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Brain Dynamics: Global Pulse and Brain State Switching

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A major challenge in systems-level neuroscience is to understand the dynamic formation and succession of brain states. A new study has extracted reproducible brain states from mouse resting-state fMRI data, revealing interactions between occurrences of these states and the phase of global signal fluctuations and alterations of the states in a mouse model of autism.

Functional magnetic resonance imaging (fMRI) allows measurement of a proxy of neuronal activity at the whole-brain level. The development of new analytical tools has made it increasingly possible to unravel the rich spatiotemporal structure of these datasets, providing insight into the dynamic and distributed nature of brain activity [1]. Insights into organizational principles of brain function could help us understand neural correlates of behavior, cognition, and consciousness [2]. As they report in this issue of *Current Biology*, Gutierrez-Barragan *et al.* [3] have used resting-state fMRI in mice to investigate dynamics of brain states characterized by whole-brain spatial patterns of activity.

Instead of relying upon conventional functional connectivity that measures average ‘coupling’ between activity during a resting-state scan, Gutierrez-Barragan *et al.* [3] deployed the co-activation patterns framework [4] that is based on recurrent patterns of activity [5]. By retaining fMRI volumes for which activity in one of four different seeds — anterior cingulate, somatosensory cortex, auditory cortex and dorsal hippocampus — is above threshold, six whole-brain spatial maps were reliably identified across three independent datasets, and these are consequently considered as the expressions of different brain states. These states showed partially opposing activations in subsystems of major functional networks, such as the default-mode and latero-cortical networks, which can be regarded as the rodent homologues of human task-negative and -positive networks, respectively.

Then, by spatially correlating the states with each fMRI volume, Gutierrez-Barragan *et al.* [3] obtained time courses for which the power spectra revealed dominant energy in the low-frequency range 0.01–0.03 Hz. For the same bandpass, the instantaneous phase and amplitude of the global signal, the spatially averaged BOLD intensity, was computed. The meaning of the global fMRI signal is still debated in the neuroimaging community, and so the relationship demonstrated by Gutierrez-Barragan *et al.* [3] between significant state occurrences and the phase of the global signal — each state manifested at specific moments during the global-signal cycle — is a new principle of brain states' temporal organization. The functional relevance of the states was further studied by scanning Chd8 haploinsufficient mice, a rodent model for a subtype of the autism spectrum disorder, and using the data to re-interpret previously reported cortico-hippocampal hyperconnectivity [6]. These alterations could be contributed to specific dynamically-occurring brain states, further highlighting the importance of looking into advanced measures of brain function.

The blood-oxygenation-level-dependent (BOLD) signal recorded by fMRI is a slow hemodynamic proxy for neuronal activity. This indirect measure is prone to cardiac, respiratory, and motion-related confounds. Consequently, the significance of the global signal in fMRI studies has been a matter of debate [7,8]. On the one hand, global signal is confounded with non-neurophysiological contributions, which is a motivation to try to statistically remove (regress out) the global signal from the data. But on the other hand, neuronal contributions to the global signal have been found related to, for example, arousal [9], schizophrenia [10], or, in animal studies, to waves of global neural activity recorded using other modalities such as calcium imaging [11] and electrophysiology [12].

Gutierrez-Barragan *et al.* [3] consider the global signal as a pulse indicating probable occurrences of different large-scale distributed networks. While previous work showed that the 'global co-activation pattern', established by averaging fMRI volumes at the local maxima of the global signal, is widespread and dominated by sensory regions [12], the new study shows that six different states govern activity at the peaks, troughs, and in-between phases of the global signal, respectively. This finding combines two fundamental viewpoints of how evolving brain activity can be described: one based on low-frequency fluctuations of the global signal that can be characterized by phase extraction, and one based on instantaneous occurrences of activity. This work is among the first to deploy the co-activation patterns methodology in rodent functional neuroimaging in order to assess brain dynamics.

Previous fMRI work in rats explored co-activation patterns and showed, for instance, differences in brain dynamics related to anesthesia [13]. In the new study [3], fMRI data were acquired from mice, and the methodology focussed in particular on the global signal in terms of different dynamically constituted patterns. The new work challenges the interpretation of sliding-window functional connectivity states [14] in which, depending on the choice of the window duration, global-signal contributions might be integrated into the states themselves (for long window duration) or into the time-dependent state weights (for short window duration). In this respect, early work that did not regress out the global signal showed that the explained variance of temporal changes of sliding-window functional connectivity was maximal for a connectivity pattern that reflected a global state [15]. This supported the hypothesis that neuronal processing underlying the global signal can be considered as additive to more specialized ones, as previously suggested [16].

The new study [3] rather favors the explanation of the global signal being a consequence of different states occurring at different moments. Further research is needed to understand whether the global signal is a by-product rather than a driver of different brain states. The role of visceral signals, in particular, the heart–brain and gastric–brain couplings, could provide additional insights [17]. One may also ask whether global neuronal processes are better characterized by the slowly-fluctuating global signal, or by temporally isolated events [18]. This dichotomy might be clarified by looking at transient brain activity obtained after regularized deconvolution, which can discriminate between temporally overlapping patterns [19].

Gutierrez-Barragan *et al.* [3] revealed spatial differences between matching states obtained in groups of wild-type mice and the Chd8 haploinsufficient mice that exhibit behavioral similarities to a subtype of autism spectrum disorder. This included aberrant opposition of thalamic and dorsal hippocampal regions; reduced activity in cingulate and mid-thalamus; and increased focal activity in motor sensory and pre-frontal regions. While no group differences were found in terms of occurrences and durations of these states, their relationship with the global signal was altered by a significant phase delay. The authors then revisited the previously reported increased functional connectivity in Chd8 mutants [6], which was confirmed but could be undone after regressing out time courses of two particular brain states, and not of other states neither of the global signal. The specificity of this finding questions the role of structural versus functional alterations in autism spectrum disorder — only a subset of dynamically occurring patterns explains functional hyperconnectivity. Future research may further clarify the neurobiology of these changes by combining different recording techniques, but also relate the findings to observations from fMRI studies of humans with autism spectrum disorder, in particular the impact of altered brain dynamics on cognitive flexibility [20].

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Habenula: A Role in Brain State Transitions during Coping Behavior

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What is the link between behavioral states and neural dynamics in the brain? New research using zebrafish has revealed a unique activity pattern in the brain, sequentially recruiting multiple habenular neurons, during the transition from active to passive coping behavior.

Our feelings or mental state have a big impact on the way we choose our actions in response to environmental cues. In fact, choosing an appropriate behavioral strategy often requires a tactical evaluation of both our current internal state and the available external information. Decades of research have led to our current understanding of how sensory information is represented in the brain. Yet emerging work now also highlights the importance of investigating internally generated neural dynamics of the brain, which can directly influence our internal state and behavior. But what defines an internal state and how such 'states' are reflected in the brain is still an open question. A new study by Andalman *et al.* [1] has revealed how the habenula, an evolutionarily conserved brain nucleus, is involved in the transition of brain dynamics during the switch in coping behavior in zebrafish.

It is not easy to define a 'brain state', as it is often used to cover slightly different concepts within distinct fields of neuroscience. The term 'brain state' frequently refers to the internally generated activity of the brain that can span diverse time periods. Hence, defining a brain state requires information about the time scale during which it is investigated. Some brain states, such as those defined by differences in attention or motivation, can be rapidly modulated within short time windows. Yet other brain states act on much slower time scales: for example chronic sleep deprivation or continuous exposure to pain and stress can lead to longer lasting state transitions implicated in the pathophysiology of several mood disorders including depression [2].

When encountering aversive stimuli, the reaction of an animal strongly depends on its internal state. For example, rats initially display a 'flight