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Review

Which "neural activity" do you mean? fMRI, MEG, oscillations and neurotransmitters

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ABSTRACT

Over the last 20 years, BOLD-FMRI has proved itself to be a powerful and versatile tool for the study of the neural substrate underpinning many of our cognitive and perceptual functions. However, exactly how it is coupled to the underlying neurophysiology, and how this coupling varies across the brain, across tasks and across individuals is still unclear. The story is further complicated by the fact that within the same cortical region, multiple evoked and induced oscillatory effects may be modulated during task execution, supporting different cognitive roles, and any or all of these may have metabolic demands that then drive the BOLD response. In this paper I shall concentrate on one experimental approach to shedding light on this problem i.e. the execution of the same experimental tasks using MEG and fMRI in order to reveal which electrophysiological responses best match the BOLD response spatially, temporally and functionally. The results demonstrate a rich and complex story that does not fit with a simplistic view of BOLD reflecting "neural activity" and suggests that we could consider the coupling between BOLD and the various parameters of neural function as an ill-posed inverse problem. Finally, I describe recent work linking individual variability in both cortical oscillations and the BOLD-fMRI response to variability in endogenous GABA concentration.

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Introduction

There is no doubt that functional MRI, using the endogenous BOLD contrast, has become an incredibly popular and useful tool for neuroscience that has created a remarkable body of work in just 20 years. Given the indirect, and largely unknown, coupling of the BOLD signal to the underlying neural substrate, its usefulness is even more remarkable.

The popularity of BOLD-fMRI is at least partly driven by its surprising spatial specificity. Early in the history of the technique, it soon became clear that BOLD had exquisite spatial resolution, allowing us to generate high-resolution maps of the borders between human visual areas (Engel et al., 1994; Sereno et al., 1995) in an individual. The fact that these human retinotopic maps revealed exactly the structures and organisation we expected to see from animal neurophysiology studies was a major step forward for the field. In addition, this amazing spatial specificity of the brain's haemodynamics appears to allow us to map structures right down to the columnar level of the visual cortex (Yacoub et al., 2008). Almost magically, our ability to extract spatial information may go beyond the fundamental resolution limit of the images, as small biases in the response properties of

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cells in each voxel may allow us to decode what information the brain is representing/processing (Kamitani and Tong, 2005).

In my opinion, although I may be biased, fMRI has been most successful in studies of human visual cortex—precisely because these studies are designed, and their results interpreted, with direct reference to previous animal neurophysiology studies. BOLD-fMRI studies can, of course, be well designed and executed without reference to previous neurophysiological research and can reveal subtle distinctions between experimental paradigms and participant groups, but the interpretation of any finding should be necessarily limited—it should always be remembered that BOLD is a measure of haemodynamic changes in the brain and these are critically dependent on the nature of the coupling between neurons and haemodynamics. Presumably, the BOLD response is related to the energy demands of modulating various aspects of neural function, including action potentials, neurotransmitter cycling and excitatory and inhibitory post-synaptic potentials, but this still a subject of much active investigation and debate (Attwell and Iadecola, 2002; Attwell and Laughlin, 2001; Mangia et al., 2009; Shulman and Rothman, 1998). In addition, it is known that hemodynamic coupling changes across the brain, across individuals, when challenged with drugs such as caffeine, with age, with disease and with subtle changes in respiration. Many of these effects can be controlled for with appropriate physiological monitoring and calibration (Iannetti and Wise, 2007).

Given all of the above, it is a shame that so many recent fMRI-BOLD studies insist on describing their measured effects as "neural activity". Of course, we hope these effects are in some sense *correlated* with neural function, but we can't be sure that this is true in all cases—this is why I emphasised the link with previous animal neurophysiological work in the visual domain as it gives at least indirect evidence that our measured BOLD-fMRI findings truly reflect neural function.

As many people have pointed out, and as I emphasise in this article, the very phrase *neural activity* is in itself a rather poorly specified and ultimately meaningless term. In most people's minds the term is probably a surrogate for the firing of action potentials. However, within the cortex there are multiple neural signals, at different oscillatory frequencies, that might all contribute to the metabolic demand that then drives the BOLD signal. Furthermore, it's not clear which of these neural signatures are most relevant to each aspect of perception and cognition. This complexity is outlined in Fig. 1. However, all is not lost—we have several tools at our disposal that allow us to investigate which aspects of neural function contribute to the BOLD response and, with appropriate links to behavioural paradigms, which signal is most relevant to each function.

Firing rates, perception and oscillations

Until recently, when people thought about the neural signatures underpinning perception and cognition, there was an implicit assumption that the key measure is the firing rates of neurons. This view arose from the seminal observations that individual neurons in visual cortex were exquisitely tuned to fundamental properties of the visual scene, such as retinotopic location and stimulus orientation (Hubel and Wiesel, 1962). Surprisingly, individual firing rates can also demonstrate specificity to what seem to be quite high-level attributes, such as Jennifer Aniston's face (Quiroga et al., 2005).

There are, however, other electrophysiological signals that also appear to be functionally relevant in the brain, namely oscillatory power increases/decreases that occur in specific frequency bands and within different cortical areas. At the invasive microscopic level, these oscillatory signals can be found in local-field potential (LFP) recordings, where they reflect the integrated post-synaptic potentials of neurons within a millimeter of the recording electrode. However, such signals can also be measured macroscopically at the cortical surface using either electrocorticography (Jerbi et al., 2009), electroencephalography (EEG) or magnetoencephalography (MEG)—these signals then represent the synchronous activity of many square millimeters or centimeters of cortex.

Oscillations in the LFP and EEG have been observed for over a hundred years, with the most well known being the strong posterior alpha oscillation (4–12 Hz), which Berger (1969) observed was strongly modulated by opening and closing the eyes. For most of the history of human EEG, these oscillations were considered a non-specific "nuisance" signal as they got in the way of recording "clean" classic average evoked potentials, especially as a strong alpha signal was usually correlated with inattention. However, in the last few decades, as experimental techniques have developed, many EEG and MEG studies have demonstrated that task-related oscillatory changes are a fundamentally important correlate of many aspects of human brain function. They occur in specific frequency bands, which are functionally specialised, and appear to be modulated in a regionally-specific way (Pfurtscheller and Lopes da Silva, 1999).

Recent animal evidence also demonstrates that, in many situations, firing rates do not correlate well either with perception or awareness but oscillatory modulations do. For example, it is possible to use a suppressive surround of moving dots to mask the perception of an otherwise easily visibly visual target, on a trial-by-trial basis (Wilke et al., 2006). When multiple electrophysiological signals induced by this task are measured in monkey, the results are striking and surprising: firing rates in visual areas V1 and V2 do not predict the perceptual visibility of the target but rather seem to code for the strength of the visual input. A similar result was found when the experimenters looked at LFP power in the gamma range (30–90 Hz). In contrast, LFP amplitude in the low-frequency alpha range (9–14 Hz) was strongly modulated by the awareness of the stimuli. Similarly, a study of binocular rivalry perception in monkeys (Gail et al., 2004) showed that modulation of V1 LFP power in the low-frequency alpha/beta range (<30 Hz) was correlated with changes in perception. In contrast, neither the multi-unit firing rate nor modulations in the gamma range correlated with perceptual changes.

So it seems clear from animal neurophysiology that there is a rich complexity of multiple neural signals that arise in the cortex during perception and cognition, and we are just starting to elucidate their roles. However some researchers have started to describe frameworks that at least attempt this, such as models that describe gamma oscillations as reflecting local representations of stimuli, whilst lower-frequency oscillations underpin longer-range cortical processes (Donner and Siegel, 2011) including decision making (Siegel et al., 2011). Others have demonstrated that the active inhibition of macroscopic alpha rhythms may be crucial in allowing a cortical area to becoming engaged in a cognitive task (Palva and Palva, 2007; van Dijk et al., 2010).

Cognitive functions may also be dependent on shifts in the properties of oscillations (Fries, 2009), such as phase-coupling between different areas (Fries, 2005) and/or frequencies (de Lange et al., 2008; Jensen and Colgin, 2007; Jerbi and Bertrand, 2009; Palva and Palva, 2007), that may have no discernible metabolic or haemodynamic consequences. Oscillations may also play a crucial role in facilitating the routing of information across cortical areas (Colgin et al., 2009; Knoblich et al., 2010), by modifying the timing and rates of firing in each area (Fries et al., 2007). It is also important to point out that it is theoretically possible that LFP or EEG/MEG correlates of the fMRI signal may not always be observable as they are dependent on temporal synchronisation of a neural population, something which is not strictly necessary for the production of a BOLD response.

Here, I can only give a brief flavour of how modelling, invasive electrophysiology and EEG/MEG recordings are being used to understand the complexity of how electrical activity in the brain supports cognitive function, and I have surely missed some important issues and references. However, for those of us who use fMRI, the key question is this: which components of this rich mixture of electrophysiological parameters drive the BOLD response?