The Behavioral Significance of Spontaneous Fluctuations in Brain Activity

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Low-frequency fluctuations in fMRI data are believed to reflect synchronous and spontaneous fluctuations in neuronal networks. A study by Fox et al. in this issue of *Neuron* shows that these spontaneous fluctuations in the motor cortex can account for significant trial-to-trial variations in both the fMRI response and behavior.

Fluctuations in functional MRI (fMRI) time series are common. The signal is never perfectly constant in the absence of an external stimulus, and it often deviates from our expected task-induced modulations. Typically, these fluctuations are ascribed to "noise"—subject motion, cardiac and respiratory fluctuations, or scanner artifacts. An increasing number of studies, however, are showing that some of these fluctuations, particularly those at low (<0.1Hz) temporal frequencies, may be functionally relevant and correlated between regions subserving similar brain functions. The correlation between low-frequency fluctuations in fMRI time series at rest (often referred to as a "resting-state network") was first studied by Biswal and colleagues in the motor cortex (Biswal et al., 1995). Subsequent studies have identified several consistent and distinct resting state networks, including motor, auditory, visual, attention, and default mode networks. (De Luca et al., 2006) The hypothesis is that these signal fluctuations reflect synchronized variations in the neuronal activity of a network of regions. The study of these networks by analyzing the coherent signal fluctuations has therefore become known as "functional connectivity" or "resting-state connectivity" analyses.

These fluctuations highlight the fact that the brain is not silent at rest, a point that should be kept in mind when designing fMRI studies. More correctly, "rest" should be thought of as a series of unconstrained or uncontrolled "tasks." Supporting this view is the observation of a number of brain regions that consistently deactivate during a wide range of tasks (Raichle et al., 2001). This "default-mode network" is believed to represent brain regions that are more active during rest. Since the correlated fluctuations within the resting state networks occur in the absence of an explicit task, they are often referred to as "spontaneous" or "task-unrelated" fluctuations.

The synchronized spontaneous activity within these networks is not restricted to rest periods, but continues during cued stimuli and task performance (cf. Fox and Raichle, 2007). In an earlier study, Fox et al. (2006) showed that these fluctuations can account for a significant fraction of trial-to-trial variability in the BOLD response. In the study described in this issue of *Neuron* (Fox et al., 2007), the authors make an important extension and show that these spontaneous fluctuations have a behavioral significance. Subjects performed two types of runs. First, they rested with their eyes open, simply looking at a crosshair. In the second run, subjects were instructed to press a button with the right hand as quickly as possible when given a visual cue, approximately once every 17–30 s. Both the reaction time and the force of the button press were found to vary across the trials.

The authors then divided up the responses based on the force of the button press. The average hemodynamic responses to the hard versus soft button presses were found to be significantly different only at the second and third time points (2.16 s and 4.32 s after the presentation of the stimulus), prior to the peak of the response, and with hard button presses associated with a lower signal. In contrast, a separate control experiment with cued hard versus cued soft button presses found a larger response for hard button presses at all time points. The results for the natural intertrial variability in force could be explained by a larger response to hard button presses and a decreased baseline. No significant differences in the peak of the response are found since at these points the decreased baseline cancels out the increased task-related response. What is particularly interesting is that this variation in the prestimulus, or baseline, activity is correlated between the left and right motor cortices—regions that also showed synchronized fluctuations during the resting runs. The authors argue that these spontaneous fluctuations reflect synchronized neuronal activity that continues during the task performance and influences the behavior—the strength of the button press.

The first question, which should be asked of all studies of "spontaneous fluctuations," is whether this effect truly represents neuronal activity or whether it may be the result of other correlated fluctuations. The heartbeat and respiration, for example, are known to cause significant and correlated BOLD signal changes throughout the brain. These can often occur at low temporal frequencies (<0.1Hz), either due to aliasing or to slower physiological processes (e.g., breath-to-breath changes in respiration depth or rate)

(Bhattacharyya and Lowe, 2004; Birn et al., 2006). Correlated fluctuations, however, have also been shown with other more direct measures of neuronal activity, such as EEG (Laufs et al., 2003) or even direct recordings in nonhuman primates (Leopold et al., 2003). Low-frequency fluctuations therefore likely represent some genuine underlying neuronal activity, provided that various nonneuronal confounds have been addressed. While no physiological correction was performed in the study by Fox et al. (2007), the observed relationship between spontaneous fluctuations and behavior is harder to ascribe to a physiological artifact, since the cardiac and respiratory fluctuations would have to be significantly different for hard versus soft button presses.

Despite the number of studies focusing on resting state and spontaneous fluctuations, the functional role or cognitive manifestation of these spontaneous fluctuations is often unclear. The correlated activity within the default mode network, for example, has most often been ascribed to daydreaming or mind wandering (Mason et al., 2007), including reflections about the past or speculations about the future—activities often considered to be uniquely human. Yet correlated fluctuations within the default mode network have recently been observed in anesthetized nonhuman primates, suggesting perhaps a more primal or intrinsic role (Vincent et al., 2007).

Could these correlated fluctuations merely be the result of an unmodeled task? After all, the force of the button press was shown to vary from trial to trial, yet this difference in performance was not modeled. An alternative explanation, therefore, is that the observed response is nothing more than the sum of two task-related responses—(1) a contralateral component independent of the button press force and (2) a bilateral component associated with the variation in force. There are several reasons why this explanation is unlikely. First, the prestimulus or baseline activity was found to be *lower* for (uncued) hard button presses. This is opposite to the finding from cued hard versus soft button presses. Second, the significant differences in the BOLD response between uncued hard and soft button presses occurs early, prior to the peak, suggesting neuronal activity several seconds prior to the button press and likely prolonged in duration. Third, the left and right motor cortex (MC) showed correlated low frequency fluctuations at rest, consistent with the slow modulation of the response baseline observed during the task.

Could these spontaneous fluctuations merely be the result of variations in attention? The authors argue that this is not a likely explanation, since the reaction time, a common indicator of variations in attention, was not significantly different between hard and soft button presses. The variations in button press force, however, were relatively small. Could there be a mechanism of attention that can affect the force of the button press, but not the reaction time?

The research by Fox et al. (2007) shows a promising new direction in functional neuroimaging, but more research is needed to determine the functional role of spontaneous fluctuations, not just for the motor system, but for all resting state networks. The study by Fox et al. (2007) focused on a relatively simple task; it remains to be seen whether this result holds for more complex cognitive tasks or other brain regions or networks. Do the fluctuations in activity within each of the resting-state networks modulate behavior? Separating task-related from spontaneous fluctuations was possible in the motor system, since left and right motor cortices are correlated at rest but can easily be independently activated. This may not be as straightforward in other systems. Multimodal studies, including combined EEG/fMRI or separate MEG studies, can more directly probe the neuronal dynamics and may therefore provide additional insights. What do the low-frequency fluctuations in the fMRI data truly reflect? What is their behavioral significance? Answers to these questions and a solid understanding of the functional role of spontaneous fluctuations are crucial for interpreting the alterations and disruptions in functional connectivity for different tasks or mental disorders.

REFERENCES

Bhattacharyya, P.K., and Lowe, M.J. (2004). Magn. Reson. Imaging *22*, 9–13.

Birn, R.M., Diamond, J.B., Smith, M.A., and Bandettini, P.A. (2006). Neuroimage *31*, 1536–1548.

Biswal, B., Yetkin, F.Z., Haughton, V.M., and Hyde, J.S. (1995). Magn. Reson. Med. *34*, 537–541.

De Luca, M., Beckmann, C.F., De Stefano, N., Matthews, P.M., and Smith, S.M. (2006). Neuroimage *29*, 1359–1367.

Fox, M.D., Snyder, A.Z., Zacks, J.M., and Raichle, M.E. (2006). Nat. Neurosci. *9*, 23–25.

Fox, M.D., and Raichle, M.E. (2007). Nat. Rev. Neurosci. *8*, 700–711.

Fox, M.D., Snyder, A.Z., Vincent, J.L., and Raichle, M.E. (2007). Neuron *56*, this issue, 171–184.

Laufs, H., Krakow, K., Sterzer, P., Eger, E., Beyerle, A., Salek-Haddadi, A., and Kleinschmidt, A. (2003). Proc. Natl. Acad. Sci. USA *100*, 11053–11058.

Leopold, D.A., Murayama, Y., and Logothetis, N.K. (2003). Cereb. Cortex *13*, 422–433.

Mason, M.F., Norton, M.I., Van Horn, J.D., Wegner, D.M., Grafton, S.T., and Macrae, C.N. (2007). Science *315*, 393–395.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., and Shulman, G.L. (2001). Proc. Natl. Acad. Sci. USA *98*, 676–682.

Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., Van Essen, D.C., Zempel, J.M., Snyder, L.H., Corbetta, M., and Raichle, M.E. (2007). Nature *447*, 83–86.