NeuroImage 133 (2016) 62–74

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Global signal modulation of single-trial fMRI response variability: Effect on positive vs negative BOLD response relationship

S.D. Mayhew [a,*], K.J. Mullinger [a,b], D. Ostwald [c,d], C. Porcaro [e,f,g], R. Bowtell [b], A.P. Bagshaw [a], S.T. Francis [b]

[a] Birmingham University Imaging Centre (BUIC), School of Psychology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
[b] Sir Peter Mansfield Magnetic Resonance Centre, School of Physics and Astronomy, University of Nottingham, Nottingham, UK
[c] Arbeitsbereich Computational Cognitive Neuroscience, Department of Education and Psychology, Free University Berlin, Berlin, Germany
[d] Center for Adaptive Rationality (ARC), Max-Planck-Institute for Human Development, Berlin, Germany
[e] Laboratory of Electrophysiology for Translational Neuroscience (LET'S) – ISTC – CNR, Department of Neuroscience, Fatebenefratelli Hospital Isola Tiberina, Rome, Italy
[f] Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK
[g] Department of Information Engineering,Università Politecnica delle Marche, Ancona, Italy

ARTICLE INFO

Article history:
Received 12 May 2015
Accepted 29 February 2016
Available online 5 March 2016

Keywords:
Negative BOLD response
Deactivation
Global signal
RSFA

ABSTRACT

In functional magnetic resonance imaging (fMRI), the relationship between positive BOLD responses (PBRs) and negative BOLD responses (NBRs) to stimulation is potentially informative about the balance of excitatory and inhibitory brain responses in sensory cortex. In this study, we performed three separate experiments delivering visual, motor or somatosensory stimulation unilaterally, to one side of the sensory field, to induce PBR and NBR in opposite brain hemispheres. We then assessed the relationship between the evoked amplitudes of contralateral PBR and ipsilateral NBR at the level of both single-trial and average responses. We measure single-trial PBR and NBR peak amplitudes from individual time-courses, and show that they were positively correlated in all experiments. In contrast, in the average response across trials the absolute magnitudes of both PBR and NBR increased with increasing stimulus intensity, resulting in a negative correlation between mean response amplitudes. Subsequent analysis showed that the amplitude of single-trial PBR was positively correlated with the BOLD response across all grey-matter voxels and was not specifically related to the ipsilateral sensory cortical response. We demonstrate that the global component of this single-trial response modulation could be fully explained by voxel-wise vascular reactivity, the BOLD signal standard deviation measured in a separate resting-state scan (resting state fluctuation amplitude, RSFA). However, bilateral positive correlation between PBR and NBR regions remained. We further report that modulations in the global brain fMRI signal cannot fully account for this positive PBR–NBR coupling and conclude that the local sensory network response reflects a combination of superimposed vascular and neuronal signals. More detailed quantification of physiological and noise contributions to the BOLD signal is required to fully understand the trial-by-trial PBR and NBR relationship compared with that of average responses.

Introduction

BOLD functional magnetic resonance imaging (fMRI) is widely used in human neuroimaging to localise the spatial origin of brain activity in response to experimental tasks or stimuli. The majority of fMRI studies utilise the increase in BOLD signal that occurs following stimulus onset, relative to pre-stimulus or "resting" baseline levels, (termed the positive BOLD response, PBR) to infer that increased neuronal activity occurred in response to the stimulus. This assumption is supported by neurophysiology experiments in both humans and primates which have shown that the fMRI signal is an indirect, vascular correlate of increased neuronal activity in the form of local field potential and multi-unit activity (Heeger et al., 2000; Logothetis et al., 2001; Magri et al., 2012; Mukamel et al., 2005; Viswanathan and Freeman, 2007).

In addition, experimental stimuli often induce a decrease in BOLD signal below the baseline level, termed the negative BOLD response (NBR). For example, when stimuli are delivered unilaterally, such as images presented to one half of the visual field or the movement of one limb, a PBR is induced in the primary sensory cortex contralateral to the stimulation and a NBR is observed in the ipsilateral primary sensory cortex. This lateralisation of PBR and NBR to opposite hemispheres has been reported in primary visual (V1), motor (M1) and somatosensory

Definition of abbreviations: P/NBR, Positive/negative BOLD response; P/NCBF, Positive/negative cerebral blood flow; RSFA, Resting state fluctuation amplitude; TFA, Task fluctuation amplitude; RSGS, Resting state global signal; TGS, Task global signal; RVT, Respiration per volume time; HRI, Heart rate interval; HC, LC, High or low contrast; MVC, Maximum voluntary contraction.

* Corresponding author.
E-mail address: s.d.mayhew@bham.ac.uk (S.D. Mayhew).

http://dx.doi.org/10.1016/j.neuroimage.2016.02.077

(S1) cortices (Allison et al., 2000; Bressler et al., 2007; Hlushchuk and Hari, 2006; Kastrup et al., 2008; Newton et al., 2005; Tootell et al., 1998). In cross-modal sensory experiments, visual stimulation induces a NBR in auditory cortex (and vice versa) (Laurienti et al., 2002; Mayhew et al., 2013b), whilst painful stimulation induces a NBR in visual cortex (Derbyshire et al., 1997; Mayhew et al., 2013a). An NBR is not restricted to sensory cortex. Its occurrence has also been reported in posterior cingulate cortex, medial prefrontal cortex and intra-parietal regions (comprising the default mode network, DMN) in response to a wide range of cognitive tasks (Gusnard et al., 2001; Northoff et al., 2004; Raichle et al., 2001; Spreng, 2012).

Despite the widespread observation of the NBR, its physiological origin and functional significance remain poorly understood and consequently the NBR is not widely utilised for brain mapping. The BOLD signal arises from a complex neurovascular coupling between cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral metabolic rate of oxygen consumption ($CMRO_2$) (Buxton et al., 1998) and consequently there are many potential combinations of relative changes in these parameters that can give rise to an NBR (Goense et al., 2012; Pasley et al., 2007; Shmuel et al., 2002).

Investigations into the physiological mechanisms of NBR can be broadly divided into those postulating a purely vascular origin, such as from the 'haemodynamic steal' of blood by an adjacent activated cortical region (Harel et al., 2002; Kannurpatti and Biswal, 2004; Olman et al., 2007; Puckett et al., 2014) and those reporting that NBR originates from local changes in metabolism, such as concurrent decreases in both CBF and $CMRO_2$ (Devor et al., 2007; Mullinger et al., 2014; Pasley et al., 2007; Schafer et al., 2012; Shmuel et al., 2002) potentially arising from decreases in local field potential neuronal activity in the NBR region (Boorman et al., 2010; Shmuel et al., 2006). A further unknown is whether a combination of these mechanisms may apply in some circumstances. However, in the case of NBR ipsilateral to the stimulus, an origin of blood steal from the contralateral PBR is unlikely to be the sole mechanism due to these regions occupying separate vascular territories (Smith et al., 2004; Tatu et al., 1998). In addition, NBR have further been reported due to local changes in blood volume in large cerebral veins (Bianciardi et al., 2011) and cerebrospinal fluid in the ventricles (Bright et al., 2014) of humans, as well as due to increases in neuronal activity and metabolism without a compensatory increase in CBF during hippocampal seizures in rats (Schridde et al., 2008).

Given the wide variety of contexts in which NBRs have been observed an important open question is whether comparable or different mechanisms underlie their generation and whether NBRs represent different physiological processes in different scenarios. Of key interest is ascertaining the circumstances in which NBR provides a useful neuroimaging marker of cortical inhibition, whether this reflects increases in local inhibitory neuron activity or decreases in excitatory input (Cauli et al., 2004; Ferbert et al., 1992; Lauritzen et al., 2012) given that increases in inhibition have been shown to lead to both increases (Enager et al., 2009; Pelled et al., 2009) and decreases (Devor et al., 2007) in BOLD signal.

Evidence for an association between NBR and measures of cortical inhibition comes from reports that individuals with higher baseline concentrations of the gamma-aminobutyric acid (GABA) inhibitory neurotransmitter in anterior cingulate cortex have been shown to display the largest magnitude (absolute value) of NBR in the same region (Northoff et al., 2007). Increased NBR magnitude ipsilateral to median nerve stimulation has been linked to increases in the perception threshold for electrical stimuli delivered to fingers of the contralateral hand (Kastrup et al., 2008; Schafer et al., 2012), which is thought to form a behavioural manifestation of ipsilateral cortical inhibition. Additionally, single-trial NBR amplitudes have been shown to correlate with the power of simultaneously recorded 8–13 Hz EEG oscillations in the somatosensory cortex (Mullinger et al., 2014), providing further evidence of a link between NBR and inhibitory neuronal processes (Jensen and Mazaheri, 2010; Mathewson et al., 2011).

The NBR displays many of the stimulus–response properties that characterise the PBR. The average magnitude of the NBR increases with increasing stimulus intensity and duration (Klingner et al., 2010; Shmuel et al., 2002), suggesting that NBR reflects neuronal inhibition required to optimise task performance, by reducing sensitivity and allocation of processing resources to the unattended or irrelevant part of the sensory field.

In addition to the average response, single-trial responses can be measured from the peak amplitude of each trial's fMRI timecourse. Trial-by-trial amplitude variability is commonly treated as "noise" by conventional general linear modelling analyses, which assume a consistent amplitude response across trials, but has been widely reported to contain information which is behaviourally relevant to the dynamics of network processing (Fox et al., 2007; Scheibe et al., 2010).

Taking into account all the caveats stated above, here we hypothesize that important functional information may be contained in the relationship between contralateral PBR and ipsilateral NBR amplitudes at the single-trial level, such as regarding the balance of excitation and inhibition within a cortical network. Therefore we will investigate how the single-trial amplitudes of PBR and NBR, evoked concurrently by the same individual stimulus, relate to each other. The degree of single-trial PBR and NBR amplitude variability, the frequency with which they display signal polarity which is opposite to the average response polarity, and the relationship between PBR and NBR are currently uncharacterised.

Here, we use unilateral visual, motor and somatosensory stimulation to induce contralateral PBR and ipsilateral NBR in primary visual (V1), motor (M1) and somatosensory (S1) cortices respectively, to allow an assessment of the generalisability of findings across these three sensory modalities. First, we investigate the unknown relationship between natural single-trial variability in the PBR and NBR amplitude and compare this to the relationship between the mean PBR and NBR response amplitudes with increasing stimulus intensity. Second, we investigate the unclear role that global fMRI signals and resting-state haemodynamic signal properties play in modulating single-trial fMRI signals and the PBR–NBR relationship.

Materials and methods

Three fMRI experiments were performed in different subject cohorts. visual: 14 subjects (4 female, 27.8 ± 5.4 years); motor: 17 right-handed subjects (7 female, 26 ± 4 years); and somatosensory: 18 right-handed subjects (8 female, 27 ± 3 years). All data were collected with approval from the local ethics committee and informed consent was obtained from all subjects. These data were initially collected for other purposes, however all data contained the primary experimental condition (unilateral stimulation of primary sensory cortex) required to answer the scientific questions which we pose in this work. Table 1 summarises the key parameters for the three fMRI experiments.

Table 1
Summary of experimental parameters for the three fMRI experiments.

	Visual	Motor	Somatosensory
Subjects analysed	14	14	13
Stimulus location	Left visual field	Right hand	Right arm
Stimulus duration (s)	1	5	10
ISI (s)	16.5, 19 or 21	5, 7 or 9	20.5–21
Stimulus conditions	100%, 25% contrast	10%, 30% MVC	Motor threshold
Trials per condition	85	60	40
Resting-state scan	Yes	Yes	No
fMRI sequence	BOLD EPI	BOLD EPI	DABS
TR (ms); TE (ms)	1500; 35	2000; 35	2600; $13_{ASL}/33_{BOLD}$
Voxel size (mm)	2.5 × 2.5 × 3	3 × 3 × 4	2.65 × 2.65 × 5
Slices	20	32	10