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## SCIENTIFIC COMMENTARY

# The flexible brain

**This scientific commentary refers to 'Neural, electrophysiological and anatomical basis of brain-network variability and its characteristic changes in mental disorders' by Zhang *et al.* (doi:10.1093/aww143).**

The vastness of the brain's dynamic repertoire is one of the remarkable features of brain function, making it possible to adapt rapidly and efficiently to external task demands, implement novel behaviours, and switch from one task to another. Variability in the neural dynamics is, nonetheless, constrained and displays heterogeneous topography—specific regions appear more or less variable over time, both in terms of their activity time courses (Garrett *et al.*, 2011) and also in terms of their interactions with other brain regions (their functional connectivity). In this issue of *Brain*, Zhang and co-workers present a novel method for characterizing the temporal variability of a region's functional connectivity profile [estimated from blood oxygen level-dependent (BOLD) functional MRI], relating this variability to the region's electrophysiology (measured with electroencephalography; EEG) and to its macroscale structural connectivity (white-matter pathways), and further demonstrating its potential utility as a neural marker for mental disorders (Zhang *et al.*, 2016).

The past decade has witnessed a burgeoning interest in the functional network architecture of the human brain. Most of these earlier studies have adopted a 'static' point of view, wherein functional connections between regions are characterized over long time scales, obscuring faster dynamics. More recently, however, it has become apparent that over the course of seconds to minutes, the human brain displays network-wide reconfigurations both at rest (Zalesky *et al.*, 2014) and during task performance (Braun *et al.*, 2015). These findings have motivated a concerted effort to understand dynamic functional connectivity: how temporal variation in brain network organization is related to behaviour, cognition, and disease (Calhoun *et al.*, 2014; Kopell *et al.*, 2014). This shift in perspective from a 'static' to a 'dynamic' point of view has been accompanied by a bevy of new methods for measuring and characterizing time-varying functional connections and has yielded insight into how dynamics may impact neural and behavioural adaptability.

A recurring finding in these studies is that distinct network elements exhibit different degrees of variability (Fig. 1). Attempts to characterize these fluctuations in terms of network topology have led to the conclusion that connections 'between' network modules—collections of mutually interconnected brain regions—tend to fluctuate more than connections 'within' modules (Zalesky *et al.*, 2014), and that the intermodular couplings between the fronto-parietal control module and other modules, in particular, have the highest variability, suggesting its relevance for the implementation of flexible task switching (Cole *et al.*, 2013). Variability in functional connectivity is also manifest in the detection and delineation of network modules and the persistence of modules over time. The network measure 'flexibility' incorporates this information by quantifying how frequently brain regions switch from one module to another. Network flexibility is correlated with working memory performance (Braun *et al.*, 2015), predicts future learning, and intuitively may be modulated by emotional state, fatigue, and arousal (Betzel *et al.*, 2016). Yet, while different measures of connectivity variability have been successfully related to behavioural measures, the factors that contribute to variability in BOLD functional MRI functional connectivity remain largely unknown.

The study by Zhang and colleagues aims to fill this gap by using multimodal imaging including functional MRI, electrophysiological, and structural data to explore network variability in a massive cohort ($n = 1180$). They began by segmenting resting state BOLD functional MRI into non-overlapping windows and generating, for each window, an estimate of the instantaneous whole-brain functional connectivity network. These networks were subsequently used to estimate variability for each brain region, defined as one minus the average correlation of that region's connectivity profile with all other regions, across all time windows. According to this definition, a variability of zero indicates that all connections (edges) incident to a region remain constant in value (weight) across time (or are shifted by a scalar), while unit variability indicates

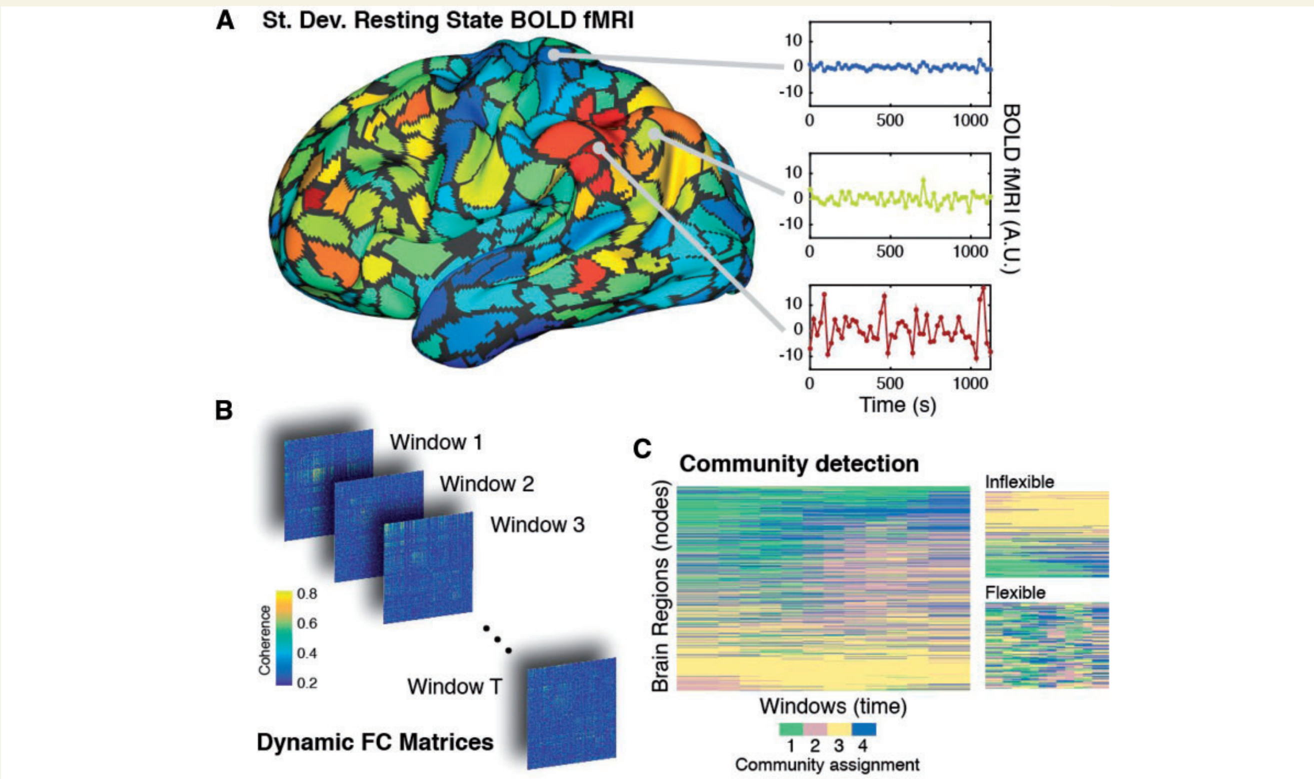


**Figure 1 Variability exists at different levels of network analysis.** (**A**) The BOLD functional MRI (fMRI) signal displays region-specific variability. (**B**) Windowing time series and estimating the functional connectivity (FC) between pairs of regions reveals dynamic functional connectivity matrices. Each edge describes the statistical relationship (strength of connectivity) between two brain regions. The organization of functional connectivity matrices changes over time, giving rise to variability in the connectivity profile of a region with the rest of the brain (Zhang *et al*., 2016). (**C**) Dynamic functional connectivity matrices can be used as input to module detection algorithms to generate estimates of the network's modular structure at each time point. Modules, in this case, refer to collections of mutually-correlated brain regions that, as a group, are weakly correlated with the rest of the network. We can characterize the dynamics of modular structure both in terms of individual brain regions and at the level of the whole network with the measure flexibility. Network flexibility indicates the extent to which brain regions change their module affiliation over time. All data, here, are taken from Betzel *et al*. (2016).

no relationship between edge weights at one time point and edge weights at another. Establishing a measure of variability at the node level allowed the authors to examine its spatial topography in the brain and its relationship to electrophysiological and structural features.

The authors first demonstrate that brain regions with the greatest variability in terms of their connectivity patterns also displayed the greatest variability in their allegiance to network modules, algorithmically defined proxies of functional systems. They then observed that early sensory regions exhibited lower variability than association and limbic areas, in line with previous work. In contrast to other studies, however, most regions of the default mode network (including medial prefrontal cortex, posterior cingulate, and angular gyrus) exhibited low variability (Zalesky *et al*., 2014). Interestingly, a region's variability was negatively correlated with the amplitude of its BOLD activity, and positively correlated with $\alpha$-band power in simultaneously acquired electroencephalography data. Furthermore, functional node variability was shown to have direct structural underpinnings, being inversely related to the ratio of within- to between-module connections in diffusion tensor imaging data, consistent with prior work (Shen *et al*., 2015). Finally, the authors applied the same analytic approach to patient data, and demonstrated that in comparison to healthy controls, individuals with autism and attention deficit hyperactivity disorder (ADHD) displayed higher default mode network variability, while patients with schizophrenia displayed lower default mode network variability.

In the growing field of network neuroscience and, in particular, the subfield investigating the dynamics of functional brain networks, this study makes several important contributions. While a number of earlier studies have presented evidence that variability in functional brain networks is related to behaviour and cognition, the structural and neurophysiological correlates of flexibility are largely unknown. The results of Zhang *et al*. suggest two potential drivers: power fluctuations in the $\alpha$-band

and the extent to which a brain region's connections are distributed across modules. These findings help bridge electrophysiological and functional MRI-based investigations into brain functional organization, all the while further reinforcing the notion that the brain's anatomical network imposes powerful constraints on neural dynamics. From a clinical perspective, this study also suggests the possibility that variability in the default mode network can serve as a biomarker of neuropsychiatric disorders.

While this study represents an important stepping-stone towards our understanding of dynamics in functional networks, much remains to be explored, both empirically and methodologically. For example, current approaches transform BOLD functional MRI data into dynamic networks using an *ad hoc* windowing procedure, but more principled, data- or model-driven approaches may prove advantageous. Ultimately, our goal is to understand the neural and computational mechanisms that describe electrophysiological activity over an underlying structural substrate, giving rise to dynamics with different levels of variability. Understanding this layered coupling in healthy conditions will then allow for a more complete description of what happens when it goes awry in neurological disease and psychiatric disorders.

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# References

Betzel RF, Satterthwaite TD, Gold JI, Bassett DS. A positive mood, a flexible brain. arXiv preprint 2016; arXiv:1601.07881.

Braun U, Sch¨afer A, Walter H, Erk S, Romanczuk-Seiferth N, Haddad L, et al. Dynamic reconfiguration of frontal brain networks during executive cognition in humans. Proc Natl Acad Sci USA 2015; 112: 11678–83.

Calhoun VD, Miller R, Pearlson G, Adalı T. The chronnectome: time-varying connectivity networks as the next frontier in fmri data discovery. Neuron 2014; 84: 262–74.

Cole MW, Reynolds JR, Power JD, Repovs G, Anticevic A, Braver TS. Multi-task connectivity reveals flexible hubs for adaptive task control. Nat Neurosci 2013; 16: 1348–55.

Garrett DD, Kovacevic N, McIntosh AR, Grady CL. The importance of being variable. J Neurosci 2011; 31: 4496–503.

Kopell NJ, Gritton HJ, Whittington MA, Kramer MA. Beyond the connectome: the dynome. Neuron 2014; 83: 1319–28.

Shen K, Hutchison RM, Bezgin G, Everling S, McIntosh AR. Network structure shapes spontaneous functional connectivity dynamics. J Neurosci 2015; 35: 5579–88.

Zalesky A, Fornito A, Cocchi L, Gollo LL, Breakspear M. Time-resolved resting-state brain networks. Proc Natl Acad Sci USA 2014; 111: 10341–6.

Zhang J, Cheng W, Liu Z, Zhang K, Lei X, Yao Y, et al. Neural, electrophysiological and anatomical basis of brain network variability and its characteristic changes in mental disorders. Brain 2016. doi: 10.1093/brain/aww143 in press.