Impact of task-related changes in heart rate on estimation of hemodynamic response and model fit

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ABSTRACT

The blood oxygen level dependent (BOLD) signal, as measured using functional magnetic resonance imaging (fMRI), is widely used as a proxy for changes in neural activity in the brain. Physiological variables such as heart rate (HR) and respiratory variation (RV) affect the BOLD signal in a way that may interfere with the estimation and detection of true task-related neural activity. This interference is of particular concern when these variables themselves show task-related modulations. We first establish that a simple movement task reliably induces a change in HR but not RV. In group data, the effect of HR on the BOLD response was larger and more widespread throughout the brain than were the effects of RV or phase regressors. The inclusion of HR regressors, but not RV or phase regressors, had a small but reliable effect on the estimated hemodynamic response function (HRF) in M1 and the cerebellum. We next asked whether the inclusion of a nested set of physiological regressors combining phase, RV, and HR significantly improved the model fit in individual participants' data sets. There was a significant improvement from HR correction in M1 for the greatest number of participants, followed by RV and phase correction. These improvements were more modest in the cerebellum. These results indicate that accounting for task-related modulation of physiological variables can improve the detection and estimation of true neural effects of interest.

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Introduction

Functional magnetic resonance imaging (fMRI) is widely used to examine responses of the human brain to a variety of tasks and stimuli. One disadvantage of the method is that it only provides an indirect measurement of neural activity by measuring changes in the blood oxygenation level dependent (or BOLD) signal (Ogawa and Lee, 1990). These changes occur on a much slower time scale than changes in the activity of local neural populations (Logothetis, 2003). A complex relationship exists between neural activity and the changes in blood flow, volume, and oxygenation that form the basis of the BOLD signal (Buxton and Frank, 1997; for review, see Logothetis & Wandell, 2004). Fortunately, the BOLD response is essentially linear and time-invariant (Boynton et al., 1996; Dale and Buckner, 1997; Friston et al., 1994); therefore, the brain response to many events can be efficiently extracted with events separated by only a few seconds (Dale, 1999).

In order to determine whether a particular brain area is active in such a task, researchers typically adopt a regression approach, using a general linear model (GLM) and regression analysis to identify brain regions in which the BOLD response matches a set of predictions (Friston et al., 1995; see Poline and Brett, 2012 for a broad evaluation of the costs and benefits of this approach). Since the coupling between the neural and BOLD responses has a similar shape across a wide variety of conditions, a canonical hemodynamic response function (HRF) is frequently employed in fMRI analyses (Friston et al., 1998). While this approach can greatly simplify fMRI analysis, it does come at a cost, given that the HRF has been shown to differ across individuals, brain regions, and events (Handwerker et al., 2004). Generating a predicted brain response using the canonical HRF can therefore result in a poorer fit in comparison to individualized, region-specific, or task-specific HRFs, potentially leading to a mischaracterization of brain activity (Hernandez et al., 2002; Handwerker et al., 2004).

The fit of any GLM can be diminished by failing to account for factors that are correlated with each other, a problem that is especially pronounced in event-related studies of BOLD signal that are more susceptible to noise. Two important, measurable, and often ignored physiological covariates are heartbeats and respiration (Glover et al., 2000). The beating of the heart causes pulsations in blood vessels and cerebrospinal fluid (CSF), creating artifacts near large blood vessels, around ventricles, and even in deep sulci (Dagli et al., 1999). Additional artifacts are introduced by respiration, as the rise and fall of the chest

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cavity during breathing causes both head motion and magnetic field disturbances (Glover et al., 2000; Raj et al., 2001). It is therefore desirable to measure heartbeats and breathing to account for their influence on the BOLD signal. The RETROICOR method developed by Glover et al. (2000) provides one such approach, charting the phase of cardiac and respiration processes relative to image acquisition. Variance attributable to the phase of these processes may be removed in preprocessing or accounted for by including nuisance regressors in a GLM.

One limitation of the RETROICOR correction is that it does not take into account how changes in the rate of physiological processes affect the BOLD signal. Changes in heart rate (HR), as well as respiration variance (RV, a measure which accounts for changes in amplitude and rate), can cause fluctuations in the BOLD signal (Birn et al., 2006, 2008; Shmueli et al., 2007; Chang et al., 2009; Chang and Glover, 2009). Taking these factors into account during resting state scans has been shown to alter the spatial spread of connectivity maps (van Buuren et al., 2009; and for review, see Birn, 2012). While resting state studies often measure correlations associated with the "default mode network" (Raichle et al., 2001; Greicius et al., 2003), one study found that these correlations were in fact robust to correction for physiological noise, but activations in a task-positive network were reduced (van Buuren et al., 2009).

Importantly, changes in HR and RV are frequently task-related, associated with variations in arousal (Tursky et al., 1969), movement preparation (Damen and Brunia, 1987), response inhibition (for review see Jennings and van der Molen, 2002), feedback processing (Crone et al., 2003, 2005), cognitive interference and planning (van 't Ent et al., 2014), and pharmacological state (Khalili-Mahani et al., 2013). Indeed, changes in HR, RV, and other autonomic indicants, such as skin conductance and pupil dilation, are common dependent variables in the study of a range of cognitive processes and their associated brain responses (for review, see Critchley, 2009). Furthermore, autonomic variables are themselves regulated by efferent signals from the brain, making the direction of influence between brain and body difficult to discern (see Iacovella and Hasson, 2011).

We previously demonstrated the importance of considering task-related changes in physiological processes in a study designed to identify brain regions responsive to movement errors (Schlerf et al., 2012). When physiological regressors were not included in the GLM analysis, reaching errors led to a broadly distributed decrease in the BOLD response in the cerebellum. However, there was also a reliable reduction in HR following movement errors. When the model included HR, the cerebellar deactivations were no longer evident. Instead, an increase in the BOLD signal was observed on error trials, restricted to the arm area of the anterior cerebellum. Thus, the expected error signal in the cerebellum was only evident after task-dependent changes in HR were included in the model of the BOLD response. Nevertheless, to our knowledge, no other study has investigated the impact of physiological noise correction on task responses in the cerebellum.

In the current study, we systematically investigated the potential consequences of task-related fluctuations in HR and RV on the HRF, as well on the model fit of the BOLD response, using a progressive series of analyses. Rather than focusing on movement errors, we examined responses to a simpler behavior: arm movements produced in the absence of visual feedback. We chose to measure responses to this simple type of event for two reasons: First, it allowed us to situate the error-specific changes observed by Schlerf et al. (2012) in the more general context of movement-related changes. Second, the use of a simple motor behavior decreases the likelihood that neural activity related to cognitive processing (e.g., error processing) is driving the physiological changes. As such, this would increase our confidence that the impact of HR and RV on the BOLD signal do not reflect the efferent regulation of autonomic processes (e.g., Kobayashi et al., 2007; Iacovella and Hasson, 2011).

We first demonstrated that HR is consistently affected by arm movement. In contrast, changes in RV are more variable. We then examined the effect of these variables on the BOLD signal throughout the brain. We next asked how the inclusion of physiological regressors in the GLM influenced the shape of the estimated arm movement-related HRF in two motor regions: primary motor cortex (M1) and the cerebellum. Finally, we quantified the added explanatory power of different sets of physiological regressors, either in isolation or in combination.

Material and methods

Participants

Eleven healthy, right-handed participants were tested (7 female, mean age 24.1 years). The participants provided written, informed consent under a protocol approved by the University of California, Berkeley Institutional Review Board.

Task

Prior to scanning, participants were fitted with a custom bite bar. During the scanning session, the bite bar was mounted to the head coil to minimize head movement. Stimuli were backprojected onto a screen mounted inside the bore of the magnet and viewed via a mirror mounted to the head coil. From a supine position, the participants held a robotic manipulandum (http://www.fmrirobot.org) in their right hand. The manipulandum was positioned over the participant's abdomen and could be freely moved in a plane parallel to the scanner bed.

Participants were trained to make short (8 cm) out-and-back reaching movements along the axis of the body toward their head, chiefly by flexion about the elbow. They were instructed to terminate each return movement such that in between trials, the hand rested comfortably near the navel. Participants were instructed to move when a central fixation crosshair changed color from red to green. For all runs, the green crosshair was presented for 500 ms, regardless of inter-trial interval. Participants were told to initiate the movement as soon as they saw the color change. To minimize corrective movements and processing load, there was no visual feedback of hand position during scanning. At the termination of each return movement (when the hand coordinates were no more than 1 cm apart for a minimum of 500 ms), the start position of the hand for the next trial was automatically adjusted to the center of fixation.

All participants completed a training session in a mock scanner 1–7 days prior to the scanning session. This session served to familiarize the participants with the bite bar, manipulandum, and scanning environment, and to train them in the movement task. The training session consisted of four runs and was designed to train participants to make movements in the scanner of approximately uniform amplitude without relying on feedback. The training runs provided feedback that became progressively less informative as the training continued. In the first run, the participants received online feedback of the cursor position and feedback about reach amplitude at the end of each movement. Reach amplitude feedback was given in numeric form, shown above the fixation crosshair as a percentage of the desired 8 cm amplitude for 500 ms immediately following completion of the return movement (Fig. 1A). For the next run, they were only given reach amplitude feedback (no online cursor feedback), and for the final two runs, no feedback was provided, as in the actual scan session (Fig. 1B). At various points in the training session, the experimenter provided verbal coaching concerning movement initiation, speed, and amplitude.

The scanning session consisted of an anatomical scan and three functional scans: one localizer run and two task runs. The localizer run lasted 6 min and 40 s and consisted of 12 12-second blocks, with rest periods lasting 21.3 s in between each block (Fig. 1C). There were two types of blocks: reach and auditory (6 of each block type). Reach blocks were indicated by the appearance of the word "Reach" on the screen. Participants then produced eight out-and-back movements, initiating each movement when they saw the fixation crosshair turn green. Over each