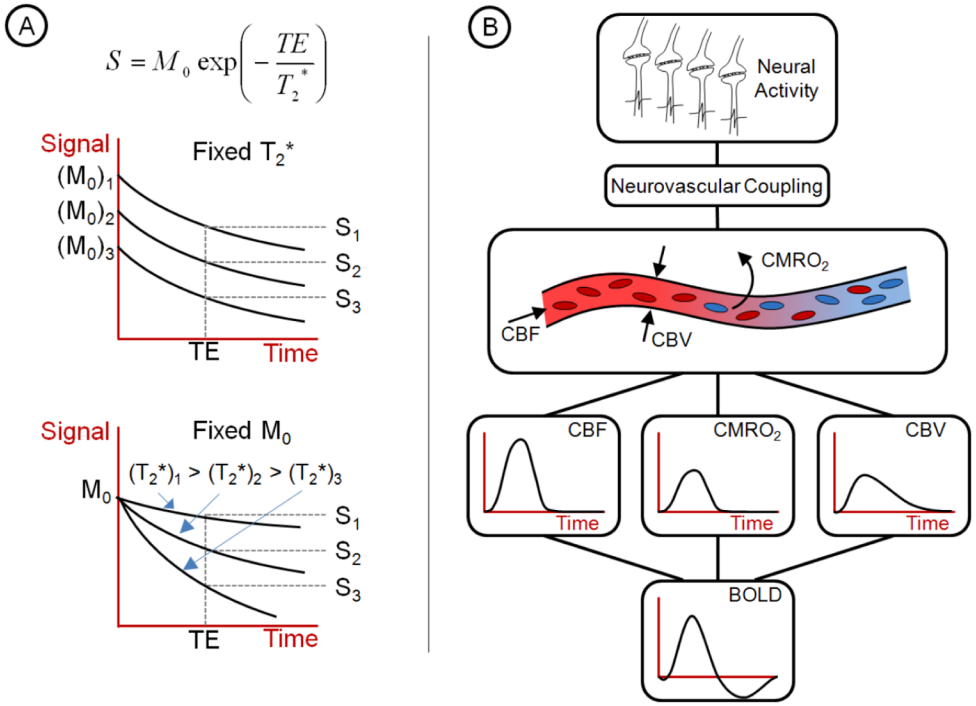

Figure 1. Origins of the BOLD signal

A) The magnitude of the BOLD signal depends on the initial magnetisation, M_0, and the decay time, T_2^*. Changes in the BOLD signal strength, S, can arise from changes in either M_0, T_2^* or a combination of both. FMRI assumes that changes in T_2^* are solely due to neural activity-related changes in deoxyhaemoglobin concentration. B) A schematic of the relationship between a transient increase in neural activity and the corresponding BOLD signal is shown. When neural activity causes increased oxygen consumption ($CMRO_2$), neurovascular coupling mechanisms alter the tone of the vasculature changing CBF and CBV. The complicated interaction between these 3 parameters leads to the BOLD signal as measured with FMRI. Changes in the BOLD signal accurately reflect neural activity fluctuations, only if the intermediary vascular steps are not significantly altered. Many of the confounds in resting-state FMRI originate from physiological changes in the vasculature.

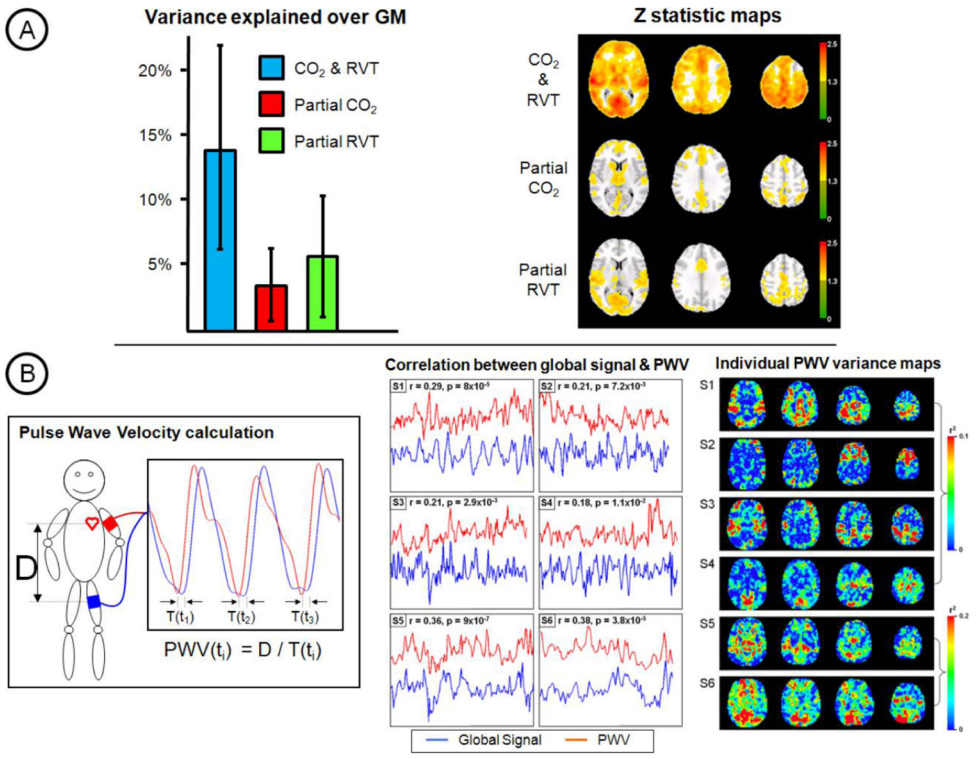

Figure 2. CO_2 and PWV resting-state FMRI confounds

A) A comparison of CO_2 and RVT correction is shown for a cohort of 12 subjects. Together, RVT and end-tidal CO_2 traces can explain ~15% of the variance in resting BOLD fluctuations. These confounds are widespread throughout gray matter. Although, common variance is removed, each type of correction captures a separate component of the noise. Complementary variance is explained in spatially similar and distinct regions. (Data first presented as a poster at the ISMRM 2009 meeting – Murphy, K., Harris, A.D. Niazy, R.K., Evans, C.J. & Wise, R.G. *Low-Frequency Respiration Related Signals in Resting State fMRI: a comparison of end-tidal CO_2 and respiration volume per time.)* B) Pulse wave velocity (PWV) can be measured using partially inflated blood pressure cuffs. This measure of arterial stiffness reflects sympathetic tone that is related to fluctuations in arterial blood pressure. Although PWV measures are inherently noisy, large correlations with the global BOLD signal can be observed (over 6 subjects). Voxel-wise correlations of BOLD signal with PWV show localisation of explained variance in highly vascular regions for some subjects. This demonstrates that blood pressure fluctuations may be a large source of confound for resting-state FMRI that, to date, has been largely ignored by researchers. (Data first presented as an e-poster at the ISMRM 2011 meeting – Murphy, K., Coulson, J., Harris, A.D. Fjordorova, M. & Wise, R.G. *The association between pulse wave velocity, as a marker of sympathetic tone, and resting state BOLD signals.)*