Causal Evidence for a Neural Component of Spatially Global Hemodynamic Signals

Kathrin Müsch[1] and Christopher J. Honey[1,*]
[1]Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD 21218, USA
*Correspondence: chris.honey@jhu.edu
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In this issue of *Neuron*, Turchi et al. (2018) reversibly inactivate the basal forebrain to show that this region magnifies global neocortical signal fluctuations without altering the topography of canonical resting-state networks. Thus, spatially diffuse signals measurable via functional neuroimaging may track large-scale neuromodulatory state changes in the primate brain.

Every scientist faces the challenge of distinguishing signal from noise. Experimental cosmology was launched when perplexing radiometer measurements were shown to result from the Big Bang rather than from pigeon droppings. In neuroscience, the distinction between signal and noise is especially vexed because different levels of function interact. For example, ''background'' fluctuations in neuronal population activity can be produced by undesirable physiological confounds but may also reflect behaviorally relevant processes such as attention (Ruff and Cohen, 2014).

A major goal of functional magnetic resonance imaging (fMRI) research in the past decade has been to sketch out large-scale functional brain architecture—a map of the areas, which covary in activity and may functionally interact. However, it has long been observed that local measurements of fMRI signal (e.g., from a voxel in visual cortex) are robustly correlated with the average signal measured across the rest of the brain (the ''global signal''). Does this correlation reflect an important feature of functional architecture or an especially widespread artifact?

Certainly, some portion of the measured global signal correlation is artifactual, related to cardiovascular and respiratory influences and also to head motion (Power et al., 2017). However, the global fMRI signal measured at rest in macaques is correlated with local electrophysiological measures of neuronal population firing, which are much less susceptible to these artifacts (Schölvinck et al., 2010), so some portion of the global signal may have a neural origin.

The basal forebrain is a set of heterogeneous structures, including the nucleus basalis of Meynert (NBM), that sends neuromodulating long-range projections to almost all areas of the cortex. The majority of the NBM projections are cholinergic (Mesulam et al., 1983), and the basal forebrain is the main source of cholinergic input to the cortex. The widespread projections of the basal forebrain make it an intriguing candidate to orchestrate spontaneous activity across the brain (Leopold and Maier, 2012), but establishing its modulation of the global signal requires causal manipulation.

In this issue of *Neuron*, Turchi et al. (2018) used pharmacological interventions to reversibly inactivate different parts of the NBM and measured the effects on whole-brain resting fMRI signals. They used muscimol to inactivate either the lateral NBM (Ch4al, which projects to lateral cortical sites) or the anteromedial NBM (Ch4am, which projects to medial cortical targets). More than 50 hr of resting-state data were recorded from two monkeys who sat silently in the scanner without any task. Turchi et al. (2018) hypothesized that the NBM modulates spontaneous signal fluctuations in the cerebral cortex, but they were uncertain of the spatial distribution of this effect.

Turchi et al. (2018) found evidence for a genuinely neural component of the global hemodynamic signal regulated by the NBM. Local regional activity became less correlated with global signal following the NBM inactivation, and, critically, this decrease was localized to the hemispheres and regions targeted by the two NBM structures (Figure 1). For example, inactivating the left Ch4al of the NBM decreased the global signal in area TEO of the left, but not right, hemisphere in accordance with the lateralized NBM projections. There was almost no overlap between the areas that were affected by Ch4al or Ch4am inactivation.

The strength of Ch4al and Ch4am projections to cortical sites—as determined by independent anatomical studies—predicted the reduction in coupling to the global signal for each site. In the absence of this projection specificity, one could argue that the NBM exerts its effects indirectly, for example, by altering cardiovascular processes, which in turn affect global signal. But the link between the hemodynamic coupling and the anatomical data suggests that the effects of NBM inactivation are indeed mediated by its widespread neuronal projections.

In contrast to its effect on global signal modulations, NBM inactivation did not alter the spatial layout of any of six canonical ''resting-state networks'': the early visual, higher visual, dorsal attention, temporal, sensorimotor, or default mode network. Resting-state networks are canonical sets of regions whose fMRI signal time courses spontaneously co-vary. Covariation between two regions may arise from their direct neural interactions but could also arise if they are both modulated by a common source. Because NBM projections target pairs of cortical regions that are mutually connected (Zaborszky et al., 2015), joint

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NBM projections might shape resting-state network topography. However, the present data show that if any of the canonical networks are generated by a common driver, it is not the NBM, which instead seems to exert a more diffuse modulatory effect.

Future studies will be needed to mechanistically determine the relationship between cholinergic tone, the global signal, and the systemic regulation of arousal. Cholinergic tone in the neocortex is generally lower in drowsy states, and Turchi et al. (2018) found that NBM inactivation had a stronger effect in the drowsy state, inducing more asymmetry in global signal correlations. This reinforces the proposal that the NBM effects are due to its cholinergic projections, but many open questions remain. To start, we do not know the relative magnitude of cholinergic changes due to (1) NBM inactivation and (2) spontaneous variation in wakefulness; nor do we know how these interact. We also do not know how NBM inactivation would affect the electrophysiological states of local circuits—perhaps via low-frequency power shifts (Disney et al., 2015). Simultaneous electrophysiological recordings are a natural next step to learn which circuit states are indexed by global signal correlations in fMRI.

A caveat for translating these results to human work is that the hemodynamic signals measured in these monkeys were enhanced with a contrast agent, monocrystalline iron oxide nanoparticles (MION). The resulting hemodynamic response has a higher signal-to-noise ratio than the blood-oxygenation-level-dependent (BOLD) signal typically measured in human functional imaging. Thus, future work should determine whether the influence of the basal forebrain is larger (and the influence of artifacts is smaller) in MION measurements than in BOLD. This is highly relevant for the ongoing debate about whether global signals should be removed from fMRI signals in human neuroimaging research.

How do these findings change our perspective on the functional role of the basal forebrain? In many neural systems, increases in cholinergic tone shift the circuit toward a feedforward mode of processing, in which circuit dynamics are shaped by incoming information more than by prior expectations (Honey et al., 2017). The process of switching between internal (feedback) and external (feedforward) processing modes can drive internal representations to better match the environment. Furthermore, cholinergic tone is associated with changes in attentional state (Yu and Dayan, 2005). Perhaps the NBM mediates large-scale state switches that shift attention and gradually drive learning.

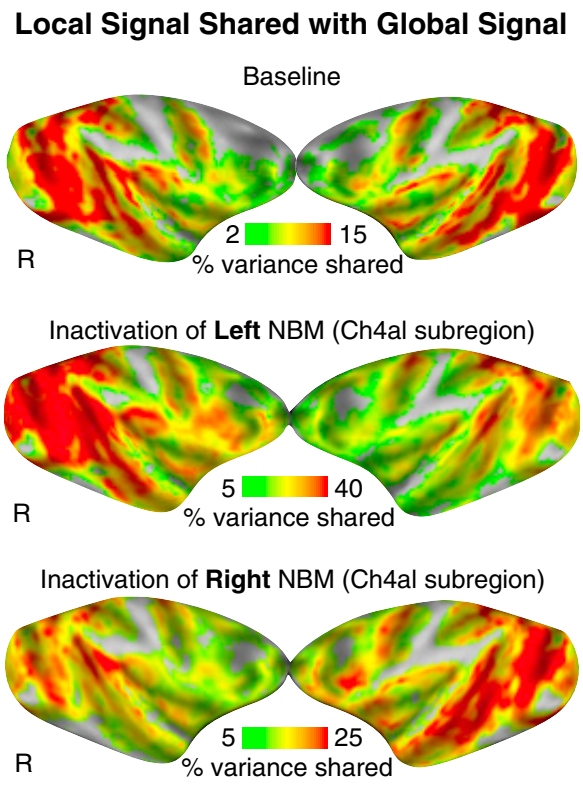

Figure 1. Correlations with Global Signal Are Selectively Reduced by Left and Right Basal Forebrain Inactivation
When the basal forebrain is functionally intact (top), hemodynamic signals in diverse cortical regions are correlated with the global (average) signal. Correlations are selectively reduced in the left hemisphere (middle) and right hemisphere (bottom) following inactivation of ipsilaterally projecting subregions. R, right hemisphere; NBM, nucleus basalis of Meynert; Ch4al, lateral subregion.

Although the effects of cholinergic tone have been studied extensively in local circuits, the findings of Turchi et al. (2018) encourage us to consider the implications at the scale of brain networks. For example, if cholinergic neuromodulation simultaneously shifts each of a dozen regions toward a feedforward processing state, then how will this affect the information flow between all the pairs of nodes in that network and across the subnetwork as a whole? In addition, these primate data raise the possibility that large-scale brain-state switches may be observable in human cognitive tasks using fMRI. Before this becomes practicable, however, we will likely need to harness our anatomical knowledge to separate NBM-related components from the physiological artifacts that also influence the global signal.

In conclusion, Turchi et al. (2018) provide causal evidence that components of the hemodynamic global signal have a neural origin. This work reminds us that, as we seek to separate the signal from the noise in our science, each experimental lens provides a new perspective: in this case we learn something by taking a global view.

REFERENCES

Disney, A.A., McKinney, C., Grissom, L., Lu, X., and Reynolds, J.H. (2015). A multi-site array for combined local electrochemistry and electrophysiology in the non-human primate brain. J. Neurosci. Methods *255*, 29–37.

Honey, C.J., Newman, E.L., and Schapiro, A.C. (2017). Switching between internal and external modes: A multiscale learning principle. Netw. Neurosci. *1*, 339–356.

Leopold, D.A., and Maier, A. (2012). Ongoing physiological processes in the cerebral cortex. Neuroimage *62*, 2190–2200.

Mesulam, M.M., Mufson, E.J., Levey, A.I., and Wainer, B.H. (1983). Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (substantia innominata), and hypothalamus in

the rhesus monkey. J. Comp. Neurol. *214*, 170–197.

Power, J.D., Plitt, M., Laumann, T.O., and Martin, A. (2017). Sources and implications of whole-brain fMRI signals in humans. Neuroimage *146*, 609–625.

Ruff, D.A., and Cohen, M.R. (2014). Global cognitive factors modulate correlated response variability between V4 neurons. J. Neurosci. *34*, 16408–16416.

Schölvinck, M.L., Maier, A., Ye, F.Q., Duyn, J.H., and Leopold, D.A. (2010). Neural basis of global resting-state fMRI activity. Proc. Natl. Acad. Sci. USA *107*, 10238–10243.

Turchi, J., Chang, C., Ye, F.Q., Russ, B.E., Yu, D.K., Cortes, C.R., Monosov, I.E., Duyn, J.H., and Leopold, D.A. (2018). The basal forebrain regulates global resting state fMRI fluctuations. Neuron *97*, this issue, 940–952.

Yu, A.J., and Dayan, P. (2005). Uncertainty, neuromodulation, and attention. Neuron *46*, 681–692.

Zaborszky, L., Csordas, A., Mosca, K., Kim, J., Gielow, M.R., Vadasz, C., and Nadasdy, Z. (2015). Neurons in the basal forebrain project to the cortex in a complex topographic organization that reflects corticocortical connectivity patterns: an experimental study based on retrograde tracing and 3D reconstruction. Cereb. Cortex *25*, 118–137.

Untangling Neural Representations in the Motor Cortex

Andrew Jackson[1,*]
[1]Institute of Neuroscience, Newcastle University, Newcastle NE2 1HP, UK
*Correspondence: andrew.jackson@ncl.ac.uk
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How the brain generates accurate movement is a long-standing problem in neuroscience. In this issue of *Neuron*, Russo et al. (2018) argue that population activity in motor cortex does not represent muscle patterns but rather untangled neural trajectories that are robust to noise.

For more than half a century, neuroscientists have endeavored to understand how neurons in motor areas of the cortex generate and control the movements that we make with our limbs. This program of research has been greatly influenced by comparable studies in sensory areas, for example, the famous experiments of Hubel and Wiesel (1959). In early visual cortex, neurons are "tuned" to particular features of stimuli, so an individual neuron may discharge action potentials when, for example, an edge with specific orientation moves across the field of view. Presumably, the distributed activity of large numbers of such neurons provides a high-dimensional representation of the entire visual scene, which is relayed to downstream brain areas. By analogy, we might expect the firing rates of single neurons in the motor cortex similarly to represent specific features of movement, for example, the direction of motion of a limb, the forces generated around a joint, or the activity of a particular muscle. Indeed, since the motor cortex comprises the major descending output from the brain and, in primates, projects directly to the final common pathway of the motoneurons, it seems that the distributed activity of motor cortex neurons should convey all the information needed by the spinal cord to execute voluntary movements. In recent years, impressive support for this view has been provided by the development of brain-machine interfaces, which decode motor intentions in real time from hundreds of motor cortical neurons, in order to restore movement after paralysis (Collinger et al., 2013).

Nevertheless, while a wealth of information can undoubtedly be decoded from motor cortical populations, there remains controversy about what specific features are represented at the level of single neurons. Experimental paradigms developed initially to distinguish encoding of "muscles versus movements" have identified an ever more diverse range of parameters that co-vary with firing rates. This has led some to question whether the representational view of motor cortex is justified (Fetz, 1992; Scott, 2008). Indeed, there is no compelling reason to expect single cells to encode recognizable movement features, since many millions of cortical neurons converge to form the low-dimensional muscle command. In this issue of *Neuron*, Russo et al. (2018) argue for an alternative interpretation of the motor cortex. In their view, the dominant dimensions contained within cortical activity do not directly represent parameters of movement at all, but instead afford the network a high-dimensional space within which neural trajectories associated with different behaviors can be "untangled."

To support this hypothesis, Russo et al. (2018) recorded neural activity while monkeys performed an upper-limb cycling task that engaged muscles in sequence during each full rotation of the arms. As expected, the firing rates of neurons also fluctuated with each cycle, and the activity of different muscles could be accurately decoded from the neural population. The monkeys then cycled in the opposite direction, engaging the muscles in approximately the reverse order. Again, muscle activity was represented within the neural population, and one might therefore expect the sequential activation of individual neurons through the cycle to similarly be reversed. Surprisingly, however, this turned out not to be the case. To visualize the dynamic patterns of both muscles and neurons, Russo et al.