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Spontaneous fMRI activity during resting wakefulness and sleep

Jeff Duyn

Section for Advanced MRI, LFMI, NINDS, National Institutes of Health, Room B1D723, Building 10, 9000 Rockville Pike, Bethesda MD 20892, USA, tel (1) 301-594-7305, jhd@helix.nih.gov, <http://www.amri.ninds.nih.gov/>

Abstract

Functional MRI (fMRI) studies performed during both waking rest and sleep show that the brain is continually active in distinct patterns that appear to reflect its underlying functional connectivity. In this review, potential sources that contribute to spontaneous fMRI activity will be discussed.

INTRODUCTION

Much of the success of blood oxygen level dependent (BOLD) fMRI over the last two decades in studying the brain's functional architecture can be attributed to its ability to map activity changes in response to carefully crafted behavioral tasks. Nevertheless, it is becoming increasingly clear that fMRI may have important applications to the study of spontaneous brain activity as well (Biswal *et al.*, 1995; Raichle, 2009). Similar to electrical and optical signals recorded from the brain (Arieli *et al.*, 1995; Kenet *et al.*, 2003; Shoham and Grinvald, 2001; Tsodyks *et al.*, 1999), fMRI signals show a rich spatio-temporal structure even during periods of apparent mental or behavioral inactivity, including sleep and anesthetized conditions. This structure appears, at least in part, to reflect the brain's underlying functional architecture (Biswal *et al.*, 1995; Damoiseaux *et al.*, 2006; Hampson *et al.*, 2002; Salvador *et al.*, 2005). fMRI of spontaneous activity may therefore aid in the mapping of the brain's major communication pathways, despite its temporal resolution being far too poor to cover the breadth of the spectrum of neural communications. Nevertheless, the origin and role of spontaneous activity are still poorly understood. In the following I will discuss some of the characteristics of spontaneous fMRI signal fluctuations and speculate on their origin.

WHAT IS SPONTANEOUS fMRI ACTIVITY?

The BOLD fMRI signal derives from repetitive MRI scans that are sensitized to changes in blood oxygenation (Ogawa *et al.*, 1990). In most brain regions, changes in neuronal activity evoked by sensory or behavioral tasks lead to disproportionately large blood flow increases, thought to overcompensate for the metabolic demands supporting the increased glutamate cycling at synapses of pyramidal cells (Logothetis, 2002). The resulting increases in blood oxygenation lead to small (1%) fMRI signal increases, the dynamics of which can be sampled at a seconds-resolution time scale.

Interestingly, in absence of behavioral and sensory tasks or overt activity, similarly sized signal fMRI fluctuations can be observed (Biswal *et al.*, 1995); these fluctuations are correlated between regions that have an apparent functional relationship (Biswal *et al.*, 1995; Krienen and Buckner, 2009) and generally occur in multiple, spatially independent, and reproducible patterns that resemble many of the patterns observed during task activation studies (Smith *et al.*, 2009). Thus, the study of spontaneous fMRI activity may provide information about the brain's architecture and function.

Despite the intriguing characteristics of spontaneous fMRI signal fluctuations, and their rapidly increasing application to neuro-scientific questions, their origin and role are still poorly understood. Importantly, BOLD fMRI signal fluctuations may contain both neuronal and non-neuronal contributions, and it is important separate these. For example, head motion and MRI system instabilities may lead to fMRI signal fluctuations (see below) that may confound any neuronal sources. In this regard, it is important to differentiate between spontaneous fMRI *fluctuations* and spontaneous fMRI *activity*, the latter presumably representing neuro-metabolic contributions only. Another often overlooked fact is that spontaneous and task-evoked fMRI activity are not mutually exclusive (Bianciardi *et al.*, 2008; de Zwart *et al.*, 2008; Fox *et al.*, 2007). An indication of this oversight is the use of the term “resting state activity”, which incorrectly suggests that spontaneous activity ceases in the presence of overt tasks. As of yet, the interaction of these two types of activity is not well understood. Summarized, it appears safe to say that fruitful application to neuroscience will require further understanding of origin and role of spontaneous and sophisticated techniques to remove potential neuronal from non-neuronal sources.

NON-NEURONAL CONTRIBUTIONS TO THE BOLD fMRI SIGNAL

As indicated in the previous section, the BOLD fMRI signal is measured as a small deviation of the baseline or mean signal. For this reason, it is relatively sensitive to subtle fluctuations in the baseline signal due to non-neuronal sources such as thermal noise, instrumental drift, head motion, and physiological variations (Bianciardi *et al.*, 2009). These need to be dealt with to properly interpret the effects of spontaneous neural activity.

Thermal noise originates from resistive electrical effects in brain tissue and the MRI detector. It can be minimized by appropriate choice of MRI acquisition parameters (e.g. spatial resolution) and the use of advanced technologies such as high magnetic field and array detectors (de Zwart *et al.*, 2004; Triantafyllou *et al.*, 2005). Unfortunately, the amplitudes of all other noise sources roughly scale with signal amplitude, and some even have BOLD like contrast behavior (Hyde *et al.*, 2001) making it difficult to reduce their contribution relative to the (neuronal) signal of interest.

A rather effective way to separate noise sources is the use of post-processing and linear model regressors. For example, head motion can be compensated for by image alignment across the time-series scans; subsequently the alignment parameters can be used as variance regressors. Similarly, regressors can be constructed for the effects of cardiac and respiratory cycles (and their rates) on the fMRI signal, all of which can be substantial (Birn *et al.*, 2006; Chang and Glover, 2009; Fukunaga *et al.*, 2006; Glover *et al.*, 2000; Shmueli *et al.*, 2007). Another important source of fMRI signal variability is low-frequency drift, which is a slow, widespread temporal variation in the baseline signal and may originate from subject motion, (neuro-) physiological sources, and instrumental instabilities (Smith *et al.*, 1999). Although low frequency drifts are generally removed using high-pass Fourier filtering, time-domain polynomial fitting or wavelet analysis may be preferable as these avoid time-series truncation effects on the Fourier spectrum. A difficulty common to all methods that tackle low frequency drift is the potential removal of slowly varying neuronal effects. This is especially true for conditions where there is a potential co-modulation of neuronal and physiological signals (Golanov *et al.*, 1994; Musizza *et al.*, 2007)

Alternative other methods for the removal of non-neuronal contributions include independent component analysis (based on spatial distribution of correlation patterns (Beckmann and Smith, 2004)) and the use of regressors derived from reference regions assumed to not to reflect neuronal activity (e.g. CSF or white matter). The effectiveness of the latter may be compromised by venous drainage from neuronally active regions,

potentially injecting a neuronal contribution into the reference signal (Bianciardi *et al.*, 2010). In summary, as the separation of neuronal and non-neuronal sources has only been partly resolved, caution needs to be exercised with the interpretation of spontaneous fMRI studies.

NEURONAL CORRELATES OF THE BOLD fMRI SIGNAL

Although the origin of spontaneous fMRI signal fluctuations is still poorly understood, there is converging evidence that these fluctuations, at least in part, represent underlying neuronal activity. One category of evidence is the similarity between the fMRI findings and electrophysiological recordings. For example, spontaneous fluctuations in synaptic membrane potentials, measured with voltage-sensitive dyes in animal models, have been shown to contain a spatially localized and functionally specific component (Arieli *et al.*, 1995; Shoham and Grinvald, 2001). In humans, electro-cortical recordings have confirmed this functionally specific correlation (He *et al.*, 2008; Nir *et al.*, 2006), and further have shown low-frequency variations with spatio-temporal properties similar to the fMRI data (He *et al.*, 2008). Lastly, non-invasive macroscopic electrical recordings with MEG have shown long range correlation in specific networks similar to that seen in fMRI (de Pasquale *et al.*, 2010; Liu *et al.*, 2010b).

Another piece of evidence for a neuronal contribution to the spontaneous fMRI signal fluctuations comes from an fMRI study recording BOLD and perfusion signals simultaneously (Fukunaga *et al.*, 2008), both of which have been shown to fluctuate spontaneously (Biswal *et al.*, 1997). During task-evoked activity, it has been demonstrated that their relative fluctuation level depends on the metabolic contribution to the underlying process (Davis *et al.*, 1998; Hoge *et al.*, 1999). This metabolic contribution is thought to be primarily associated with the ATP turnover underlying glutamate cycling at neuronal synapses (Attwell and Iadecola, 2002). Applying this approach to the study of spontaneous activity, Fukunaga *et al.* (2008) found that the metabolic contribution to spontaneous activity is similar to that during task evoked activity. The tentative interpretation is that similar neuronal events are responsible for both task evoked and spontaneous activity.

Finally, multi-modal recordings in humans such as positron emission tomography (PET)-EEG and fMRI-EEG are also suggestive of a neuro-electrical contribution to spontaneous fMRI signal fluctuations. For example, during awake rest, substantial negative correlation with EEG band-limited power in the alpha range has been observed over extended brain regions (Goldman *et al.*, 2002; Laufs *et al.*, 2006; Laufs *et al.*, 2003a; Moosmann *et al.*, 2003; Sadato *et al.*, 1998), and correlation with other EEG bands and features have been found as well (Britz *et al.*, 2010; de Munck *et al.*, 2009; Laufs *et al.*, 2003b; Mantini *et al.*, 2007; Musso *et al.*, 2010). During sleep and anesthesia, significant correlation with EEG delta and sub-delta, and with spindle activity has been found (Dang-Vu *et al.*, 2005; Dang-Vu *et al.*, 2008; Schabus *et al.*, 2007). Finally, studies recording intra-cortical electrical signals concurrently with fMRI in macaque have found substantial inter-modal correlation in various frequency ranges, including the gamma band (Scholvinck *et al.*, 2010; Shmuel and Leopold, 2008).

SPONTANEOUS fMRI ACTIVITY DURING SLEEP

To the extent that spontaneous fMRI fluctuations represent neuro-electrical processes, how do they relate to brain function? Do they simply represent ongoing and uncontrolled conscious mentation? This is probably at least partly true for many of the fMRI studies on spontaneous activity presented in the literature, as they often used poorly controlled behavioral conditions that may have included periods of “Random Episodic Silent Thinking” or “REST” (Kanwisher, 2001), mental imagery (Kosslyn *et al.*, 1999; Wheeler *et*

al., 2000), monitoring of body posture and the environment, and fluctuations in vigilance, arousal, and attention. Although initial reports of a dependence on behavioral state appeared to confirm a primary contribution of uncontrolled mental activity (Fox *et al.*, 2005; Fransson, 2005; McKiernan *et al.*, 2003), this has been recently put into doubt by studies showing at least maintained (Boly *et al.*, 2008; Boly *et al.*, 2009; Fukunaga *et al.*, 2008; Fukunaga *et al.*, 2006; Horovitz *et al.*, 2008; Kiviniemi *et al.*, 2000; Larson-Prior *et al.*, 2009; Vincent *et al.*, 2007) or only partly reduced (Horovitz *et al.*, 2009; Lu *et al.*, 2007; Martuzzi *et al.*, 2010; Peltier *et al.*, 2005) levels of spontaneous fMRI activity during conditions of reduced consciousness. Notably, in sleep, which is a natural condition of reduced consciousness, spontaneous activity is largely maintained (Fukunaga *et al.*, 2006; Horovitz *et al.*, 2009; Horovitz *et al.*, 2008; Larson-Prior *et al.*, 2009). The figure illustrates this point: the widespread involvement of the brain in spontaneous activity observed during the waking condition is also observed during states of light and deep sleep.

In contrast, baseline metabolic activity may be reduced during conditions of reduced consciousness in most brain regions, and most notably in the thalamus and frontal cortex (Alkire *et al.*, 1999; Braun *et al.*, 1997; Buchsbaum *et al.*, 2001; Maquet *et al.*, 1990). However, this does not necessarily contradict the fMRI findings, which report on *fluctuations in* rather than *mean levels of* baseline metabolic levels underlying synaptic activity. The continuation of spontaneous fMRI activity during sleep and anesthesia suggests that this activity may not simply represent mentation and sensory processing, but at least in part subserves more basic brain functions, possibly including (synaptic) homeostasis and memory consolidation (Fukunaga *et al.*, 2005; Fukunaga *et al.*, 2006). Conversely, the study of spontaneous activity could elucidate the role of sleep for brain function, which remains a fascinating and poorly understood issue.

ORIGIN AND ROLE OF SPONTANEOUS FMRI ACTIVITY

Despite the increasing evidence of a neuronal contribution to spontaneous fMRI signals, the suggestions of their behavioral relevance (Sadaghiani *et al.*), and the rapidly increasing application of spontaneous fMRI to the study of brain functional connectivity in health and disease, the origin of role of this neuronal activity is still poorly understood. One question that is relevant to the functional connectivity is whether spontaneous activity represents cortico-cortical communication or rather the effect of a common driving source. For example, the apparent cortico-cortical correlations may result from changes in excitability or homeostatic processes orchestrated from brainstem and midbrain regions; such processes could, for example, be effectuated by cholinergic brain stem neurons (Mena-Segovia *et al.*, 2008a; Mena-Segovia *et al.*, 2008b), neurons in the rostral ventrolateral medulla (Golanov *et al.*, 1994), or neurons in the reticular complex of the thalamus, amongst others. Arguing against this “common source” hypothesis are recent studies of spontaneous activity with voltage sensitive dyes and fMRI, which found much reduced interhemispheric cortico-cortical correlation of spontaneous activity when integrity of the corpus callosum, which form the main body of inter-hemispheric fibers, was compromised (Johnston *et al.*, 2008; Mohajerani *et al.*, 2010; Quigley *et al.*, 2003). A caveat however with these studies is that the integrity of the “common source” may rely on an intact corpus callosum, as may be the case for the thalamus (Raos and Bentivoglio, 1993).

One potential role for spontaneous brain activity may be a homeostatic one in support of synaptic downscaling and/or consolidation (Fukunaga *et al.*, 2005; Fukunaga *et al.*, 2006; Miall and Robertson, 2006). A number of electrophysiological studies has reported on hippocampal-cortical communications preferentially active during “off-line” waking periods and sleep, that may support a hebbian adjustment of synaptic strengths for memory consolidation (Diba and Buzsaki, 2007; Foster and Wilson, 2006; Hahn *et al.*, 2006; Isomura

et al., 2006; Ji and Wilson, 2007; Sirota *et al.*, 2003); Notably, during sleep, this hippocampal-cortical dialogue is primarily played out during so-called cortical “Up” states, during which the firing rates of large neuronal groups synchronously increase; additionally, the repetitive cycling between “Up” and “Down” states, observed in electrical recordings as a neo-cortical slow oscillation (Steriade *et al.*, 1993), has been suggested to facilitate sleep dependent synaptic plasticity (Brazier, 1949; Luczak *et al.*, 2007; Massimini *et al.*, 2004; Petersen *et al.*, 2003; Tononi and Cirelli, 2003). Furthermore, learning has been demonstrated to affect the pattern of slow oscillations during subsequent sleep (Huber *et al.*, 2004; Molle *et al.*, 2009; Molle *et al.*, 2004). Importantly, preliminary evidence from studies of deep sleep in humans and anesthesia in animals (the latter also show a repetitive cycling of “Up” and “Down” states) suggest that slow oscillations may have a substantial fMRI correlate (Dang-Vu *et al.*, 2008; Liu *et al.*, 2010a), although their scalp distribution may not possess the spatial specificity exhibited by the fMRI activity (Dang-Vu *et al.*, 2008; Murphy *et al.*, 2009).

On the other hand, both the slow oscillation and the alternation between “Up” and “Down” states are virtually absent during the waking state, during which a substantial level of spontaneous fMRI persists. These hypothesized sources therefore do not fully explain the characteristics of spontaneous fMRI activity, and it is possible that some of the activity relates to “off-line” learning during the waking state without the need for facilitatory slow oscillations. In fact, there have been a number of recent reports showing increased spontaneous activity in specific functional networks during off-line periods following learning tasks, including motor learning (Albert *et al.*, 2009), visual processing (Stevens *et al.*, 2010), and visual perceptual learning (Lewis *et al.*, 2009).

USE OF SPONTANEOUS FMRI TO STUDY BRAIN CONNECTIVITY

Concurrently with the attempts to establish the origin and role of spontaneous activity, an increasing number of researchers are starting to analyze spontaneous fMRI activity to improve the understanding of brain connectivity. Recent work has shown that the major correlation patterns in spontaneous activity show a striking resemblance with predictions derived from structural connectivity modeling based on diffusion tensor imaging (Honey *et al.*, 2009). The major network patterns of spontaneous activity may therefore reflect communication between cortical hubs that subserve, in a highly efficient manner, the elaborate connectivity between the local processing modules of the human brain (Buckner *et al.*, 2009). Spontaneous fMRI activity may therefore provide complimentary information to DTI in studying brain connectivity, and provide functional information that is difficult to obtain from electrophysiological studies, which are either too spatially constrained (in the case of intracortical electrodes) or have poor spatial specificity (in the case of EEG and MEG).

One potentially important clinical application that is developing rapidly is the study of mental and neurological disorders (Fox and Greicius, 2010). Striking examples are altered network activity (and possibly connectivity) in diseases of consciousness (Boly *et al.*, 2008; Boly *et al.*, 2009) and in dementia, including Alzheimer’s Disease (Zhang *et al.*, 2010; Zhou *et al.*, 2010). What is currently not well understood is what the causal relationship is between the fMRI findings and the disease process, their neuro-biological origin, and their specificity to the disease. Future mechanistic studies on animal models may shed a light on these issues.

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ABBREVIATIONS

ATP	Adenosinetriphosphate
DTI	Diffusion Tensor Imaging
EEG	Electro-Encephalography
fMRI	functional Magnetic Resonance Imaging
MEG	Magneto-Encephalography
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography

FIGURE. Inter-subject consistency of ICA-derived spatial components of spontaneous activity accross sleep stages

Left half of figure: different colors indicate the individual consistent components (colors were randomly assigned). Right half of figure: color scale indicates probability of spatial overlap of components across subjects. Across both wake and sleep, much of the brain involved in spontaneous activity. From: Masaki Fukunaga, Silvina Horovitz, Walter Carr, Dante Picchioni, Jacco de Zwart, Tom Balkin, Allen Braun, Jeff Duyun, presented at the Organization for Human Brain Mapping 2007 conference.