

Resting brains never rest: computational insights into potential cognitive architectures

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Resting-state networks (RSNs), which have become a main focus in neuroimaging research, can be best simulated by large-scale cortical models in which networks teeter on the edge of instability. In this state, the functional networks are in a low firing stable state while they are continuously pulled towards multiple other configurations. Small extrinsic perturbations can shape task-related network dynamics, whereas perturbations from intrinsic noise generate excursions reflecting the range of available functional networks. This is particularly advantageous for the efficiency and speed of network mobilization. Thus, the resting state reflects the dynamical capabilities of the brain, which emphasizes the vital interplay of time and space. In this article, we propose a new theoretical framework for RSNs that can serve as a fertile ground for empirical testing.

The phenomenology of resting brains

Interest in the interplay between the intrinsic activity of the brain and the external world has seen a revival over the past decade, especially in neuroimaging. An assumption in many of the early studies was that such intrinsic brain activity is irrelevant and sufficiently random that it averages out in statistical analysis. Hence, the use of ‘activation paradigms’ (see [Glossary](#)) in these studies, where experimental manipulation resulted in the activation of cerebral circuits that were necessary for performing the task [1,2]. However, despite the most elegant experimental designs, there were consistent patterns of deactivation that often accompanied increased cognitive demands. Several researchers began to examine these deactivations based on the idea that the low-level baseline tasks were active states and that the patterns of activation and deactivation represented a shift in the balance from a focus on the internal state of the subject and its ruminations, to one on the external environment [3–5]. This pattern was later dubbed the ‘default mode’ [6] or, more recently, the ‘default mode network’ (DMN) [7].

The observation that there are relatively consistent distributed patterns of activity during rest led to the suggestion that it might be possible to characterize network dynamics without needing an explicit task to drive brain activity. This possibility has been explored in studies of RSNs in functional magnetic resonance imaging (fMRI). Probably the first demonstration of resting-state correlations using fMRI examined the cross-correlation (i.e., functional connectivity) between activity in the primary motor cortex (M1) and other brain regions independent of any overt task [8]. Spatially, the functional connectivity pattern seemed to mimic the pattern of activation seen when subjects executed an overt motor response. This observation led to a veritable explosion of work exclusively focused on the identification and characterization of these networks [7,9,10]. More recently, RSNs have been studied with magnetoencephalography (MEG) and electroencephalography (EEG) [11,12]. In general, EEG and MEG studies of resting-state activity have found slow fluctuations in the power of alpha and beta-frequency oscillations, which correlate across distant brain areas. Notably, these band-limited power (BLP) fluctuations yield large-scale spatial maps, some of which correspond quantitatively to the RSNs derived from fMRI [13]. Overall, these results indicate that resting state functional connectivity in blood oxygen-level dependence (BOLD) responses corresponds to a spatially structured modulation of BLP fluctuations.

Much of the RSN work in neuroimaging has emphasized the consistency of the spatial pattern, but that is likely a reflection of the relatively long time course over which the functional connectivity was estimated. RSNs have a rich spatiotemporal signature. The first clue to this behavior came from large-scale network simulations using anatomically realistic cortical connectivity [14]. Across a long time window, distinct functional networks formed that related to the structural connections. At shorter time steps, however, subnetworks formed and dissolved as the full network evolved. The regions within each of the broad spatial patterns would move away from their core network to form other networks, and then transition to a new set of spatial

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Glossary

Activation paradigm: experimental design in which the subject is asked to execute a perceptual, motor, or cognitive task relative to a low-level baseline task (e.g., visual fixation or 'rest'). During execution of the task, the associated brain activation is measured and is considered to be the only neural correlate of that specific function.

Attractor networks: brain dynamics can be modeled by attractor network models. These comprise a network of neurons that is a dynamical system that, in general, has the tendency to settle in stationary states, fixed points called 'attractors', typically characterized by a stable pattern of firing activity. External or even intrinsic noise that appears in the form of finite size effects could provoke destabilization of an attractor, therefore inducing transitions between different stable attractors. The dynamics of the network can be detailed by coupling the dynamical equations describing each neuron and the synaptic variables associated with their mutual coupling.

Bifurcation: one of the basic tools of analysis of dynamical systems. A bifurcation is defined by qualitative changes of the asymptotic behavior of the system ('attractors') under parameter variation.

Chaos: behavior of a dynamical system that is highly sensitive to initial conditions in such a way that extremely small differences in initial conditions yield widely diverging outcomes; thus, the evolution of the system is effectively unpredictable, even if the system is purely deterministic.

Criticality: at the brink of a bifurcation, the system displays certain characteristic dynamic features, most of which are related to enhanced fluctuations.

Diffusion spectrum imaging (DSI): an MRI technique that is similar to DTI, but with the added capability of resolving multiple directions of diffusion in each voxel of white matter. This enables multiple groups of fibers at each location, including intersecting fiber pathways, to be mapped.

Diffusion tensor imaging (DTI): an MRI technique that takes advantage of the restricted diffusion of water through myelinated nerve fibers in the brain to infer the anatomical connectivity between brain areas.

Functional connectivity: the statistical relation between activity in two or more neural sources. This usually refers to the temporal correlation between sources, but has been extended to include correlations across trials or different experimental subjects. Functional connectivity methods include estimation of correlation coefficients and coherence. The estimation cannot be used to infer the direction of the relation between sources.

Mean field: the mean-field approximation involves replacing the temporally averaged discharge rate of a cell with an equivalent momentary activity of a neural population (ensemble average) that corresponds to the assumption of ergodicity. According to this approximation, each cell assembly is characterized by means of its activity population rate.

Neural avalanches: bursts of elevated population activity, correlated in space and time, that are distinguished by a particular statistical character: activity clusters of size s occur with probability $P(s)$ equal to $s^{-\alpha}$ (i.e., a power law with exponent $\alpha=1.5$).

Noise: in neurodynamical systems, noise is mainly produced by the probabilistic spiking times of neurons and usually plays an important and advantageous role in brain function. Spiking noise is a significant factor in a network with a finite (i.e., limited) number of neurons. The spiking noise can be described as introducing statistical fluctuations into the finite-size system.

Spiking dynamics: a network of spiking neurons establishes a high-dimensional dynamic system, in which individual neurons (usually expressed by integrate-and-fire or Hodgkin-Huxley models) interact with each other through different types of dynamical synapse (e.g., AMPA, NMDA, or GABA).

Wilson-Cowan oscillator: a mean field-like rate model expressing the coupling between two populations of excitatory and inhibitory neurons. In general, the Wilson-Cowan model is tuned such that the population rate of the pools oscillates. It is one of the simple neural oscillators.

patterns. A schematic of this behavior is shown in Figure 1, where a 'core' pattern of functional connectivity is identified (Figure 1A), for example by looking at the correlation across a long time window; however, when smaller time windows are considered (Figure 1B), the core pattern dissolves and re-emerges. This temporal dependency has been empirically validated in fMRI studies [15–18] and emphasizes the rich spatiotemporal dynamics of resting-state brain networks.

Neurodynamical mechanisms underlying the resting state

Spatiotemporal functional connectivity in RSNs was originally hypothesized to reflect the underlying anatomical

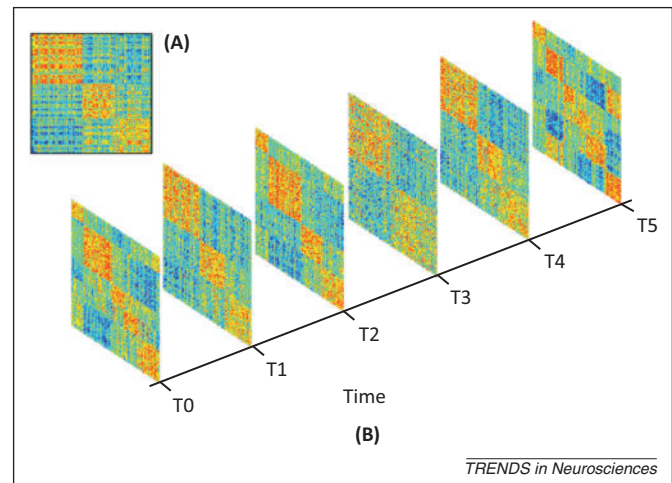


Figure 1. Schematic of the transitions of functional connectivity in different resting state networks (RSNs) across time. (A) The left most panel represents a correlation matrix (functional connectivity) from simulated data among network nodes across a long time interval. In actual functional magnetic resonance imaging (fMRI) blood oxygen-level dependence (BOLD) studies, this can be as long as 10 min. Each square represents a correlation between two regions and the matrix is symmetric about the diagonal. The clustering in the matrix indicates three networks dominant at that time window. (B) The change in functional connectivity of the nodes over shorter time window. Here, the dominant pattern in (A) repeats (e.g., times T1 and T4), but different subnetworks form as the system 'explores' different functional architectures. This behavior of RSNs has been shown in both simulations and empirical work.

connectivity structure. If we assume that each independent local cortical area shows low level noisy neural ongoing activity (i.e., Poissonian spiking activity at approximately 3–10 Hz), as evidenced experimentally with neuronal recordings [19–21], then the spatial structure of the underlying anatomical coupling between those brain areas would support correlations of the noisy fluctuations. Indeed, the correlation structure of spontaneous BOLD fluctuations relates to the underlying anatomical circuitry in monkeys [22]. In particular, there is a strong similarity between retrograde tracer maps reflecting anatomical connectivity and the resting BOLD functional connectivity. Furthermore, the networks of coherent spontaneous BOLD fluctuations under anesthesia are similar to networks commonly engaged during task performance in awake animals.

Despite the relation between anatomical and functional connectivity, the link is not perfect. Areas can show functional connectivity without a direct anatomical link and that is likely mediated through a series of indirect links [23,24] and, as noted above, are also dependent on the time window over which functional connectivity is computed. Thus, although RSNs may depend on the anatomical connectivity, they cannot be understood in those terms alone [25–27]. The missing link for understanding the formation and dissolution of RSNs is the dynamics [26]. Different local brain areas show specific dynamics; how these different dynamics interact through the anatomical coupling is not intuitive. Thus, theoretical models that bind structure and dynamics are fundamental for studying the relation between anatomical structure and RSN dynamics, and explicitly show that structure shapes functional connectivity but is definitively not identical to the latter [14,23,28,29]. Models of resting state activity have three ingredients: (i) the underlying

anatomical connectivity; (ii) the time delays due to signal transmission across different distances; and (iii) the local brain area dynamics (Figure 2). The main theoretical goal is to study the critical dynamical features of the model that are able to fit RSNs to understand the mechanisms that explain their origin.

The first ingredient of these models is the anatomical structure. In all models, structural information is extracted from databases compiling different types of tracing studies; for example, for the macaque cortex, this information is provided by CoCoMac neuroinformatics [30], or by diffusion tensor imaging and/or diffusion spectrum imaging (DTI/DSI) techniques [31]. The second ingredient is the signal transmission time delays. Generally, time delays do not alter the stationary spatial patterns in a network, but they do change their stability [32]. Although time delays play an essential role in the synchronization behavior of oscillatory patterns, it is less clear to what extent they influence patterns of spiking neurons. Various RSN models have demonstrated that the space–time structure of the couplings shapes the emergent network dynamics [25,27,29,33], although RSN models based on spiking neurons ignore the time delays due to the absence of oscillations [34]. The third ingredient of the models is the type of intrinsic dynamics of the local nodes: models

considered simple oscillatory dynamics [25,27,29,33], chaotic dynamics [14], and finally, detailed realistic local networks with excitatory and inhibitory populations of spiking neurons coupled through NMDA, AMPA, and GABA synaptic dynamics [34].

A common characteristic of all models is that the optimal working point for explaining the emergence of RSN is at the edge of instability, the critical point of a bifurcation. The first account of the RSN dynamics arising under conditions of criticality [27] demonstrated that the resting state emerges from noise-induced transient fluctuations around the stable equilibrium state of a network of coupled FitzHugh–Nagumo oscillators just below the edge of instability. The noise provokes fluctuations between different multistable oscillatory brain states in a network of Wilson–Cowan oscillators, again in the neighborhood of the critical point, but above the edge of instability [25]. RSNs also result from instability due to chaotic fluctuations [14]. In other words, the type of local dynamics is relevant for determining whether those particular dynamics show the relevant criticality, such that working at that point generates the resting functional connectivity. Nevertheless, in all models, the underlying anatomical structure shapes the structure of the dynamical landscape, which the fluctuations of the network model can explore. The time

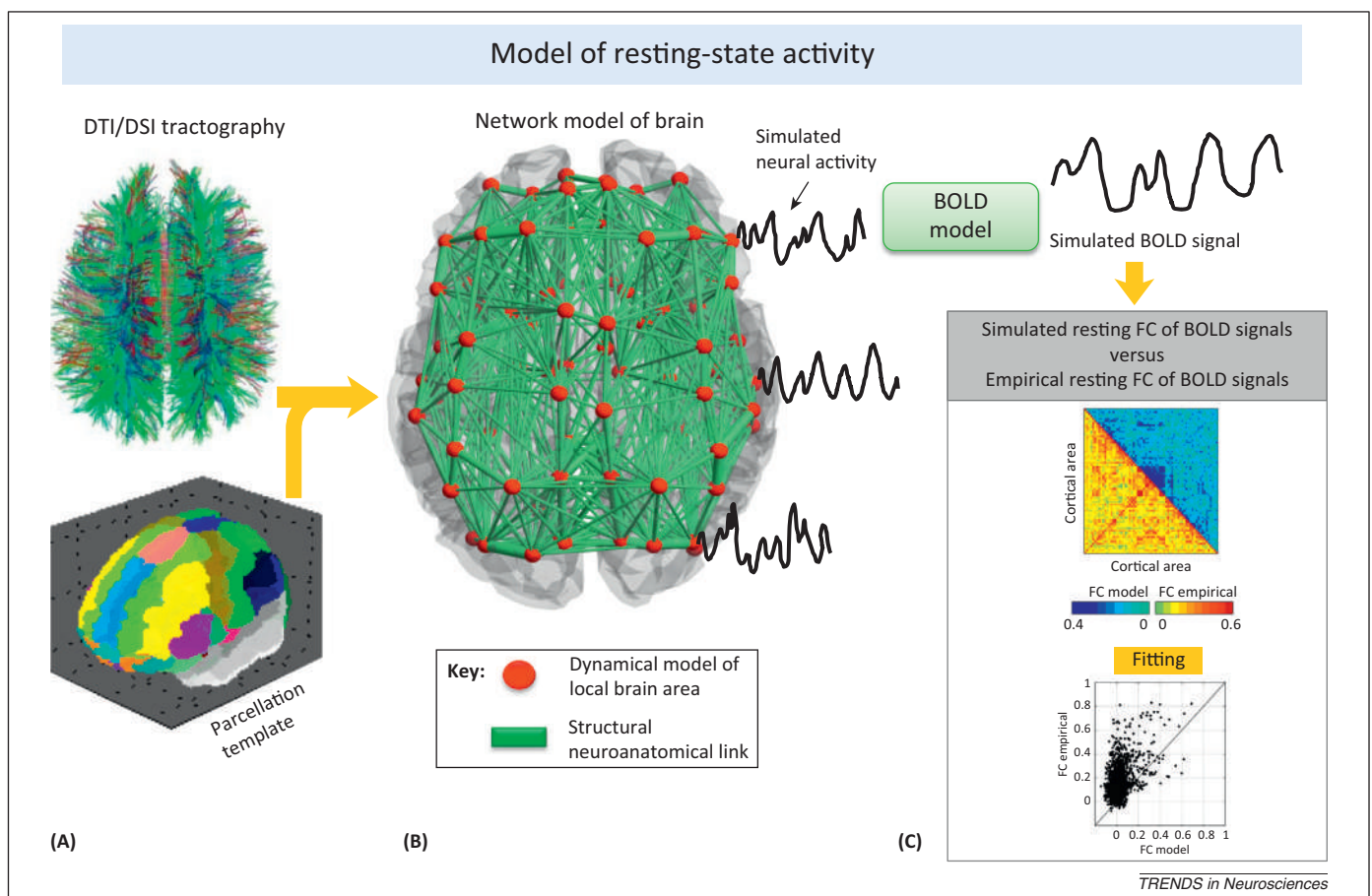


Figure 2. Neuroanatomical connectivity data obtained by DTI/DSI techniques are used for defining the structural connectivity between the different brain areas. (A) For a given parcellation, a neuroanatomical structural connectivity matrix links the N-parcellated cortical regions with clear anatomical landmarks. (B) A neurodynamical model is then constructed using a set of stochastic differential equations coupled according to the connectivity matrix. (C) The model is then constrained by fitting the functional connectivity (FC) observed in empirical data. In our case, the empirical FC was measured using functional magnetic resonance imaging (fMRI) blood oxygen-level dependence (BOLD) activity. This framework enables one to study the link between anatomical structure and resting-state dynamics. Abbreviation: FC, functional connectivity; DTI, diffusion tensor imaging; DSI, diffusion spectrum imaging.

delays may then alter the location of the instability, but will not change the actual structure of spatial patterns in the dynamical landscape. This is the reason why, generally, all the models could explain the spatial functional correlations defining the different RSNs. At the edge of the critical instability of any model, the spatial correlations of the noisy excursions are mainly shaped by the anatomical structure. The degree to which the RSNs are expressed depends on the proximity to the instability, which is determined by the space–time structure of the couplings (i.e., the topology of the connectivity and its associated time delays). In other words, by working near instability, RSNs reflect the dynamical capacity of that system to take on

different functional networks. The global dynamics of a brain working at a critical point amplifies the underlying structure of the anatomical connections and of its interactions with the local dynamics. Importantly, if the system were not working at that critical point, then the noisy fluctuations would reflect no structure whatsoever, the RSNs would not exist, and the resting state would be uncorrelated noise.

Hypotheses related to criticality and brain function have been put forward previously; for instance, one example [35] posits that the brain operates in the close proximity of so-called ‘saddle points’, which are characterized by stable and unstable directions in the state space of the

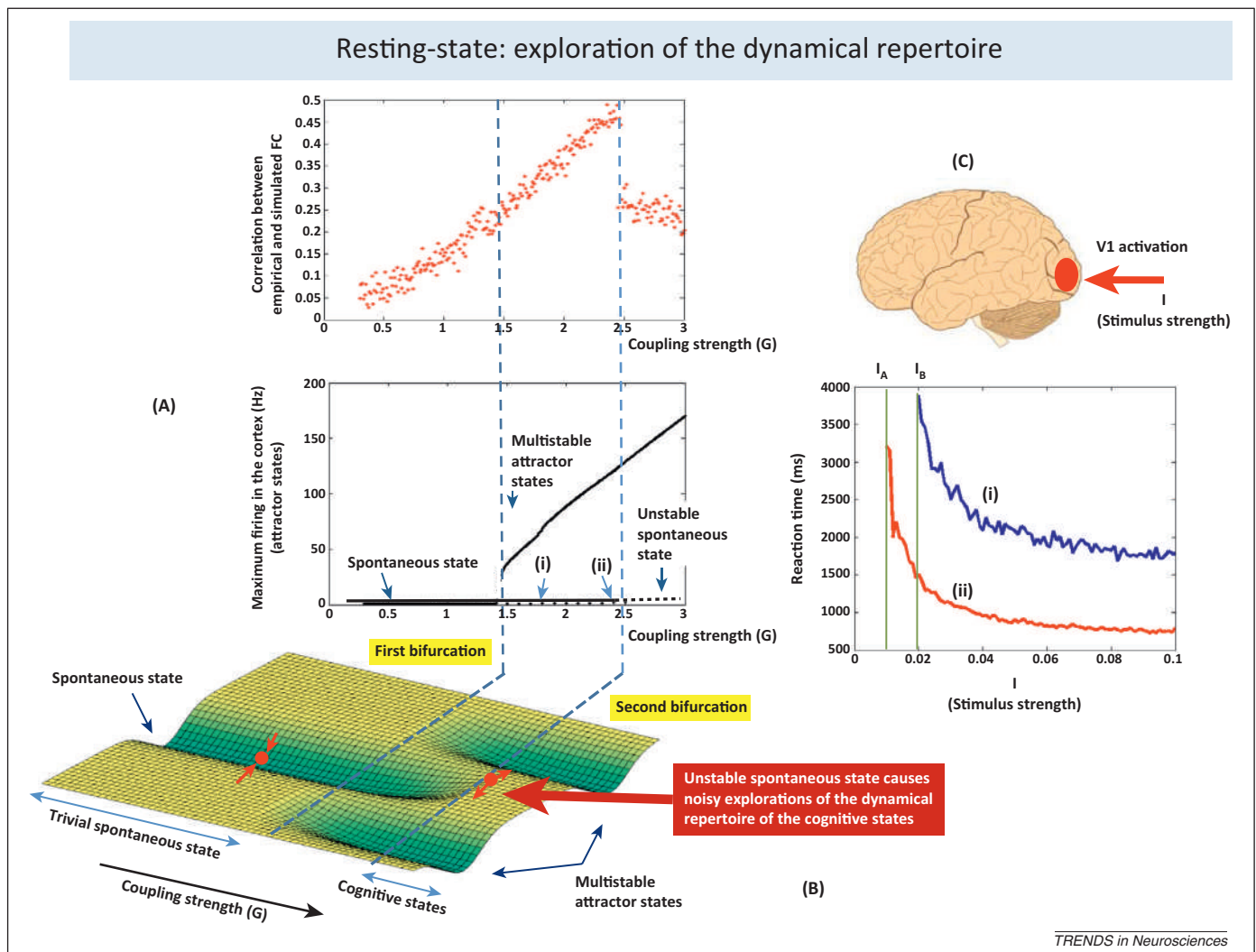


Figure 3. The large-scale dynamical brain model is able to best fit the empirical resting functional magnetic resonance imaging (fMRI) data when the brain network is critical (i.e., at the border of a dynamical bifurcation point), so that, at that operating point, the system defines a meaningful dynamic repertoire that is inherent to the neuroanatomical connectivity. **(A)** To determine the dynamical operating point of the system, we contrasted the results of the simulated model with the experimental resting functional connectivity (FC) as a function of the control parameter G describing the scaling or global strength of the intercortical coupling. The fit between both the empirical and the simulated FC matrix was measured by the Pearson correlation coefficient. In the same plot, the second bifurcation line obtained below is also shown. The best fit of the empirical data is observed at the brink of the second bifurcation model. **(B)** Bifurcation diagrams characterizing the stationary states of the brain system as a function of the control parameter G . We plotted the maximal firing rate activity over all cortical areas for the different possible stable states. We studied 1000 different random initial conditions to identify all possible new stationary states, and also the case where the initial condition was just the spontaneous state, to identify when the spontaneous state loses stability. For small values of the global coupling G , only one stable state exists, namely the spontaneous state characterized by low firing activity in all cortical areas. For a critical value of G , a first bifurcation emerges where at least one new multistable state appears while the spontaneous state is still stable. For even larger values of G , a second bifurcation appears where the spontaneous state becomes unstable. **(C)** Sensitivity to external stimulations with stimulus strength I . The critical point, where the trivial spontaneous state loses stability, is an optimal working point from an economical and ecological point of view. At that particular point, the system is maximally sensitive to external stimulations (i.e., is able to respond fast and efficiently even to weak ‘gentle’ stimulations). The figure plots how fast the system converges to the appropriate network attractor as a function of the strength of the external stimulating bias. In particular, we show the convergence characteristics for two different working points, one at the edge of the second bifurcation (in red) and one further away (in blue). The most optimal working point is indeed the one observed experimentally (i.e., at the brink of the second bifurcation), because it offers an advantage in terms of response time and sensitivity to incoming information.

brain. As the brain network dynamics evolve, various saddle points are visited, giving rise to the expression of brain states, because the dwell times at these points are significantly longer than anywhere else. These states might be related to cognitive processes, which is reminiscent of another proposal [36,37] that heteroclinic cycles comprise chains of cognitively relevant brain states. The working point of neural networks at criticality has also been noted in the context of optimized information processing. Simulations predicted that, at this point of criticality, neuronal networks optimize several aspects of information processing [38,39]. Experimental support of these predictions has been provided by the demonstration that, *in vitro*, cortical networks have maximum dynamic range when spontaneous activity takes the form of ‘neuronal avalanches’ [40]. During rest in the awake monkey, the avalanches constitute the dominant form of ongoing cortical activity [41].

For RSN dynamics, the discussion of the potential role of criticality as an organizing principle has been further explored with a realistic spiking cortical network that was microscopically organized as standard attractor models (known from neural models of memory, attention, decision making, etc. [42,43]) and macroscopically organized through a large-scale anatomical connection matrix obtained from human subjects via DTI/DSI tractography [31]. The model of a local brain area comprises integrate-and-fire spiking neurons with excitatory (AMPA and NMDA) and inhibitory (GABA-A) synaptic receptor types. **Figure 3** shows the main results and explains the mechanisms causing resting state activity. Let us assume that the control parameter is the coupling strength between different brain areas. The global dynamical states of the system can be described by a so-called ‘bifurcation diagram’, which captures the stationary states (attractors) of the system as a function of the coupling strength. For low coupling strength, only a stable spontaneous state occurs, characterized by asynchronous low-level firing activity in all brain areas. By increasing the coupling strength at the first bifurcation point, new stable attractors emerge. These new attractors reflect increased activity in some brain areas, defining the emergence and stabilization of specific networks of brain areas. In **Figure 3**, this is shown in the landscape cartoon (**Figure 3B**), and in the bifurcation diagram on top of that, where the maximal rate activity in the brain is plotted. After the first bifurcation, a new branch appears, which is evidence of the emergence of new attractors. Nevertheless, after this first bifurcation, the spontaneous state is still stable. Only after a second bifurcation does the spontaneous state lose stability. The brain appears to operate precisely at the edge of this second bifurcation point. In the top panel of **Figure 3B**, we show the fitting between the empirical and simulated resting BOLD functional connectivity. The best fit (maximal correlation) occurs exactly at the edge of the second bifurcation, where the spontaneous state loses its stability and, therefore, the noisy fluctuations of the dynamics are able to explore and reflect the structure of the other ‘cognitive’ attractors shaped by the underlying anatomy. Although this constitutes the origin and explanation of the resting state, it does not explain why the brain operates at that

particular bifurcation. The right panel of **Figure 3** provides the answer. The critical point is an optimal working point from an economical and ecological point of view. At that particular point, the system is maximally sensitive to external stimulations and able to respond fast and efficiently even to weak ‘gentle’ stimulations. In **Figure 3**, the visual network was stimulated by the application of an external bias in the V1 area, and the convergence to the appropriate network attractor for different strengths of the external stimulating bias was measured. **Figure 3C** shows the convergence characteristics for two different working points, one at the edge of the second bifurcation and one further away. The most optimal working point is indeed the one observed experimentally (i.e., at the brink of the second bifurcation), because it offers an advantage in terms of response time and sensitivity to incoming information.

Concluding remarks and outlook

As brain network properties change, be it due to inter-subject variability, learning, disease, aging, or development, the critical point of the network will also change, as will its associated dynamic features, including the subspace spanned by the RSNs and optimality of information processing through the network. If criticality is indeed a principle of functional brain organization, then homeostatic mechanisms are required to maintain the brain network at criticality, which can be explored in theoretical and empirical work (e.g., **Box 1**).

Consideration of criticality as a principle of functional brain organization has implications for the emergence of cognitive processes in the context of RSNs. Rather than embodying specific cognitive or behavioral operations, RSN dynamics is the gateway to the array of cognitive architectures that the brain has available (**Box 2**). From this perspective, RSN dynamics represent the instigation of lower-dimensional subspaces within the available high-dimensional space. The lower-dimensional subspaces define a specific workspace that constitutes some sort of prospective exploration of potential functions, but not their

Box 1. Outstanding issues and questions

Can we measure the critical point empirically?

To address this question, we need to measure the critical point directly from empirical studies. The mixing of deterministic and stochastic contributions of the network dynamics renders this task difficult, but not impossible. The variability of the brain signals will typically scale with the ratio Q/L , in which L denotes the linear stability strength of the equilibrium attractor and Q the noise strength. The disentangling of deterministic and noise contributions is possible by measuring statistical quantifiers, including the variance of the brain signals and the dwell time at individual attractors, as well as the mean escape time of resting state attractors (e.g., [44]).

Can we manipulate the critical point?

Exogenous drives, such as transcranial magnetic stimulation (TMS) or deep brain stimulation (DBS), offer independent means of testing understanding of RSN dynamics. In particular, criticality predicts that the RSNs are closer to instability than other networks, as quantified by the linear stability strength L . The networks closest to instability (with the smallest L) will determine the overall brain dynamics after a perturbation and show the longest relaxation times (scaling inversely to L) returning towards equilibrium.

Box 2. Hypotheses about resting-state dynamics and cognitive potential

The potential should increase with maturation

This was confirmed in EEG and MEG studies of infants and children up to 15 years old, where the entropy increased with age. Importantly, the greater entropy and, more specifically, the multi-scale entropy (MSE), correlated with higher cognitive performance [45–47]. Also of interest was the observation that this increase in entropy could be attributed to the high exchange of information between distal brain regions, rather than an increase in local dynamics [48].

The potential should change in senescence

Recent studies examined variability in BOLD fMRI across different aged adults and showed a general decrease in dynamics, although across a less broad range than during early maturation [49–52]. This is consistent with the fact that cognitive changes during aging, although significant, are not nearly as striking as during early maturation.

The potential should be affected by brain disease and disorders

Studies of dementia clearly show reduced MSE with disease severity [53], whereas studies of recovery of function from head injury show increased dynamics linked to better recovery [54,55].

The potential should increase with learning

Recent work with EEG demonstrated that, as an individual acquires more knowledge about an object, the dynamics elicited by that object (i.e., the number of potential network configurations) also increases [56].

instantiation. In a sense, RSNs represent exploration by the brain of what is possible.

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