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# Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses

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**Trial-to-trial variability in the blood oxygen level–dependent (BOLD) response of functional magnetic resonance imaging has been shown to be relevant to human perception and behavior, but the sources of this variability remain unknown. We demonstrate that coherent spontaneous fluctuations in human brain activity account for a significant fraction of the variability in measured event-related BOLD responses and that spontaneous and task-related activity are linearly superimposed in the human brain.**

The BOLD signal of functional magnetic resonance imaging (fMRI) provides a useful index of the changes in neuronal activity associated with discrete events. Trial-to-trial variability in the magnitude of event-related BOLD responses is relevant to human perception and behavior[1–4]. For example, BOLD response magnitude can predict the perception of visual contrast[1], the identification of fearful expressions[2], working memory performance[4] and even whether the stimulus on a given trial will be remembered or forgotten[3]. This intertrial variability cannot be attributed to variability in the stimuli[1–4]. Despite its demonstrated relevance to human behavior, the sources of event-related BOLD response variability remain unknown.

Animal studies suggest that one factor contributing to this variability in measured event-related responses may be spontaneous neuronal activity unrelated to the task or the stimulus[5–7]. Spontaneous fluctuations in neuronal activity have been observed in the human brain with fMRI[8]. These BOLD fluctuations are not random but coherent within specific neuroanatomical systems[8–12]. One highly reproducible example of these spontaneous BOLD correlations, which we exploited in the present study, is the observation that spontaneous fluctuations in the left somatomotor cortex (LMC) are specifically correlated with spontaneous fluctuations in the right somatomotor cortex (RMC) as well as with those in medial motor areas[8,10,11].

In the current study, we address two related hypotheses: first, that coherent spontaneous fluctuations in human brain activity account for variability in measured event-related BOLD responses, and second, that spontaneous and task-related activity are linearly superimposed in the human brain. The LMC and RMC provide a useful system for testing these hypotheses because they are correlated in their spontaneous activity but differentially activated by a right-handed button press.

The current analysis used fMRI data from a previously published study of perceptual event boundaries in which 16 normal, right-handed subjects viewed videos depicting ordinary domestic chores (such as making a bed or washing the dishes)[13]. Informed written consent was obtained from all subjects. We included two run types in our analysis: passive and active runs. Passive runs were acquired first; in these, subjects were instructed simply to watch the movie. During active runs, subjects were asked to press a button with their right index finger every time they perceived a transition between major events in the movie[13]. Only widely spaced (at least 14 seconds apart) button press responses were included. Subjects were excluded if they had fewer than ten widely spaced responses, leaving 14 of 16 subjects with an average of 18.5 button presses per subject (additional methodological details in **Supplementary Note** online).

For each subject we defined two somatomotor regions, an LMC region significantly activated by right-handed button press responses

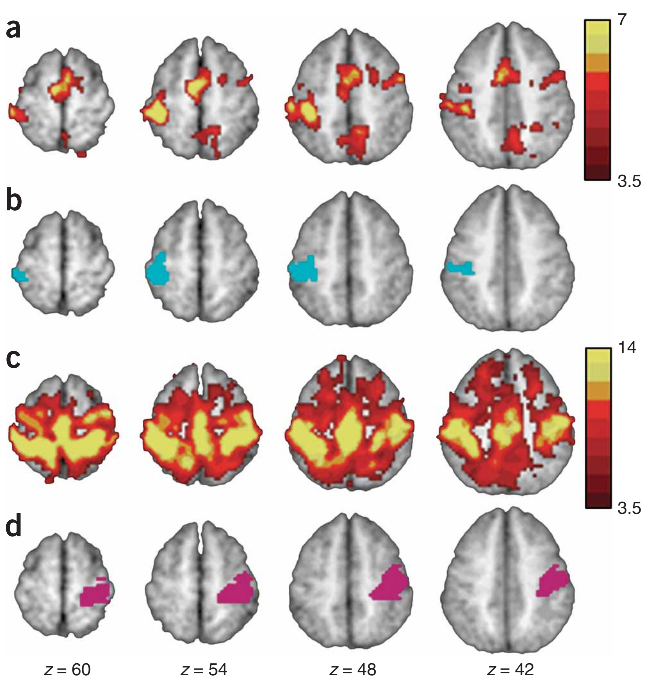


**Figure 1** Identification of regions of interest in the LMC and RMC for a single subject (subject 1). (**a**) Statistical parametric map showing voxels significantly activated by a right-handed button press. (**b**) LMC region of interest identified using the activation map from **a**. (**c**) Correlation map showing voxels whose activity was significantly correlated with that of the LMC region during passive viewing of movie stimuli. (**d**) RMC region of interest identified using the spontaneous correlation map from **c**.

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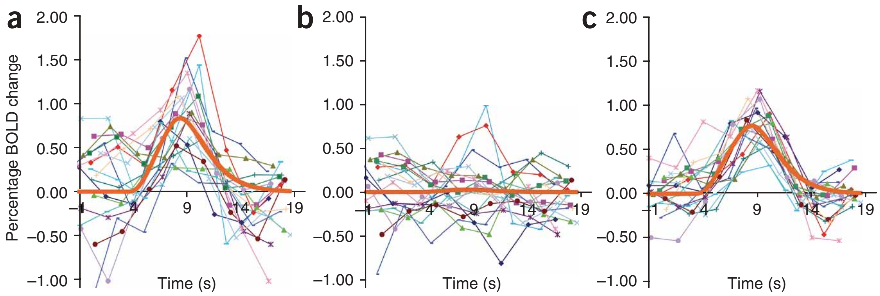


**Figure 2** Coherent spontaneous fluctuations account for a significant fraction of the variance in measured event-related responses. (**a**) Raw event-related responses in the LMC for 18 button presses from a single subject (subject 1). (**b**) The corresponding activity in the RMC for each button press. (**c**) Task-related responses in the LMC after subtraction of spontaneous fluctuations measured in the RMC. The thick orange line in each graph represents the best fit gamma function to all data points.

and an RMC region whose activity was significantly correlated ($P < 0.0001$) with that of the LMC region during the passive viewing condition (**Fig. 1** and **Supplementary Table 1** online). For each subject, the RMC signal was scaled by a regression coefficient calculated using the passive runs and subtracted from the LMC active-run time series. We will henceforth refer to the resulting time series as the 'regressed LMC'. The BOLD response time courses following individual button presses were extracted from the raw LMC signal (**Fig. 2a**), the raw RMC signal (**Fig. 2b**) and the regressed LMC signal (**Fig. 2c**). We varied the delay, duration and magnitude parameters of a gamma function so as to obtain the best fit to the data (thick orange trace, **Fig. 2**). The raw LMC responses (**Fig. 2a**) contained a robust average button press response, but also considerable trial-to-trial variability. RMC activity (**Fig. 2b**) showed little to no average response related to the button press event. In the regressed LMC responses (**Fig. 2c**), subtraction of the scaled RMC signal substantially reduced the LMC trial-to-trial variability with little alteration in the mean response.

These qualitative observations were quantified using measures of signal power, noise power and signal-to-noise ratio. For subject 1 (**Fig. 2**), we observed a 65% reduction in noise ($P < 0.0001$), a 9% reduction in signal and a 157% improvement in signal to noise ($P < 0.001$). All subjects (**Supplementary Table 2** and **Supplementary Fig. 1** online) showed a reduction in noise and in 12 of 14 subjects, this reduction was significant ($P < 0.05$). All but two subjects showed an improvement in the signal-to-noise ratio, and in 11 subjects, this improvement was significant ($P < 0.05$). Averaging results across subjects, we observed a 40% decrease in noise ($P < 0.001$), a non-significant 11% decrease in signal ($P = 0.25$) and a 60% increase in signal to noise ($P < 0.005$). These results indicate that a significant fraction of trial-to-trial variability in LMC responses can be accounted for by spontaneous fluctuations as measured in the opposite hemisphere.

If the observed reduction in variance is indeed due to the removal of coherent spontaneous fluctuations, one would expect that the variance reduction in a particular subject would be proportional to the coherence of the spontaneous fluctuations. Consistent with this prediction, the reduction in LMC response variance across subjects was proportional to the correlation coefficient between the LMC and RMC activity during the passive runs ($r = 0.68$, $P < 0.01$) (**Supplementary Table 1**). LMC response variability was reduced more in subjects with stronger resting interhemispheric correlations. This correlation remained even when the regression coefficients were set to the same value (0.8) for all subjects ($r = 0.63$, $P < 0.05$). Additional research is needed to characterize the nature and possible causes of this individual variability in the coherence of spontaneous fluctuations.

Having shown that coherent spontaneous fluctuations contribute to variability in measured event-related responses, our next question concerned the interaction between spontaneous and task-related activity. Does the magnitude of the task-related response depend on whether the button press coincides with a peak, as opposed to a trough, in the underlying spontaneous activity? To address this question, we sorted responses into either a peak bin or a trough bin based on the median magnitude of activity in the RMC. The results are illustrated for a single subject (**Fig. 3**) and are listed for all subjects (**Supplementary Table 3** online). Significance was assessed at the group level. There was a predictably significant difference between the two bins in the RMC response magnitude ($P < 10^{-7}$; **Fig. 3a**). A similar difference was seen in the raw LMC responses ($P < 10^{-5}$; **Fig. 3b**). However, there was almost no difference between the two bins in the regressed LMC responses ($P = 0.96$; **Fig. 3c**). This outcome indicates that spontaneous BOLD fluctuations and task-related responses superimpose in an approximately linear fashion.

We have suggested that the signal measured in the RMC represents spontaneous fluctuations that are coherent within the somatomotor system, but several confounds must be addressed to justify such an assertion. In additional analyses, we found that fluctuations in the right somatomotor cortex were not due to the movie stimulus, were not driven by button press responses and were relatively specific to the somatomotor system (see **Supplementary Note**).

Previous work on the interaction between spontaneous and task-related neuronal activity has been conducted in the visual cortex of the

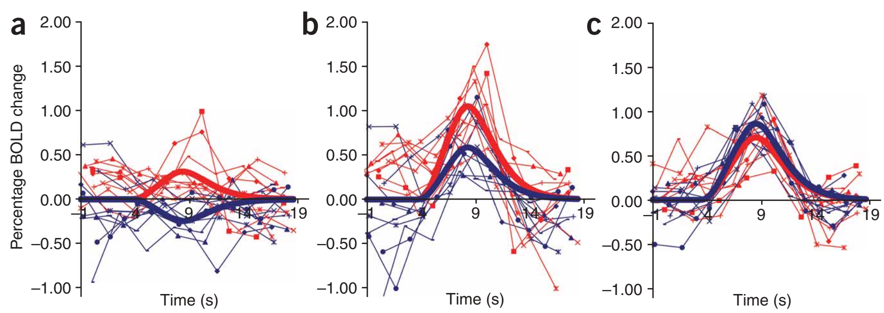


**Figure 3** Coherent spontaneous fluctuations and task-related responses are linearly superimposed. Shown is the same data from **Figure 2**, but now sorted (based on the median fluctuation magnitude in the RMC) into a peak bin (red) or a trough bin (dark blue). The thick red and blue lines represent the best fit gamma functions for the peak and trough bins, respectively. (**a**) Raw activity in the RMC. (**b**) Raw event-related responses in the LMC. (**c**) Task-related responses in the LMC after subtraction of spontaneous fluctuations measured in the RMC. The magnitude of the task-related response did not depend on whether the event occurred during a peak or a trough in the underlying spontaneous activity.

anesthetized cat[5,7]. Despite major differences in anesthesia, species, modality, stimuli, cortical systems, and spatial and temporal resolution, the present results are consistent with these previous findings in suggesting an approximately linear superposition between spontaneous and task-related neuronal activity. The current analysis also expands upon these previous results in two important ways. First, we demonstrated that superposition involves not just spontaneous neuronal noise present at the recording site, but intrinsic fluctuations coherent within widely distributed neuroanatomical systems. Second, we showed superposition in the brain of an awake behaving human, making our results directly relevant to studies on response variability in human perception and behavior[1–4].

The present results have several important implications. First, the ability to reduce noise by 40% and improve the signal-to-noise ratio by 60% in a select region of interest may be of practical use in future fMRI analyses. Second, the demonstration of a superposition of spontaneous and task-related activity influences the interpretation of studies observing changes in regional BOLD correlations during task conditions (for example, see ref. 12). Finally, and most notably, the present results have theoretical implications with regard to understanding the neural correlates of human behavior. Trial-to-trial variability in BOLD event-related responses is relevant to human perception and performance[1–4]. The current results indicate that coherent spontaneous fluctuations account for a large fraction of trial-to-trial variability in BOLD event-related responses. Taken together, these findings suggest that coherent spontaneous fluctuations in neuronal activity may account for variability in human behavior.

An important question is how to understand this influence of coherent spontaneous activity on task-related responses and, potentially, on behavior. One possible interpretation stems from the observation that spontaneous activity is important for the development and organization of neuronal systems[14]. This requirement may come at a cost, introducing variability into neuronal responses and behavior. Another possibility reflects the idea that the brain develops and maintains an intrinsic probabilistic model of anticipated events[15]. Spontaneous fluctuations in human brain activity may represent dynamic modulations in this internal representation. These hypotheses are not mutually exclusive, and both suggest that the brain's intrinsic spontaneous activity may provide the context in which perception and behavior occur, shaping the manner in which we respond to external events.

*Note: Supplementary information is available on the Nature Neuroscience website.*

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**COMPETING INTERESTS STATEMENT**
The authors declare that they have no competing financial interests.

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