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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.



**Contents**



## 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?

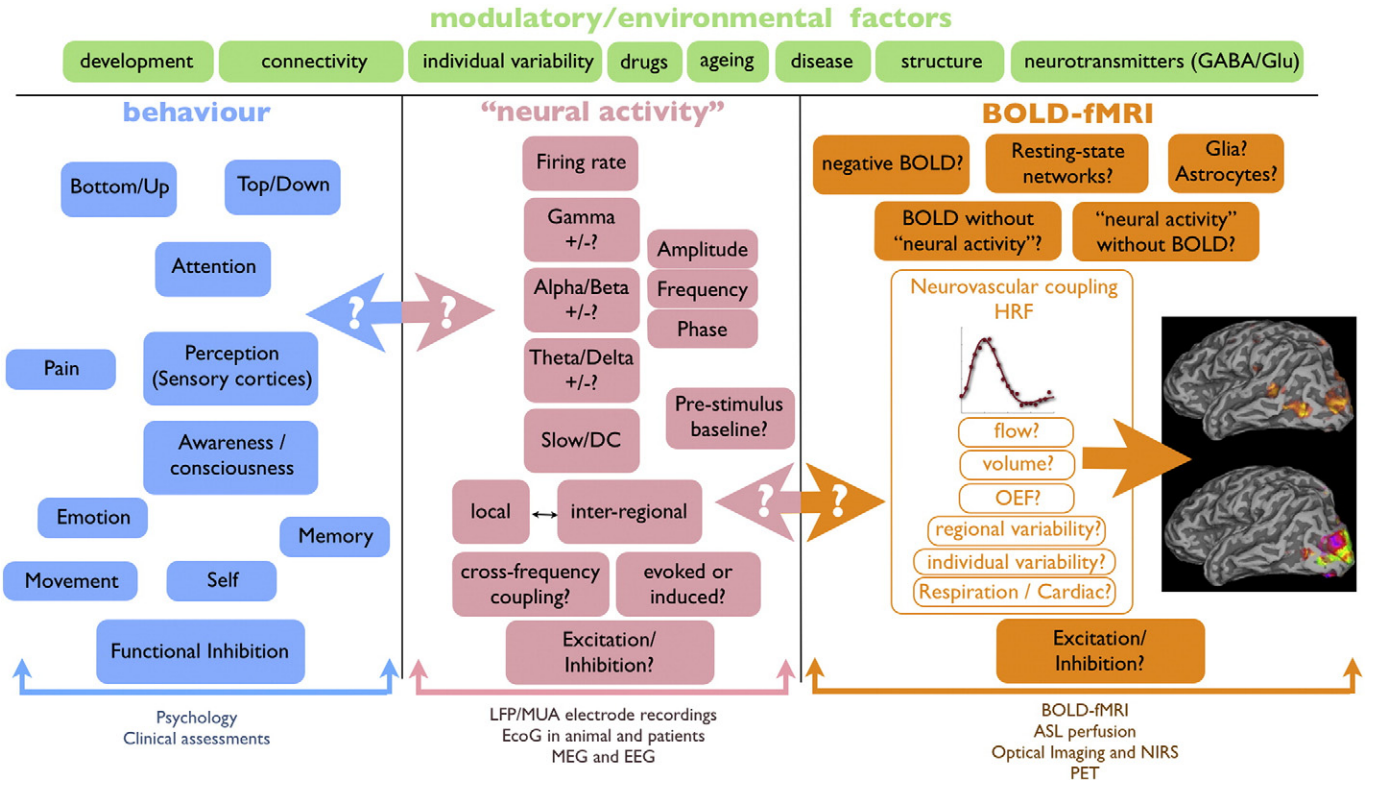


**Fig. 1.** It's a long way from behaviour to BOLD. This schematic attempts to show the complexity of the situation, with multiple neural effects (pink boxes) sitting between human function (blue) and the haemodynamic signal underpinning BOLD (orange boxes). This figure doesn't attempt a complete description of all the relevant issues, and readers will be able to identify missing boxes in all of these domains. Note that inhibition, in one form or another, is relevant in all sections: In the behavioural section (blue) functional inhibition is involved in many tasks, some of which have been linked to variability in baseline neurotransmitter (GABA) concentration (Boy et al., 2011; Boy et al., 2010; Edden et al., 2009; Sumner et al., 2010; Yoon et al., 2010). Excitation and inhibition are obviously key features in the neural domain, but it is increasingly clear that variations in the balance between these neural effects might also modulate fMRI-BOLD responses. For example, shifts in the local excitation/inhibition balance could induce either positive or negative apparent BOLD responses in a population of neurons (Logothetis, 2008; Tagamets and Horwitz, 2001). Note that the arrow between the neural and BOLD-fMRI sections is deliberately bi-directional—some have proposed that haemodynamic changes may directly modulate local "neural activity" (Moore and Cao, 2008).

## The relationship between BOLD and oscillatory activity in the cortex

There are many experimental approaches that we can adopt to try and understand which aspects of neural function drive the haemodynamic response in BOLD-fMRI. These include simultaneous invasive electrode recordings and BOLD-fMRI in animals such as rat (Boorman et al., 2010) and macaque (Logothetis et al., 2001) and studies comparing electrode recordings in implanted human epilepsy patients with BOLD-fMRI in healthy human participants performing the same tasks (Mukamel et al., 2005). The results of these studies are striking and usually quite complex. In the primary sensory cortices, BOLD-fMRI appears to temporally correlate well with local-field potential (LFP) power, particularly in the gamma range (30 Hz and upwards) (Logothetis et al., 2001). Interestingly, when looking at intrinsic variability of responses over time, BOLD appears to correlate better with LFP in the gamma range than it does with the firing rates of neurons i.e. multi-unit activity (Niessing et al., 2005). However, this strong relationship between task-related gamma and BOLD is not always evident. For example, BOLD and gamma have different tuning characteristics for stimulus properties such as spatial frequency (Muthukumaraswamy and Singh, 2008, 2009). Similarly, in human primary visual cortex, isoluminant red-green stimuli induce no measurable gamma (Adjamian et al., 2008), whilst the BOLD response appears strong to both colour and luminance contrast (Mullen et al., 2007).

At lower frequencies, such as the Alpha (5–15 Hz) and Beta (15–25 Hz) range, often a negative correlation is observed (Mukamel et al., 2005; Zumer et al., 2010) i.e. when oscillatory power is highest in these lower-frequency ranges, BOLD is at its weakest. So, even for the simplest experimental paradigms in primary visual cortex, there are multiple neural signatures that are correlated with the BOLD response and may contribute to the generation of the fMRI signal.

## MEG and fMRI

An alternative, non-invasive, experimental approach is to perform the same experiments in human using BOLD-fMRI and techniques such as EEG and MEG and see which electrophysiological signals seem to match the BOLD response. To a certain extent, this can be done using simultaneous EEG–fMRI, but due to the MR environment, it can be difficult to measure the full spectrum of oscillatory responses and true source-localisation, as opposed to simple temporal correlation with the BOLD signal, can be problematical.

In my own work, we have concentrated on comparing responses recorded using MRI and MEG in separate sessions. This is valid, so long as an analysis of trial-to-trial variability in individual subjects is not needed. Using this approach, there are several useful sources of variance that we can investigate: 1) Does the spatial location of the MEG-measured signals match that of the fMRI response? 2) Does the BOLD response amplitude behave in the same way as the electrophysiological signal(s)? 3) Does individual variability in the BOLD response predict individual variability in some aspect of the MEG signal?

Starting in the mid-1990s, several studies used this comparison approach (Ahlfors et al., 1999; Dale et al., 2000; Moradi et al., 2003) and significant methodological advances were made in terms of using fMRI spatial information to improve the MEG inverse problem i.e. the goal was to create a spatiotemporal imaging approach that combined the temporal resolution and moderate spatial resolution

of MEG with the much better spatial information found in fMRI. For example, it was shown that MEG could be used to follow the anterior–posterior "sweep" of activity that occurred across the cortex during a reading task (Dale et al., 2000) and that the cortical localisation of these effects was much improved by fMRI constraints. Although an important step forward, these papers assumed that the only MEG-measured signal that was functionally relevant were phase-locked evoked responses i.e. transient signals that are exquisitely time-locked to the trial onset. A further assumption was that the BOLD response is the haemodynamic reflection of these evoked responses. As we have discussed above, neither of the assumptions are guaranteed to be true.

*Oscillations and BOLD in human*

In the last few years, several groups, including my own, have used beamformer algorithms (Hillebrand et al., 2005; Vrba and Robinson, 2001) to localise task-related oscillatory modulations measured with MEG, and to compare these responses with those measured using fMRI. Beamformer reconstructions are particularly well-suited to this task (Hillebrand et al., 2005) and in particular can reconstruct non phase-locked, i.e. *induced* responses. To do this, averaging over trials is done in the Fourier domain, to give a more complete picture of activity. A conventional evoked-response analysis will usually average all trials in the time domain. This reveals only *evoked* activity i.e. those responses that occur at the same latency after trial onset on every trial—any variability in the response phase will result in no visible average activity.

In 2002 we performed two experiments using this approach (Singh et al., 2002), and the results are reproduced in the upper panels of Fig. 2. Participants performed two tasks: a verbal fluency language task in which subjects must silently generate words beginning with a given letter, and a biological motion discrimination task in which subjects had to identify the direction of walking of a scrambled point-light figure. These tasks were performed using the same experimental designs in both MEG and MRI, but note that the participants are different in all four experiments. The designs of these two experiments were optimised for fMRI, in that they were "classic" 15-second boxcar designs. In this regard the designs were not suitable for a classic event-related EEG or MEG experiment. This type of design is, however, well-suited to a frequency-domain beamformer analysis of the MEG data, in which we look for task-related power increases or decreases in particular frequency bands.

Despite the fact that these tasks are so different, we found the same oscillatory signatures spatially matched the BOLD i.e. a suppression of oscillatory power in the beta band, specifically 15–25 Hz. Similar suppressive effects were also seen in the alpha-band (5–15 Hz) and high-beta band (25–35 Hz) (Singh et al., 2003). Our data is therefore consistent with subsequent human electrocorticography and MEG studies showing a negative temporal correlation between BOLD and alpha/beta (Mukamel et al., 2005; Zumer et al., 2010) and recent models suggesting the importance of suppression of low-frequency rhythms as a mechanism of release from inhibition (van Dijk et al., 2010). MEG localisations of task-related reductions in alpha/beta, and in some cases a spatial match to the same BOLD experiment, have also been demonstrated in a range of tasks, including simple activation of V1 (Brookes et al., 2005), visual motion perception—both real and implied (Fawcett et al., 2004; Fawcett et al., 2007), sensorimotor execution (Gaetz and Cheyne, 2003; Muthukumaraswamy, 2010; Stevenson et al., 2011), reading (Pammer et al., 2004), object perception (Maratos et al.,

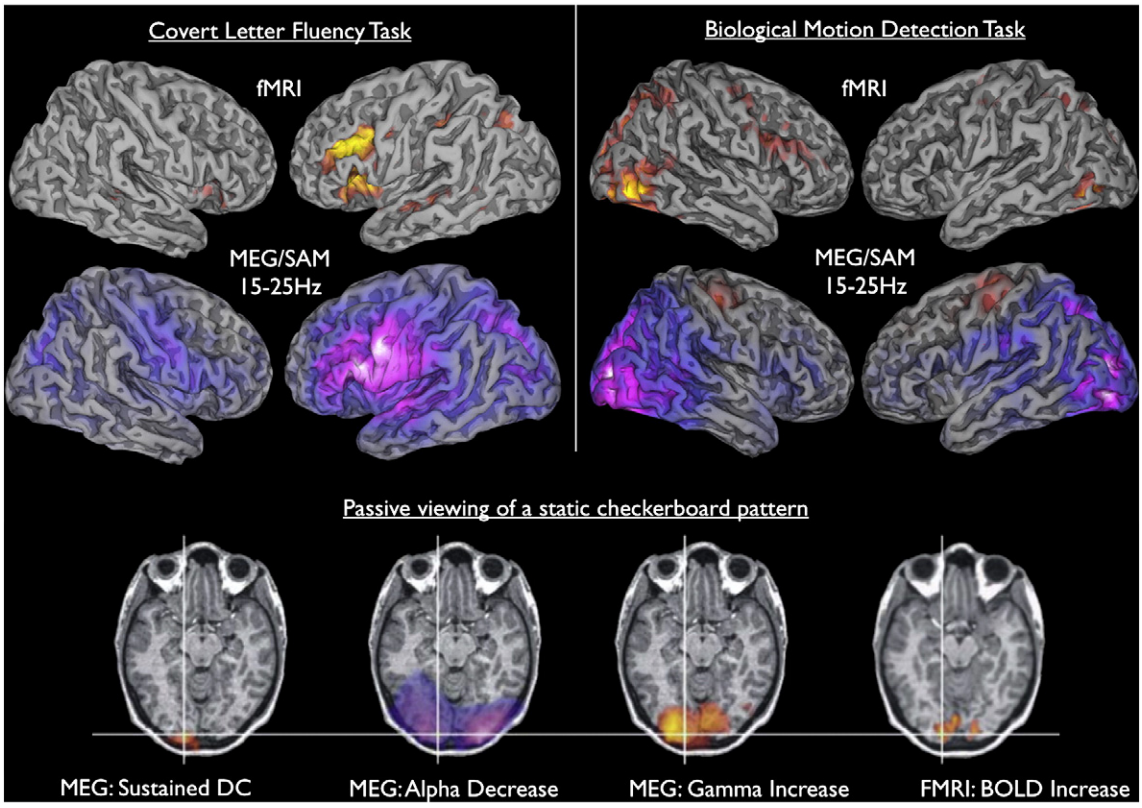


**Fig. 2.** MEG and BOLD fMRI comparison studies. In the top panels, we see a comparison of the group average fMRI response in two different tasks (covert letter fluency and biological motion perception) to the oscillatory modulations revealed by performing the same task using MEG and beamformer source reconstructions. For both tasks, the main oscillatory response was a suppression of the alpha/beta rhythm (shown as blue/purple colours). These occurred in the same locations as the BOLD response (Singh et al., 2002). The bottom row shows individual data from a different experiment in which participants viewed a static visual checkerboard pattern. In this individual, the MEG beamformer reconstructions show three different electrical responses, all of which occur in the same location as the BOLD response (Brookes et al., 2005). Note that the MEG source reconstructions have a poorer spatial resolution than the fMRI.

2007), semantic processing (McNab et al., 2007) a choice reaction-time paradigm (Winterer et al., 2007) and smooth pursuit eye-movement control (Dunkley et al., in press).

In many of these studies, a complex mixture of electrophysiological signals is evident that both positively and negatively correlate with the BOLD response. This is true for even the most simple of tasks—the passive viewing of a checkerboard pattern, that we showed induced alpha power reductions, gamma power increases and an evoked DC change, all measured with MEG (Brookes et al., 2005). These were closely co-localised with the fMRI-BOLD response in the same participant and are shown in the lower panel of Fig. 2.

Given this complexity, the challenge now is to understand how each of these electrical signals contributes to the BOLD response, and clarifying their functional role. Starting with what we hoped was the simplest oscillatory signal, in recent years myself and colleagues have concentrated our efforts on a measure that probably reflects initial local processing of the stimulus and its attributes—the induced gamma oscillation in primary visual cortex.

## Primary visual cortex gamma

In the 1980s and 90s investigations of the local-field potential in cat primary visual cortex revealed that presentation of simple static stimuli induced an oscillation in the visual gamma band (30–90 Hz) that was sustained throughout the presentation of the stimulus (Gray and Singer, 1989; Kayser et al., 2003). Note that the stimulus itself is not temporally varying—the oscillation, and its properties such as frequency and bandwidth, are intrinsic properties of the cortex itself and arise from local synchrony in a population of cells. Importantly, the greatest synchronisation across the cortex appeared to occur for long continuous edges, leading to theories that this gamma band synchrony underpins perceptual binding of an object (Singer and Gray, 1995).

It is thought that this oscillation arises within a cortical population of excitatory pyramidal cells and inhibitory interneurons (Whittington et al., 2011) and is an emergent property i.e. it's properties do not directly reflect the firing rates of individual neurons in the network (Henrie and Shapley, 2005). For example, its amplitude is greatest for very high-contrast stimuli, whilst firing rates saturate at modest contrasts (Henrie and Shapley, 2005). It also increases in amplitude with stimulus size, even as firing rates decrease when the stimulus encroaches on a cell's inhibitory surround (Gieselmann and Thiele, 2008). Taken together, all of these studies point to a critical role of GABAergic inhibition in determining the properties of visual gamma.

In 2004, we demonstrated it was possible to measure, localise and characterise the induced visual gamma oscillation in human using MEG (Adjamian et al., 2004) and showed that the optimal stimulus was a black-white high-contrast square-wave grating patch, of spatial frequency 3 cycles/degree. If such a stimulus is shown to a participant, then a gamma oscillation is induced at the retinotopic location and occurs in a specific narrow-band frequency (see Fig. 3). Such a narrow-band response has previously been shown in local-field potential recordings in cat (Kayser et al., 2003) and ECoG recording in monkey (Ray and Maunsell, 2010, 2011; Rols et al., 2001). Since then, ourselves (Edden et al., 2009; Muthukumaraswamy et al., 2009; Muthukumaraswamy and Singh, 2008, 2009; Muthukumaraswamy et al., 2010; Swettenham et al., 2009) and other groups (Donner and Siegel, 2011; Hoogenboom et al., 2006) have demonstrated that these visual gamma responses can be detected using MEG and appear to match well those signals previously identified in invasive LFP recordings.

The time–frequency representation shown in Fig. 3 demonstrates just how rich the MEG-measured electrophysiological record is, even to simple passive viewing of a static grating stimulus. As well as the sustained gamma response, initially there is a low-frequency transient, which is the signature of the classic pattern-onset, P100, evoked response. There is also a transient high-frequency evoked gamma "spike" that is thought to occur in both the retina and LGN, before being coupled up to cortex (Castelo-Branco et al., 1998). Recent LFP recordings in Macaque monkey suggest that this gamma spike is highly correlated with neuronal firing rates in V1, but the sustained induced gamma signal is not (Ray and Maunsell, 2011). So even in the gamma frequency range, there are at least two signals that may, or may not, be drivers of the BOLD response. As discussed in the previous section, there is also a reduction in power in the alpha/beta band, which may reflect longer-range attention and integration processes (Donner and Siegel, 2011).

Given the previous literature linking BOLD to gamma responses (Donner and Siegel, 2011; Logothetis et al., 2001; Mukamel et al., 2005; Niessing et al., 2005) we, and others, have performed several fMRI/MEG experiments in which we modulated the properties of the visual stimulus. The results are mixed: gamma amplitude tunes monotonically with contrast (Hall et al., 2005) as does BOLD, but is it more sharply tuned for spatial frequency than BOLD (Muthukumaraswamy and Singh, 2008, 2009) and has a different sensitivity to the temporal frequency of the stimulus. Other groups have also demonstrated that BOLD and gamma have very different sensitivities to luminance and colour contrast (Adjamian et al., 2008; Mullen et al., 2007). Taken together, the human gamma literature suggests that although BOLD and induced gamma effects occur at the same location during the task, the BOLD response may only be partially driven by these gamma responses. Other studies have shown that BOLD amplitude might be more related to transient evoked responses, perhaps linked to neuronal firing rates, than it is to the induced, sustained, gamma signal (Zaehle et al., 2009).

## Individual variability: induced gamma as a biomarker of inhibition?

Another way of investigating the coupling between function, neural signals and the BOLD response is to study the variability of each parameter across participants. Individual variability and repeatability of the BOLD response have been studied several times (See McGonigle, in press) but relatively little work has been done on the variability/repeatability of cortical oscillatory signals. Recently, our group and others (Hoogenboom et al., 2006; Muthukumaraswamy et al., 2010) have shown that MEG-measured oscillatory responses in primary visual cortex are remarkably stable (Fig. 4). Importantly, there is significant individual variability in parameters such as the sustained visual gamma frequency, which is stable over weeks, but appears to decline with age (Gaetz et al., in press; Muthukumaraswamy et al., 2010). So what drives individual variability in gamma frequency?

Modelling studies suggest that visual gamma frequency may be related to the balance between excitation and GABAergic inhibition (Brunel and Wang, 2003) and recent developments in edited Magnetic Resonance Spectroscopy (MRS) methods allow the quantification of GABA concentration within specific regions of the cortex (Edden and Barker, 2007; Mescher et al., 1998; Puts and Edden, 2012). MRS is, in some ways, a rather blunt tool in that it can only be used to measure GABA concentration in a relatively large single voxel—typically tens of cubic centimeters in size. The measurements also take several minutes, so these are only really suited to assessing baseline resting GABA, rather than functional changes. However, several recent studies have demonstrated that GABA-MRS measures do seem to reflect a behaviourally relevant measure of inhibitory function in humans (Boy et al., 2011; Boy et al., 2010; Edden et al., 2009; Stagg et al., 2011; Sumner et al., 2010; Yoon et al., 2010).

Our hypothesis, therefore, was that individual variability in gamma frequency might be predicted by individual variability in resting GABA concentration. In two recent studies (Edden et al., 2009; Muthukumaraswamy et al., 2009) we demonstrated a clear correlation i.e. people with higher GABA concentrations appear to have a

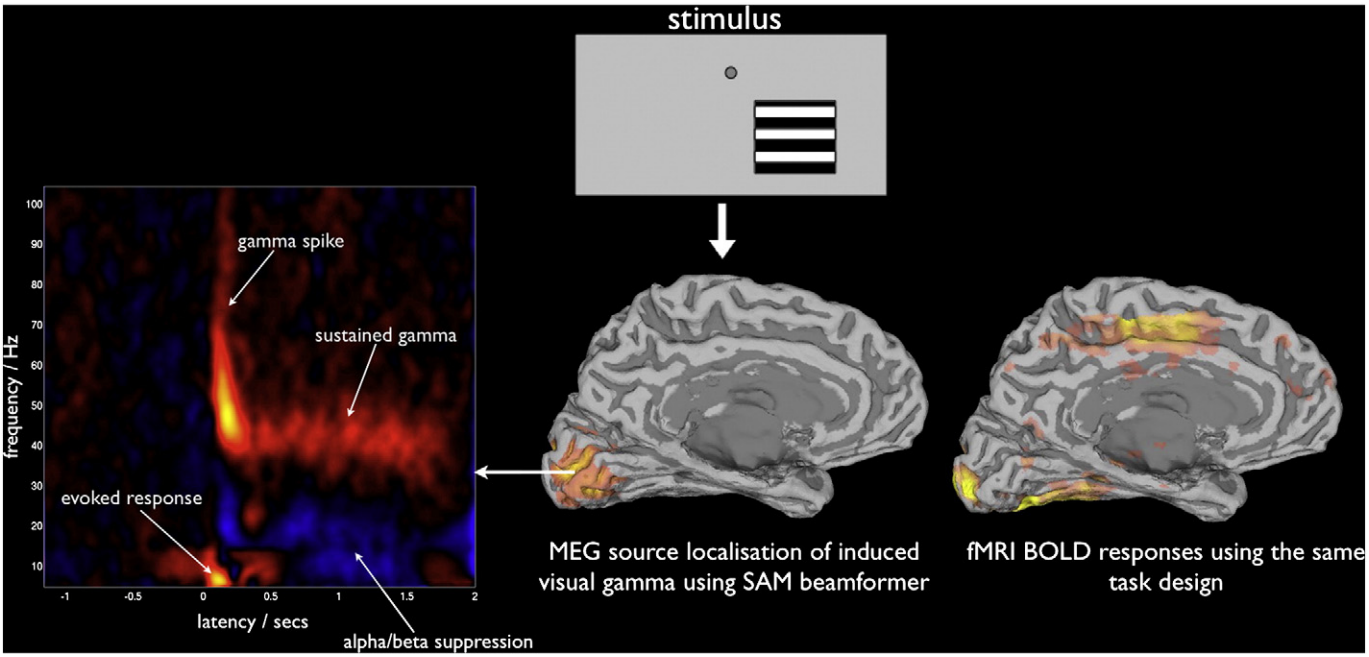


**Fig. 3.** A description of the visual gamma experiment. Participants view a simple high-contrast grating stimulus that is present for approximately 2 s. The MEG recordings are analysed using a SAM beamformer, which reveals a peak response in the primary visual cortex. A "virtual electrode" can then be placed at this peak location and the time–frequency response profile can be calculated (leftmost panel). This analysis reflects the complexity of the response—there are at least four different electrophysiological signals evoked/induced by the stimulus. All of these can be compared to the response properties of the BOLD signal in the same individual. See (Muthukumaraswamy et al., 2009; Swettenham et al., 2009) for a more detailed description of the methods used.

higher sustained gamma oscillation frequency (Fig. 5). This suggests that the spectral characteristics of the response to a static visual stimulus may provide a biomarker of GABAergic inhibition in the cortex. Similar results have been found for the oscillatory signals in human motor cortex (Gaetz et al., 2011). If true this would provide us with a sensitive window onto diseases such as schizophrenia (Gonzalez-Burgos et al., 2010) and epilepsy, which may well involve a GABAergic deficit. It might also provide a biomarker for the action of novel CNS drug targets, particularly those designed to modulate the GABA system (Hall et al., 2010a,b; Licata et al., 2011). Importantly, MEG-measured oscillatory biomarkers offer a direct link to the electrical properties of synaptic function, yielding an advantage over MRS GABA measures, in which it is not yet clear how bulk concentration is related to, for example, GABA receptor density and activity. One promising future direction for this type of work is the use of biophysical models of synaptic function. For example, it was recently shown that such a model can be used with drug-induced changes in MEG oscillatory parameters to infer dopaminergic changes in AMPA/NMDA receptor signalling within the cortex (Moran et al., 2011).

*Individual variability in induced visual Gamma, the BOLD response and GABA concentration*

We also studied how individual variability in the BOLD response correlated with parameters of the gamma response (Fig. 5). Surprisingly, individual variability in gamma amplitude was not correlated with BOLD response amplitude. However, visual gamma frequency was strongly inversely correlated with the BOLD response amplitude—participants with a high gamma frequency tended to have a smaller BOLD response (Muthukumaraswamy et al., 2009). Given that we have already shown that gamma frequency is correlated

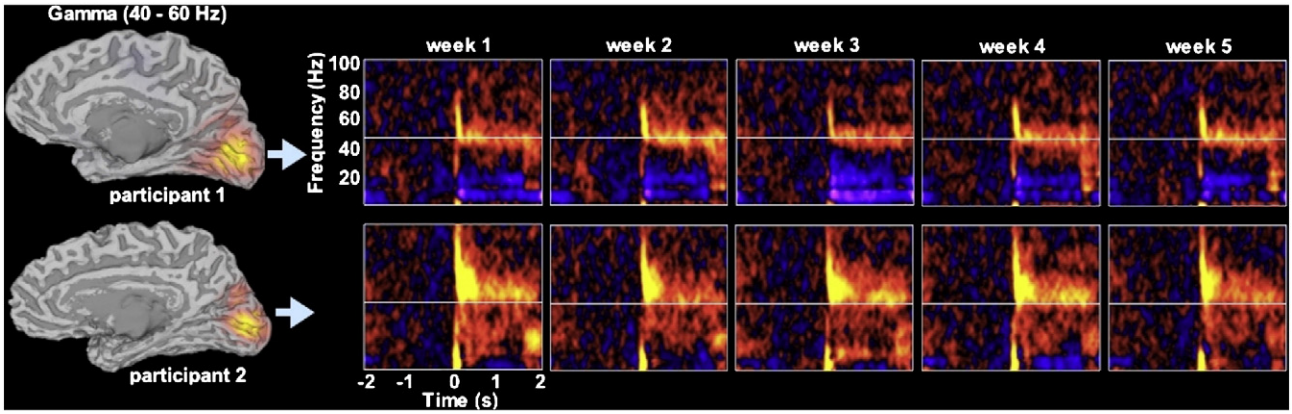


**Fig. 4.** Visual oscillatory responses are stable over weeks. This figure shows MEG/SAM source reconstructions of the visual gamma response in two individuals (left side). This experiment was repeated every week for five weeks and the virtual electrode time–frequency reconstructions are remarkably consistent. In particular the sustained gamma frequency appears stable over this period of time.
Data taken from Muthukumaraswamy et al. (2010).

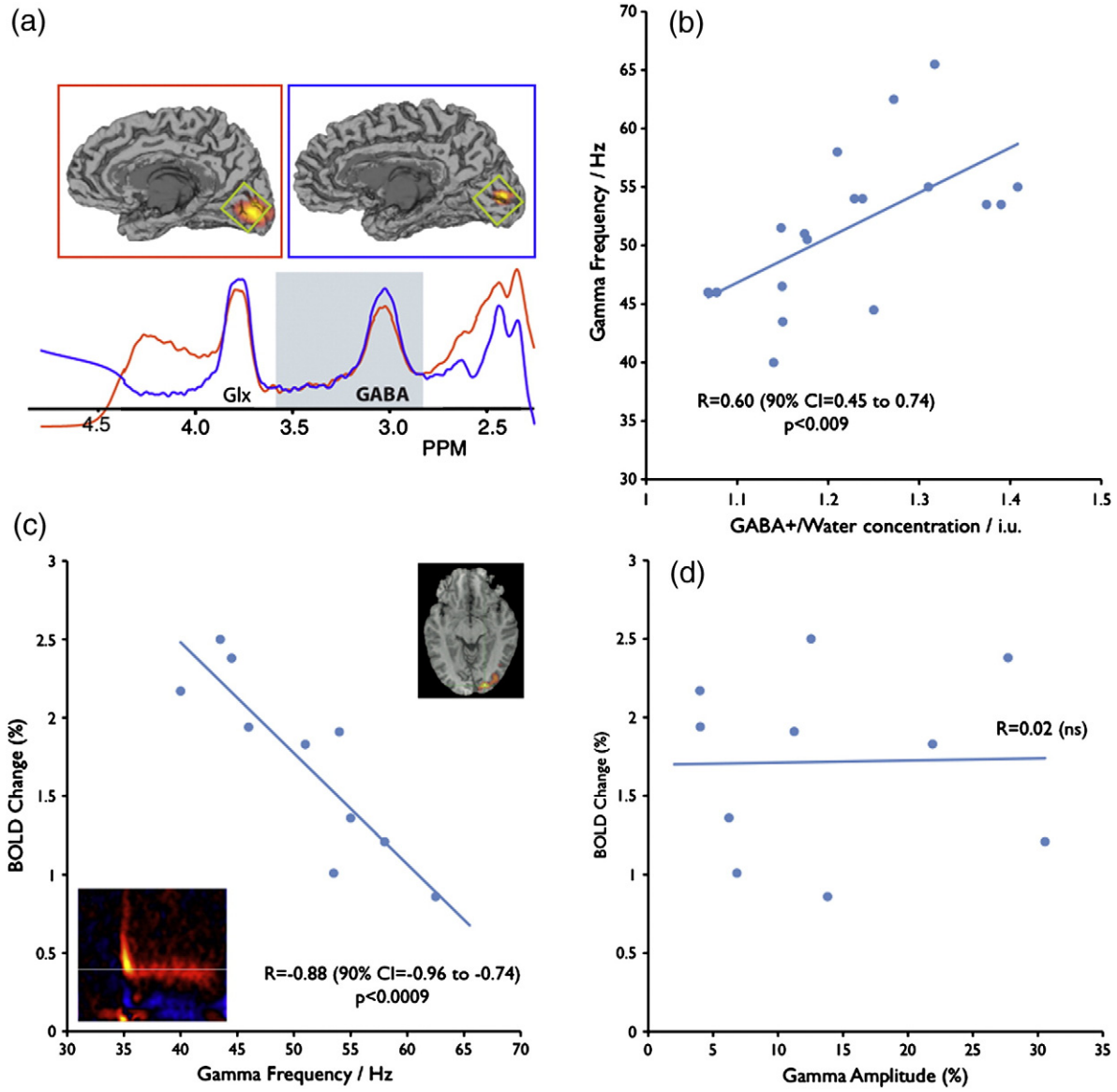


**Fig. 5.** Correlations between GABA concentration, gamma frequency, gamma amplitude and BOLD. Using an edited MRS sequence we are able to measure baseline GABA concentration in an individual. For two individuals, in (a) we show the placement of the MRS acquisition voxel as a green box on the participant's cortical surface—the voxel is typically $3\times3\times3$ cm in size. The orange activation map is the MEG/SAM localisation of the visual gamma response in each individual. Below this the edited spectra are shown for these individuals. In both cases a clearly resolved GABA peak is shown at 3 ppm. Our estimate of GABA concentration is the integral of the peak, normalised by the water signal in the same voxel. (b) Shows the positive correlation between visual gamma frequency and the estimated GABA concentration for 18 individuals. Here we have pooled the cohorts from two studies (Edden et al., 2009; Muthukumaraswamy et al., 2009). c) In those participants who also had BOLD-fMRI measures for the same task, we also saw a negative correlation between gamma frequency and BOLD amplitude. Surprisingly, there was no correlation, across participants, between BOLD amplitude and gamma amplitude (d).

with GABA concentration, it makes sense to conclude that baseline GABA concentration may also be negatively correlated with the magnitude of the BOLD response.

In support of this, previous animal evidence suggests that the magnitude of the BOLD response is closely related to resting GABA concentration. For example, rats that are given vigabatrin, a drug that blocks the action of gabatransaminase, show a significant increase in MRS measures of GABA concentration and a concomitant reduction in the sensorimotor cortex BOLD response to forepaw stimulation (Chen et al., 2005). There is now evidence from several human studies that the BOLD response is also related to variability in GABA concentration and these are summarised in Fig. 6. In two studies, we showed that the BOLD response magnitude in primary visual cortex was inversely correlated with GABA concentration (Muthukumaraswamy et al., 2009, 2012) (Figs. 6a and d), a finding that was replicated by Donahue et al. (2010) using a different visual stimulation paradigm (Fig. 6b). Recently, it has been shown that BOLD responses in motor cortex are also inversely correlated with baseline GABA concentration (Stagg et al., 2011). Interestingly, it has also previously been shown that the negative BOLD response associated with task-related suppression of the default-mode network (DMN) was also negatively correlated with GABA concentration in the anterior-cingulate region of the cortex (Northoff et al., 2007) (Fig. 6e). Importantly, Donahue et al. (2010) also used ASL and VASO sequences in the same participants to look at how blood flow and blood volume may also be influenced by variability in GABA concentration. As with BOLD, blood volume reactivity was inversely correlated with GABA, whereas ASL estimates of flow reactivity appeared to be positively correlated with GABA. The authors speculate that this unexpected finding is perhaps due to either greater baseline tonic inhibition necessitating increased excitatory drive, with an increased associated vascular response, or a correlated variation in the arterial

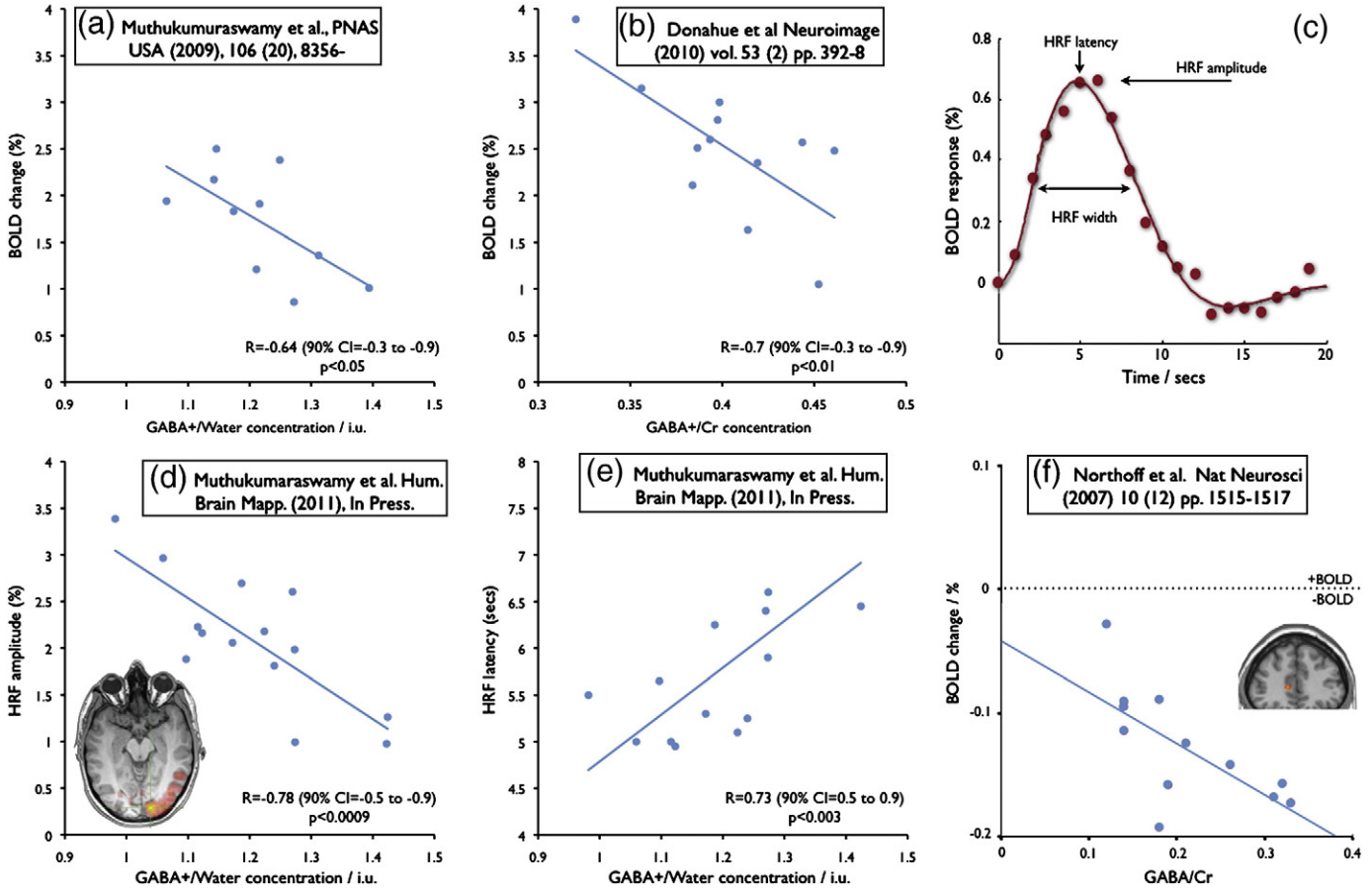


**Fig. 6.** Here are summaries of the results of 4 studies, all of which demonstrate that individual variability in the BOLD response is related to individual variability in baseline occipital GABA concentration. Three of these studies (a, b, d) show that the positive BOLD response across individuals is negatively correlated with GABA concentration. One study also revealed that those individuals with higher resting GABA concentration tended to have a slower BOLD response (e). Interestingly, the negative BOLD response that occurs in the anterior portion of the default-mode network (DMN) during a picture task shows a similar dependency on GABA concentration (f).

blood arrival times. In our second study (Muthukumaraswamy et al., 2012), we also found that timing parameters of the HRF appeared to be related to variability in GABA—those participants with greater occipital GABA concentration appeared to have a slower haemodynamic response (Fig. 6e). Taken together, these studies suggest that variability in baseline GABA concentration may lead to variability in the magnitude of the BOLD response either via changes in neuronal activity, by modulation of the vascular properties of the haemodynamic response itself or a combination of the two effects.

All of the above studies have important implications for BOLD-fMRI studies, particularly those looking at differences within and between population groups. If GABA has a direct modulatory effect on the BOLD response, then we would expect to see differences in BOLD magnitude in patient populations that are hypothesised to have a GABAergic deficit, such as Schizophrenia, Epilepsy and Autism. These differences may be due to difference in neural activity or, as we show above, differences in the haemodynamic coupling between neural activity and the BOLD response. It also suggests a difficulty in interpreting whether increased BOLD in a particular participant cohort is a good or bad thing. For example, a pathological reduction in GABAergic inhibition would likely result in an increased BOLD response. As people age, and GABAergic inhibition declines, it's possible that we would also see an increased and more widespread fMRI signal. Such effects have indeed been seen in fMRI ageing studies and are often cited as evidence of compensatory recruitment (Cabeza et al., 2002)—but could they, at least in part, be due to reduced inhibition?

As a note of caution, it's important to note that all of the above studies are correlative in nature. It is entirely possible that the relationships described between gamma frequency, GABA and BOLD are mediated by one or more hidden variables, although our hypotheses of direct links between these parameters were driven by modelling (Brunel and Wang, 2003) and animal evidence (Chen et al., 2005). The best way to show a causal relationship between these parameters in humans is to use drug and trans-cranial stimulation interventions and these studies are starting to appear in the literature. For example, a recent study (Licata et al., 2011) used Zolpidem, a drug known to boost GABAergic inhibition via positive allosteric modulation at the GABA-A benzodiazepine receptor site, to study the visual BOLD response in a cohort of healthy humans. As predicted, the visual BOLD response was reduced after Zolpidem administration, confirming a causal relationship between variations in GABA and the magnitude of the fMRI signal. However, this modulation could either be via modulation of neural activity or changes in neurovascular coupling—performing similar pharmacological studies using MEG to measure, for example, visual gamma, will further help to unravel the complex nature of these relationships.

## Conclusion: The BOLD "inverse problem"

In this article, I've attempted to show how adopting a multi-modal imaging approach, using MEG, fMRI and MRS can start to help us understand some of the complexity underpinning the tri-partite relationship between human cognition, neural responses and the BOLD-fMRI signal. These non-invasive approaches are complementary to animal studies attempting to shed light on the same problems.

In some ways, the use of fMRI in cognitive and clinical neuroscience has raced ahead of our understanding of these complex issues,

and often the link to the underlying neurophysiology is simply assumed, if it is thought about at all. In contrast, animal neurophysiological studies and human EEG/MEG experiments are revealing a deep complexity and richness in the neural domain that is presumably telling us something fundamental about how the brain works—parameters in the oscillatory domain such as amplitude, frequency and synchrony appear to play a key role in perception and cognition, both locally within cortical regions and globally across the brain. If, as we hope, fMRI, with its exceptional spatial resolution and ease of use, is going to contribute to our understanding of how the brain works, we need to fully understand how the BOLD contrast relates to all of these neural signals, across the brain and across individuals.

One oft-made valid criticism of EEG and MEG is that they suffer from a non-unique inverse problem—there is simply not enough information in the external recordings to unambiguously reconstruct the spatial distribution of activity within the brain. A source-reconstruction can only be performed by imposing extra information, such as constraints on the source geometry or the temporal relationships of the sources. This is one of the original reasons why many of us perform the same experiments using both MEG and fMRI—it allows us to at least partially validate the spatial localisations we get from our inverse-problem reconstructions.

However, I'd like to argue that fMRI suffers from a similarly inconvenient inverse problem. When we see a positive or negative BOLD response in our data, there are many different ways that this could have occurred. Any of the neural signatures that I have described in this article (and in the middle panel of Fig. 1) could have been modified by the task, not to mention shifts in modulatory factors such as physiological state or the excitation/inhibition balance. In the BOLD response itself there is simply not enough information to unambiguously resolve which of these factors have resulted in a measurable signal. This is why we need to combine information from other imaging modalities, so we can fully understand what BOLD is telling us.

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