Cell Reports

CellPress
OPEN ACCESS

Review

Brain States and Transitions: Insights from Computational Neuroscience

Morten L. Kringelbach[1,2,3,*] and Gustavo Deco[4,5,6,7,*]
[1]Department of Psychiatry, University of Oxford, Oxford, UK
[2]Center for Music in the Brain, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[3]Centre for Eudaimonia and Human Flourishing, University of Oxford, Oxford, UK
[4]Center for Brain and Cognition, Computational Neuroscience Group, Department of Information and Communication Technologies, Universitat Pompeu Fabra, Roc Boronat 138, Barcelona 08018, Spain
[5]Institució Catalana de la Recerca i Estudis Avançats (ICREA), Passeig Lluís Companys 23, Barcelona 08010, Spain
[6]Department of Neuropsychology, Max Planck Institute for Human Cognitive and Brain Sciences, 04103 Leipzig, Germany
[7]School of Psychological Sciences, Monash University, Melbourne, Clayton, VIC 3800, Australia
*Correspondence: morten.kringelbach@psych.ox.ac.uk (M.L.K.), gustavo.deco@upf.edu (G.D.)
https://doi.org/10.1016/j.celrep.2020.108128

SUMMARY

Within the field of computational neuroscience there are great expectations of finding new ways to rebalance the complex dynamic system of the human brain through controlled pharmacological or electromagnetic perturbation. Yet many obstacles remain between the ability to accurately predict how and where best to perturb to force a transition from one brain state to another. The foremost challenge is a commonly agreed definition of a given brain state. Recent progress in computational neuroscience has made it possible to robustly define brain states and force transitions between them. Here, we review the state of the art and propose a framework for determining the functional hierarchical organization describing any given brain state. We describe the latest advances in creating sophisticated whole-brain computational models with interacting neuronal and neurotransmitter systems that can be studied fully *in silico* to predict and design novel pharmacological and electromagnetic interventions to rebalance them in disease.

INTRODUCTION

In the broadest sense, *brain states* are often referred to as states of, for example, wakefulness, sleep, and anesthesia (Gervasoni et al., 2004; Northoff, 2013; Tononi et al., 1994). Nevertheless, a precise and commonly agreed definition of a brain state is still missing and the underlying dynamical complexity remains unknown. The contention here is that computational neuroscience offers a *mechanistic* framework for characterizing brain states in terms of the underlying causal mechanisms and dynamical complexity.

Brain states consist of the continuously evolving dynamics of widespread networks that are characterized by condition-dependent self-organization, going through stable, "quasi-stable," high or low activities, and transient arrangements. The key question is how best to identify states from functional neuroimaging data with a focus on capturing their whole-brain dynamics over time and space (Deco et al., 2019b). Until now, existing definitions of brain states have been restricted to resting-state networks and mainly to describing grand average descriptions of functional brain activity (Barttfeld et al., 2015; Carhart-Harris et al., 2016; Tagliazucchi et al., 2016).

Yet time is crucial for describing brain states, and any potential definition would need to be extended to include dynamics in order to understand the underlying information processing across time and space. As shown in Figure 1, it is possible to create a detailed taxonomy of the many different empirical and analytical tools that have been developed to try to fill this gap (see also Bolton et al., 2020). In particular, there has been significant progress in characterizing the spatiotemporal dynamics of neuroimaging data (de Pasquale et al., 2016; Hansen et al., 2015; Hutchison et al., 2013; Preti et al., 2017).

Still, moving beyond such correlational descriptions will need mechanistic whole-brain modeling of the dynamics underlying the brain states. It is, of course, important to realize that brain-state dynamics and organization are emergent properties of the computational model, and as such the main aim is to find the best definition and identification method for brain states that maximally reflect the capabilities of the model and meaningfully summarize features of the data. In other words, not all measures that characterize the empirical data can be extractable from the whole-brain computational model data.

Using whole-brain modeling to bring about an enhanced description of brain states is not just useful for understanding the healthy brain but holds great promise for helping support diagnosis and therapeutic interventions in disease (Deco and Kringelbach, 2014; Gilson et al., 2020). Recent evidence of the usefulness of whole-brain models for disease has emerged from clinical conditions such as stroke (Adhikari et al., 2017), epilepsy (Hashemi et al., 2020), and brain tumors (Aerts et al., 2020). Still, although promising, the methods have yet to be used to their full potential for clinical treatments.

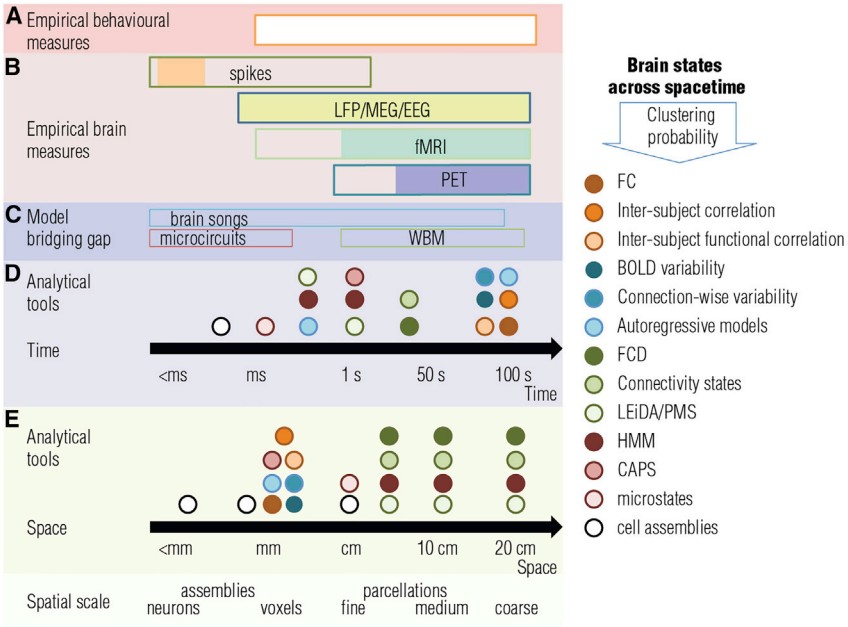

Figure 1. Taxonomy of Tools for Characterizing Brain States over Time and Space

Brain activity with concomitant behavior can be measured over many different temporal and spatial scales.

(A) Empirical behavioral measures can capture information starting at a timescale of tens of milliseconds.

(B) On the other hand, empirical brain measures, for example neuronal recordings, can capture information such as spiking activity on a much faster sub-millisecond timescale. Other technologies such as local field potential recordings, EEG, and MEG can similarly capture fast temporal information but on a much less localized spatial scale. fMRI remains one of the most widespread methods for measuring brain-wide activity with excellent sub-millimeter spatial resolution but is limited in the temporal domain by hemodynamics. Another popular whole-brain imaging method is PET, which is less precise in both temporal and spatial information but can measure important information about neurotransmitter density.

(C) The empirical measures can be combined in whole-brain models, which helps bridge the gap between the measurements on their own and a causal mechanistic understanding of them.

(D) This summarizes the temporal properties of many different analytical tools.

(E) Similarly, these analytical tools have different strengths in characterizing the spatial properties of the brain from neurons to assemblies of neurons, to neuroimaging voxels incorporating millions of these to fine-, medium-, and coarse-grade parcellations of the brain.

BOLD, blood-oxygenation-level-dependent ; CAPs, co-activation patterns; EEG, electroencephalography; FC, functional connectivity; FCD, functional connectivity dynamics; fMRI, functional magnetic resonance imaging; HMM, hidden Markov model; LEiDA, leading eigenvector dynamics analysis; LFP, local field potential; PMS, probabilistic metastable substate; WBM, whole-brain model.

In this review, we focus on how whole-brain models can provide a robust quantitative definition of brain states, providing a possible basis for the precise prediction of the effects of pharmacological and electromagnetic perturbations needed to force transitions between brain states. Long term, such a framework would be highly useful for biomarkers needed for the diagnosis, for instance, of comatose patients—and actual interventional treatment to awaken these patients. Finally, we propose and discuss novel approaches, which could be used to advance the field beyond the state of the art.

Principles of Brain States Revealed by Whole-Brain Modeling

The main aim of computational neuroscience is to reverse engineer the human brain to discover the mechanistic principles that allow the brain to orchestrate the complex behavior needed for survival. This is inspired by the success of modern physics, which is based on its ability to model the constitutive elements of a system and to systematically perturb these elements to discover the emergence of the underlying dynamics (Feynman et al., 2005). As an example, the detailed understanding of fluid dynamics has come about through careful modeling of the statistical properties of the necessary and sufficient elements over multiple scales (Frisch, 1995).

In a similar way, the progress of neuroscience has been facilitated by the use of whole-brain modeling in simulating brain dynamics. The fundamental principle is to link anatomical structure with functional dynamics (Deco et al., 2009; Jirsa et al., 2002) (Figure 2A). The anatomy can be represented in many ways, ideally through large-scale tract tracing providing directional anatomical connectivity (Kötter, 2004; Markov et al., 2014). This information is not currently possible to obtain in humans but instead researchers have measured unidirectional connectivity using *in vivo* diffusion magnetic resonance imaging (dMRI) combined with probabilistic tractography (Basser and Pierpaoli, 1996; Beaulieu, 2002; Hagmann et al., 2010; Johansen-Berg and Rushworth, 2009).

These tractography measures are not without problems, given that fiber tracking is complex and involves many steps inherently subject to potential errors from and decisions regarding local fiber orientation modeling, integration/propagation, interpolation, seeding, masking, and stopping criteria (Jeurissen et al., 2019). Recent comparisons between connectomes created with diffusion tractography-based and neuroanatomical tracer studies have shown that state-of-the-art tractography does not detect all neuroanatomical pathways and their corresponding connection strengths (Donahue et al., 2016). Thus, even when using state-of-the-art methods with high-quality diffusion data, many issues are currently unresolved. Still, many of these issues can be overcome with the use of model-based estimates of the effective connectivity, where measures of functional connectivity can enhance and supplement the anatomical structural connectivity, especially the strengths of connectivity even at the individual level (Gilson et al., 2016; Pallarés et al., 2018).

In order to further reduce the complexity of modeling, the brain is typically divided into a meaningful parcellation based on structural and functional information, typically on the order of 80–150 nodes (Eickhoff et al., 2018a, 2018b). The functional global

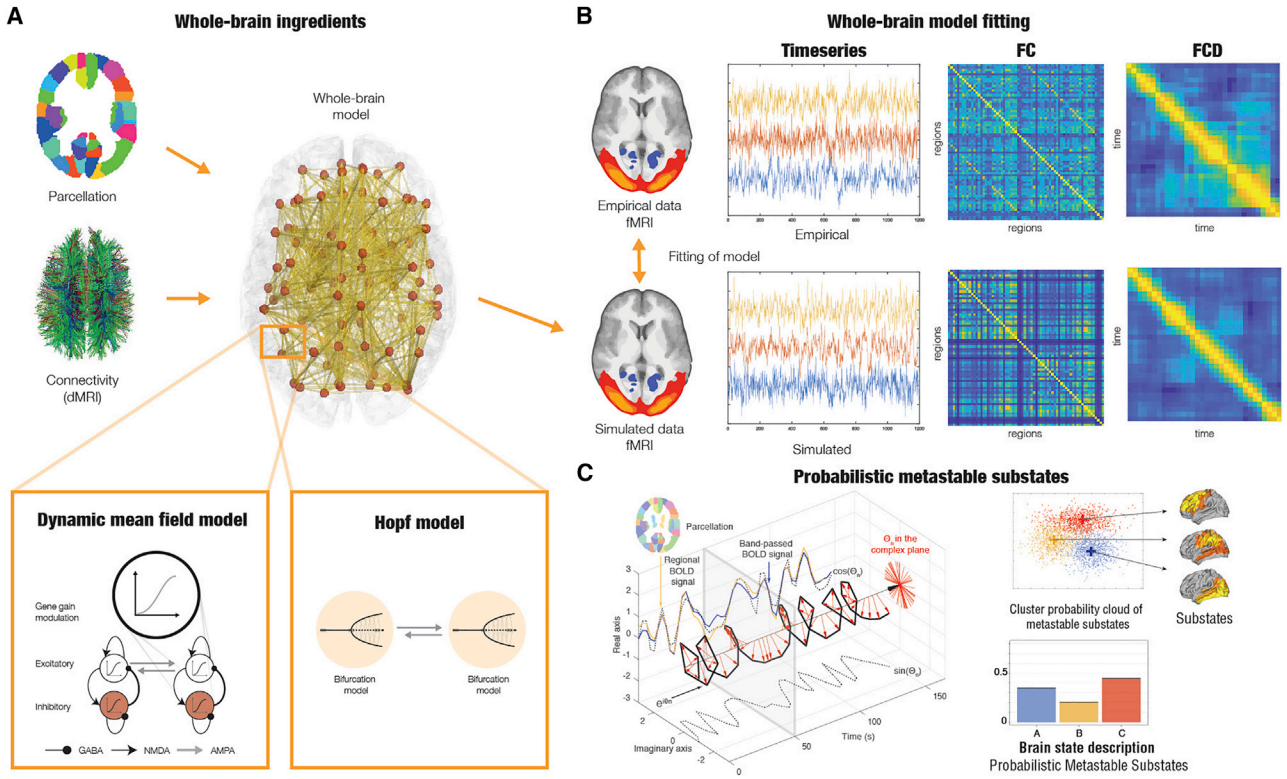

Figure 2. Whole-Brain Modeling of Brain States

(A) The fundamental idea is to couple the local dynamics of a region through the anatomical connectivity to other regions in order to accurately generate the empirical whole-brain data coming from measurements across different timescales (e.g., fMRI, MEG, EEG, and PET). Thus, the main ingredients in this whole-brain model of brain-state dynamics are (1) the local dynamics, (2) the anatomical structural connectivity between regions, and (3) their functional whole-brain activity data. The local neuronal dynamics can be expressed, for example, as a spiking neuronal network or mean field model or with mesoscopic models such as the Hopf model.

(B) The model is fitted to the dynamics, originally only using the average FC but now using temporal dynamics such as the FCD.

(C) An even more accurate version of brain dynamics can be obtained through using the LEiDA framework. Left: how the phase of the BOLD signal is computed for every time point in a given brain region. This is repeated for all brain regions and, at each time point, the BOLD phase coherence matrix between brain regions is computed. Left panel: how the leading eigenvectors for all phase coherence matrices in all participants are clustered in order to define the substates. Right panel : the PMS space, which captures the center of the clusters (top) with their probability of occurrence and associated lifetimes (bottom). This framework allows for a given brain state to be accurately quantified.

dynamics emerge from the mutual interactions of local node dynamics coupled through the underlying empirical anatomical connectivity. This functional activity can be captured with whole-brain neuroimaging methods, typically fMRI (functional magnetic resonance imaging), MEG (magnetoencephalography), and EEG (electroencephalography). These measures capture different timescales of brain activity (see Figure 1).

Whole-brain models aim to balance between complexity and realism in order to describe the most important functional features of the brain *in vivo* (Breakspear et al., 2010; Deco et al., 2011). The most successful whole-brain computational models have taken their lead from statistical physics, where it has been shown that macroscopic physical systems obey laws that are independent of their mesoscopic constituents (Haken, 1988). Each node typically consists of a suitable approximation of the local neuronal dynamics, which can be expressed as a spiking neuronal network (Deco and Jirsa, 2012; Ghosh et al., 2008), mean field model (Deco et al., 2014b; Honey et al., 2007), or mesoscopic model (for instance, the Hopf model; Deco et al., 2017b; Freyer et al., 2012). Typically, these models fit the empirical data by optimizing the global coupling parameter that scales the underlying structural connectivity, which assumes that the conductivity is uniform across the brain. But it is, of course, also possible to model potential heterogeneity in conductivity by adapting the effective connectivity to the empirical data (Gilson et al., 2016). The emergent collective macroscopic behavior of brain models has been shown to depend only weakly on individual neuron behavior (Breakspear et al., 2010).

The whole-brain-modeling framework has been successful in explaining the patterns of spontaneous inter-regional functional activity correlations, forming the so-called resting-state networks captured by fMRI (Breakspear, 2004; Deco et al., 2011, 2013; Deco and Kringelbach, 2014; Ghosh et al., 2008; Honey et al., 2007). Recent developments have shown that whole-brain models are able to describe not only static *functional*

connectivity (FC; averaged over all time points) (Deco et al., 2017b) but also dynamical measurements such as the temporal structure of the activity fluctuations in *functional connectivity dynamics* (FCD) (Figure 2B) (Hansen et al., 2015). Whole-brain models can also be used to explain brain activity on faster timescales (milliseconds) as measured, for example, with MEG (Cabral et al., 2014; Deco et al., 2017a) but many challenges remain to unify the different timescales. Crucially, it has also been demonstrated that whole-brain models can bridge the gap between different timescales from milliseconds to tens of seconds, offering unparalleled mechanistic insights into the multi-scale nature of whole-brain activity (Deco et al., 2019b).

Brain States: Descriptions of Dynamics

Early descriptions of brain states have focused on them as merely a point in a state space, a high-dimensional coordinate system characterizing the activity of the brain at a given time. But this does not capture the dynamical nature of a brain state over time. Some have instead proposed describing a brain state as an attractor of interacting brain regions (Deco and Jirsa, 2012; Gu et al., 2018), but this does not capture the metastable nature of brain states (Shanahan, 2010; Tognoli and Kelso, 2014). All of these methods provide more or less accurate descriptions of the fundamental underlying ensemble or "cloud" of possible steady states (attractors). These descriptions have nevertheless been very useful tools for thinking about brain function but without capturing all aspects of the rich functional dynamics of brain states.

Recently, a novel framework called leading eigenvector dynamics analysis (LEiDA) was proposed to characterize probabilistic metastable substates (PMSs) as stochastic subdivisions of regular and persistent brain states (Cabral et al., 2017; Deco et al., 2019a). The fundamental framework of LEiDA is shown in Figure 2C. In brief, the method uses the blood-oxygenation-level-dependent (BOLD) phase signal to determine the state of whole-brain synchronization between different brain regions at every time point. This is computed for all participants and group results are clustered to find the metastable substates where their probability of occurrence characterizes a given brain state. More specifically, for every time point, in every brain region of each participant, the Hilbert transform is used to compute the phase of the BOLD signal, giving rise to the BOLD phase coherence matrix between brain regions. The dimensionality is reduced by extracting the leading eigenvector V1(t) of this matrix. The PMS is then computed by using a clustering algorithm on all the concatenated leading eigenvectors for all time points in all participants. The resulting PMS space captures the center of the clusters with their probability of occurrence and associated lifetimes and is thus a strong candidate for an operational definition of a brain state.

Figure 1 shows how LEiDA, and other analytical tools, can be characterized in terms of their spatiotemporal taxonomy. However, in addition to these measures, LEiDA differs in important ways from other analytical tools. As an example, LEiDA is related to brain activity and not to measures of connectivity/correlation, such as co-activation patterns (CAPs) (Liu and Duyn, 2013), innovation-driven co-activation patterns (iCAPs) (Karahanoğlu and Van De Ville, 2015), and connection-wise variability (Kucyi and Davis, 2014). Similarly, the method uses the fluctuations at a specific timescale defined by a band-pass filter, and is based on oscillatory/phase features, rather than transients (Baker et al., 2014; Vidaurre et al., 2018) and microstates (Lehmann et al., 1998; Michel and Koenig, 2018). Finally, LEiDA defines discrete states in time (determined by clustering) instead of overlapping states determined by subspace methods.

Indeed, the LEiDA framework has been shown to be highly flexible, robust, and precise. It has allowed for recurrent substates to be detected and characterized for resting state (Cabral et al., 2017) and task (Stark et al., 2020) in the healthy brain. It can also distinguish between brain states in disease (Figueroa et al., 2019) and even in altered states such as psilocybin (Kringelbach et al., 2020; Lord et al., 2019) and sleep (Deco et al., 2019a). Furthermore, it has been shown that a whole-brain model can simulate the PMS space describing the necessary and sufficient dynamical features of the functional empirical data (Deco et al., 2019a).

Forcing Controlled Transitions: Model-Based and Empirical Evidence

There is a growing interest in how best to control the brain and its transitions in health and disease. But the full potential has yet to be fulfilled, i.e., where a model has predicted a perturbation forcing a state transition and where this prediction has subsequently been empirically tested and validated. Still, as shown in the following, many strategies are being explored at this point.

One framework is to use a strategy where the dynamical trajectory of brain activity is continuously controlled by external stimulation predicted by a computational model (Gu et al., 2017). However, the viability of this strategy has been questioned (Tu et al., 2018).

More generally, manipulation of the brain must encompass more than simply controlling individual trajectories. Instead, it must solve the fundamental problem of how to force transitions between different brain states. Given a robust definition of brain state, one strategy could be to find the optimal, precise perturbation that can force a transition between different brain states. The key idea is shown in Figure 3A, which sketches how to use whole-brain models to predict loci of stimulation that can offer a route to change the dynamical landscape of a brain state such that the brain will self-organize into a desired target brain state. Such a strategy could be termed "homeostatic rebalancing."

In terms of empirical evidence of how individual trajectories can change with brain state, Massimini and colleagues used transcranial magnetic stimulation (TMS)-EEG to investigate the perturbation-elicited changes in global brain activity during wakefulness, sleep, anesthesia, and coma (Figure 3B). The results showed that non-REM (rapid eye movement) sleep is accompanied by a breakdown in cortical effective connectivity, where the stimuli rapidly extinguish and do not propagate beyond the stimulation site (Casali et al., 2013; Ferrarelli et al., 2010; Massimini et al., 2005). The results also showed significant differences in brain-wide spatiotemporal propagation of external stimulation, which distinguishes between different brain states (Casali et al., 2013).

In addition, a very recent study also used TMS-EEG to characterize individual brain dynamics at high temporal resolution, where TMS was used to create transitions to individually defined nodes of

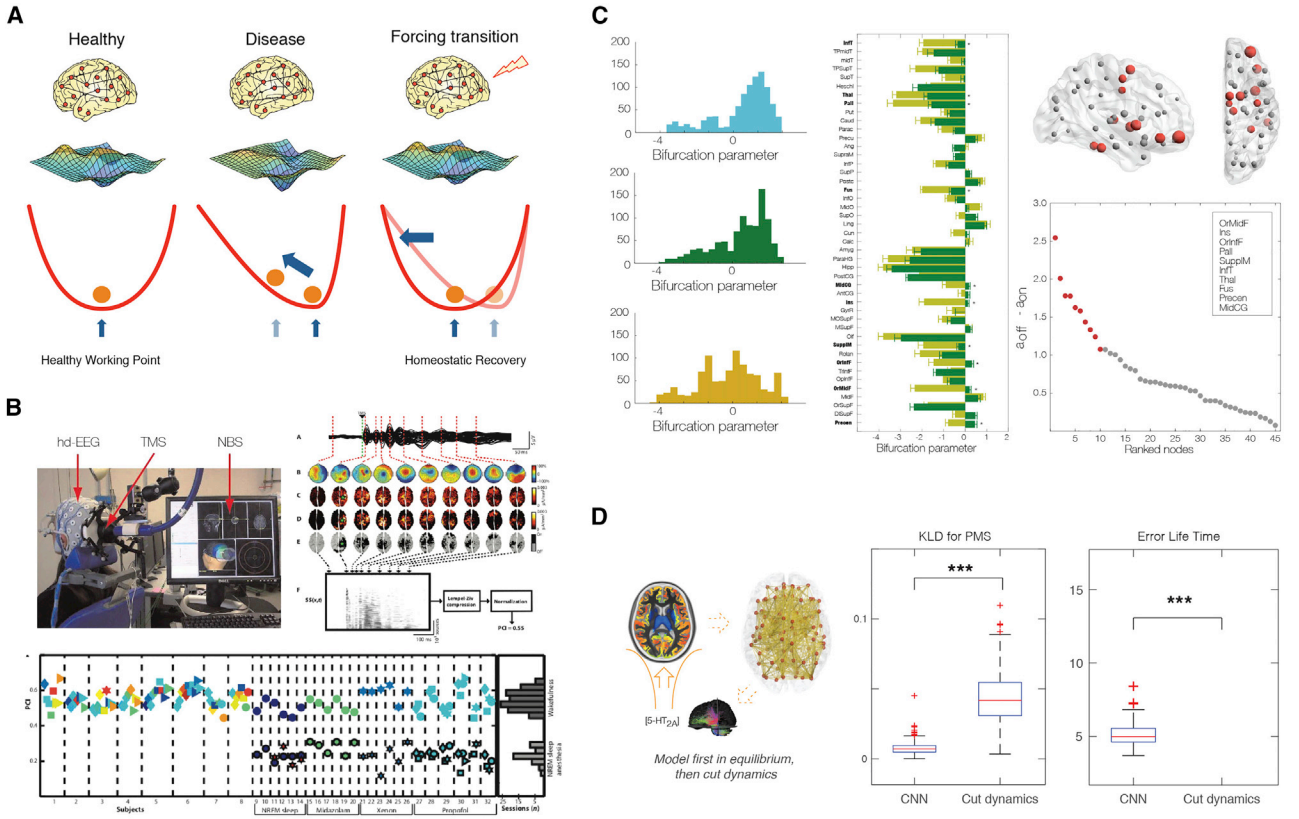

Figure 3. Summary of Examples of Empirical Brain Stimulations

(A) The goal of whole-brain modeling is to predict potential perturbations that can change the dynamical landscape of a source brain state such that the brain will self-organize into a desired target brain state. The figure is a cartoon of how a healthy brain state is associated with a dynamical landscape (left), which is perturbed in disease (middle), and showing "homeostatic rebalancing" following a precise perturbation (right).

(B) Empirical evidence of how brain stimulation can affect brain activity comes from Massimini and colleagues, who investigated the perturbation-elicited changes in global brain activity during wakefulness, sleep, anesthesia, and coma using TMS-EEG. They found significant differences in brain-wide spatio-temporal propagation of external stimulation, which distinguishes between different brain states. Further details are available in Casali et al. (2013).

(C) Beyond such short-lasting changes, longer-lasting changes have been caused by direct deep brain stimulation to alleviate symptoms in disease. The figure shows the results of using a whole-brain model of simultaneous neuroimaging activity and direct ON-OFF deep brain stimulation. Left: histograms of whole-brain-model parameters associated with each brain region for healthy individuals (top) and individuals with Parkinson's disease OFF stimulation (middle) and ON stimulation (bottom). Middle: specific differences between brain region ON and OFF stimulation. Right: significant differences (in red) in the brain (for details, see Saenger et al., 2017).

(D) Another example of global dynamical changes following perturbations comes from pharmacological stimulation with psilocybin, which stimulates serotonin release. This has been explicitly modeled with a whole-brain model. Left: coupling between neuronal and neurotransmitter systems through a raphe nucleus releasing serotonin. Right: significant improvement in fitting the empirical data with and without this dynamical feedback coupling in terms of PMS and lifetime of the PMS states (see full details in Kringelbach et al., 2020).

two well-known resting-state networks (Ozdemir et al., 2020). The study found network-specific source-level EEG propagation patterns that were highly reproducible across sessions 1 month apart.

Further evidence comes from whole-brain models of the longer-lasting direct stimulation offered by deep brain stimulation (Kringelbach et al., 2007), which can help alleviate otherwise treatment-resistant symptoms in neuropsychiatric and motor disorders. Figure 3C shows the results from whole-brain models of simultaneous neuroimaging activity and direct ON-OFF deep brain stimulation (Kahan et al., 2014) alleviating symptoms of brain disease (Saenger et al., 2017; van Hartevelt et al., 2014, 2015). This has revealed the underlying brain networks changing with long-lasting stimulation—as well as identified potential new targets for rebalancing.

This empirical evidence clearly reflects the change of dynamics following perturbation but the field awaits confirmation of the predictive power of whole-brain modeling for forcing transitions between brain states. A potential route to conducting such crucial experiments could come from the whole-brain models that have been constructed for other animals including non-human primates (Deco et al., 2014a; Shen et al., 2019) and rodents (Melozzi et al., 2017). In the future, these models could be used for investigating the changes in brain state between awake and anesthetized non-human primates (Autio et al., 2020; Barttfeld et al., 2015; Uhrig et al., 2014), and suggest potential stimulation sites for transitioning between brain states, which can then be further probed in these animal models.

It stands to reason that such models will need to combine structural, functional, and neurotransmitter neuroimaging data to properly simulate the underlying brain dynamics (Deco et al., 2018). Figure 3D shows the result of dynamically coupling neuronal activity with neurotransmitter release, in this case the dynamic serotonin release in connection with the use of psilocybin (Kringelbach et al., 2020). Once the model is fully established, the regional drug receptor modulation could be optimized by finding the optimal weighting of the receptor density such that the optimized model generates the functional dynamics of the healthy state (Deco et al., 2018). The current evidence suggests that it would be important to combine such direct brain manipulations with environmental manipulations, e.g., drug-assisted psychotherapy, which could be a particularly fruitful approach for neuropsychiatric disorders such as depression (Carhart-Harris et al., 2018) or addiction (Johnson et al., 2017).

Forcing Controlled Transitions: Insights from Whole-Brain Models

Although the cited data are promising in terms of mapping and understanding the effects of brain manipulation, there is clearly a need for a more principled way to establish the causal transitioning between brain states. This would allow for the potential to predict where and how to intervene to rebalance diseased brain states.

Recently, exactly such evidence has started to emerge (Deco et al., 2019a), based on the ability to quantify a brain state with the PMS framework described above. The basic idea is to exhaustively stimulate offline a realistic whole-brain model accurately modeling different brain states, in order to detect the types and loci of stimulation that would be most effective in forcing a transition between the brain states. In a clinical context, the transition would aim for a homeostatic rebalancing of healthy whole-brain dynamics in order to predict the condition where Hebbian learning will cause a meaningful recovery.

Specifically, Figure 4A shows how a whole-brain model would be able to fit the PMS space of the two radically different brain states of human sleep and wakefulness (Stevner et al., 2019). The strategy was to investigate the best stimulation of this whole-brain model to force transitions between different brain states and thus ''awaken'' the brain from deep sleep to wakefulness and vice versa. The whole-brain model was able to model these two states (Figure 4B), which were extracted from unique continuous neuroimaging data of healthy participants falling asleep during simultaneous fMRI and EEG (Tagliazucchi and Laufs, 2014).

The results provided evidence for the role of regions in promoting a transition (Figure 4C) but also provided proof of principle that multi-site stimulation can achieve similar results with lower stimulation in each site. The results showed that, as expected, for the transition from deep sleep to wakefulness, there are many regions that are able to promote a transition (given sufficient stimulation), whereas other regions are less suitable for this. In contrast, it is much harder to find targets to make the whole-brain model of wakefulness fall asleep, requiring higher levels of stimulation and much more specific targets. This provides the first evidence for externally forcing controlled transitions between different brain states by means of *in silico* stimulation of the whole-brain model (Deco et al., 2019a).

In general, although this review has mainly focused on pharmacological and electromagnetic stimulation, sensory stimulation is equally an ecologically valid and important approach. Specifically, whole-brain modeling could, for example, contribute to the enhanced use of the exciting modest improvement after somatomotor stimulation in stroke rehabilitation (French et al., 2010).

Functional Hierarchical Organization: Toward Better Descriptions of a Brain State

This new *in silico* brain-state-transition framework currently explores the potential of all brain regions in promoting transitions. However, this exhaustive search could likely be improved given that the brain is well known to be hierarchically organized (Huntenburg et al., 2018; Margulies et al., 2016; Mesulam, 1998; Preti and Van De Ville, 2019) (Figure 5A). Recent progress includes a characterization of the brain's fundamental metastable states (Vidaurre et al., 2017) and work on graph signal processing decomposing functional data on harmonic modes of structural connectivity (Preti and Van De Ville, 2019). This allows for a quantification of coupling/decoupling between activity and underlying structure and relates the coupling strength to behavior.

Primarily sensory areas such as visual and auditory are unlikely to play a role in orchestrating higher brain function. Instead, the historical record of accidental lesions of higher-order regions in humans has been shown to have a direct impact on behavior (Broca, 1861; Eslinger and Damasio, 1985; Rorden and Karnath, 2004; Wernicke, 1874), and therefore likely to have a direct impact on the orchestration of brain function. In terms of forcing transitions between different brain states, this means that the search space for suitable regions could be limited to the regions located toward the top of the hierarchy. Consequently, it is fundamental to quantify the functional hierarchy of the human brain.

One promising framework for establishing the functional hierarchy is to apply harmonic modes to functional connectivity data. Figure 5B shows how this has been used to reveal the multi-dimensional hierarchical nature of brain organization (Glomb et al., 2019).

A complementary approach is to estimate the bidirectional information flow between brain regions (Figure 5C), where the spatial map of outgoing information corresponds strongly to the hierarchical organization revealed by the myelination of brain regions, whereas the incoming information reflects high-order integrative processing (Figure 5D). This has been used to discover the functional rich club of interacting brain regions for resting and seven different tasks (Deco et al., 2019c), revealing a common core, akin to the global workspace originally proposed by Baars (Baars, 1989; Dehaene and Changeux, 2011; Dehaene et al., 1998). As such, this could be a major step forward in understanding and defining the complex choreography of information flow within the functional hierarchical organization underlying brain states. Ultimately, this may help identify the necessary and sufficient networks needed to force transitions between brain states.

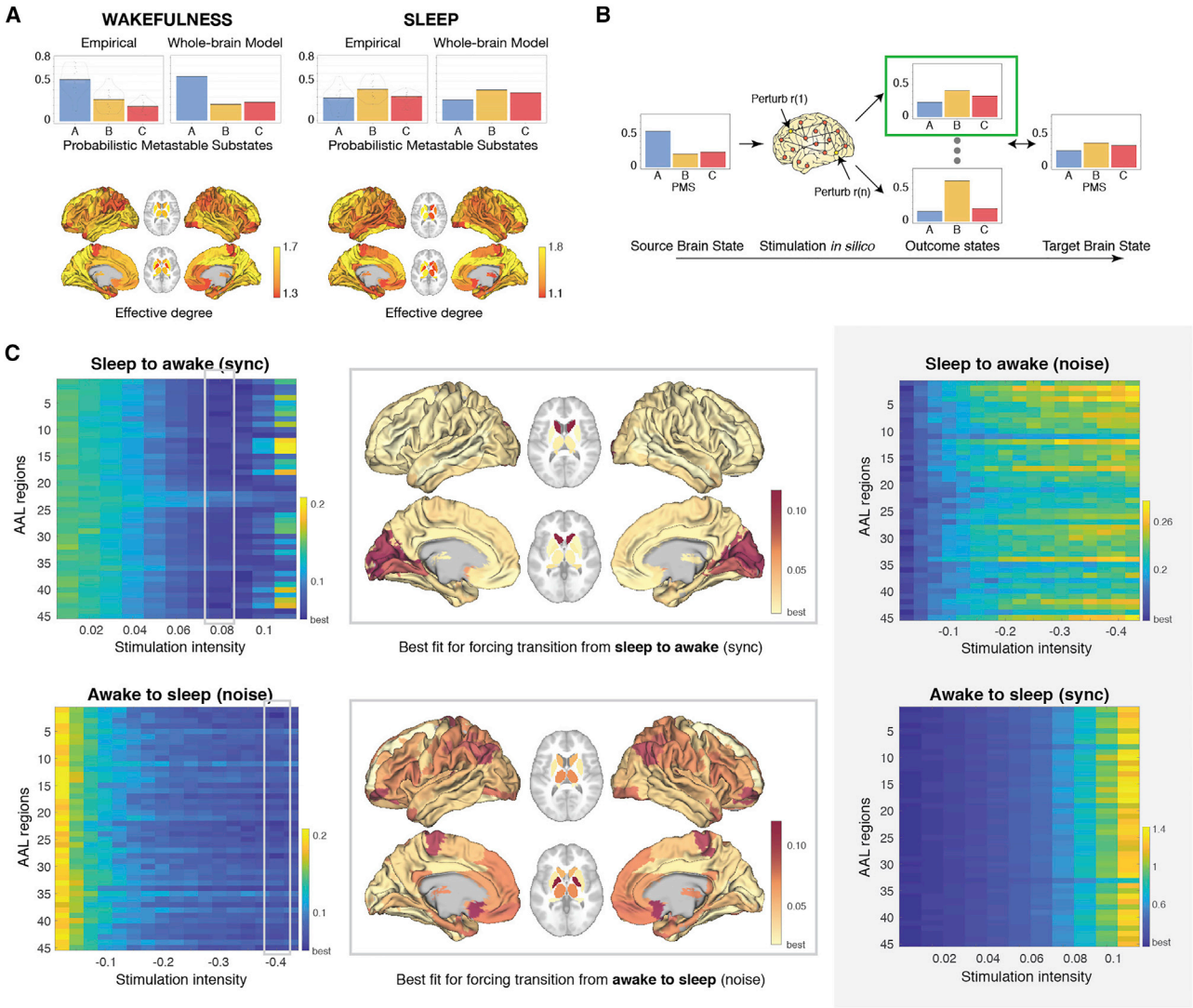

Figure 4. A Whole-Brain-Model-Based Framework Forcing Transitions between Brain States

The aim of this review is to show the potential of using whole-brain modeling to predict how best to force transitions between brain states. Although much research remains, this figure shows recent proof of principle in the context of the normally occurring wake and deep sleep states in healthy participants (Deco et al., 2019a).

(A) In this study, these two different brain states are characterized in terms of their PMS profile and fitted to whole-brain models. Here are shown the results obtained for wakefulness (left) and sleep (right) comparing the empirical and whole-brain-model results. The rendering shows the differences between these states (bottom).

(B) Summary of the main framework for identifying potential regions forcing a transition. This is an iterative process where all the brain regions in the whole-brain model in the source state (e.g., awake) are systematically stimulated *in silico* and the resulting state is compared to the fit with the PMS profile of the target (e.g., sleep) brain state.

(C) The large middle panel shows the results of systematic, exhaustive stimulation of the whole-brain regions. As can be seen, this led to different transitions from sleep to awake (top) and from awake to sleep (bottom). The results show that whereas many regions are able to promote a transition (given sufficient stimulation), other regions are less suitable for this (see burgundy areas). Overall, this shows in principle how to identify regions that promote transitions and could provide the basis for future empirical confirmation. Full details are provided in Deco et al. (2019a). Abbreviations: AAL, automated anatomical labeling.

Conclusion and Perspectives

In this review, we have shown that we could soon be in a position to accurately characterize and control brain states in health and disease. Further progress will require (1) a deeper understanding and quantitative definition of what constitutes a brain state, (2) further work on how best to predict transition between brain states using causal whole-brain computational modeling, and (3) experimental research in other animals to validate that the predicted stimulation causally brings out transitions between brain states using pharmacological or electromagnetic stimulation.

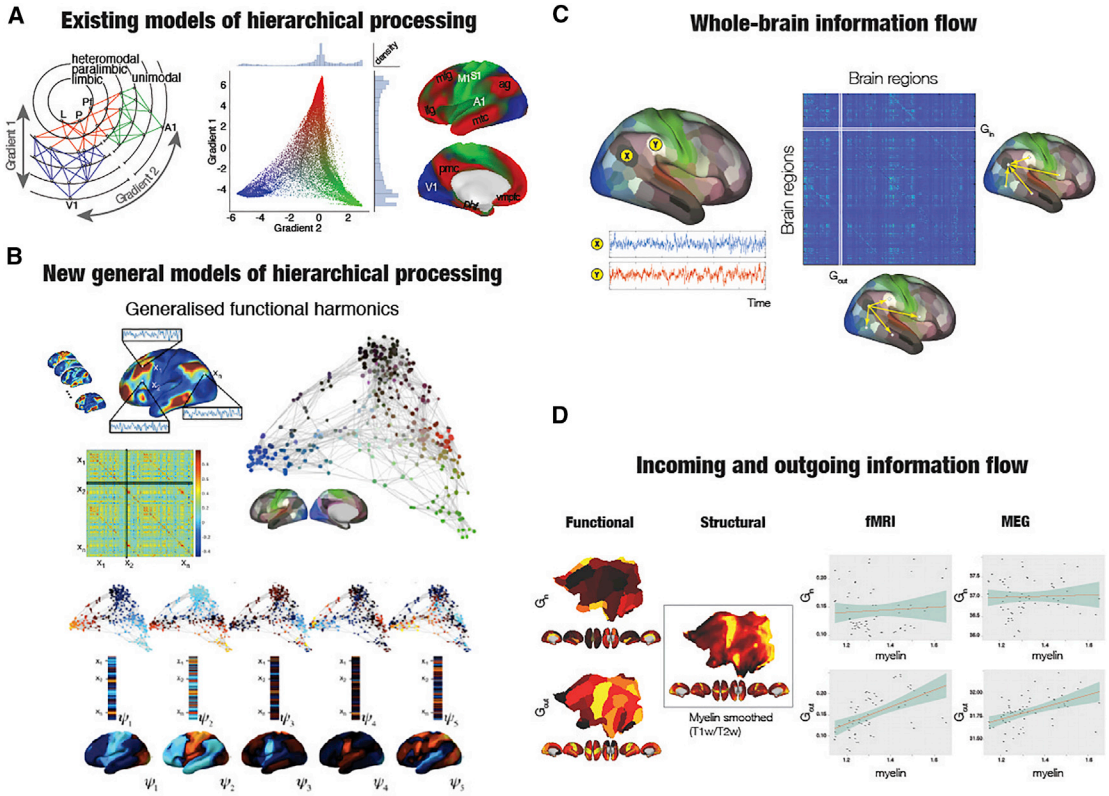

Figure 5. Functional Hierarchical Organization of Brain States

(A) Left: Mesulam's seminal proposal that brain processing is shaped by a hierarchy of distinct unimodal areas (blue and green) to integrative transmodal areas (red) (Mesulam, 1998). Right: subsequent research by Margulies and colleagues has used neuroimaging to confirm and extend this proposal by showing how the functional gradients show hierarchical organization (Margulies et al., 2016).

(B) More recent research has significantly extended this idea by revealing the multi-dimensional hierarchical nature of brain organization (Glomb et al., 2019). This approach uses applied harmonic modes to functional connectivity data in a large sample of human healthy participants (top left), and builds the harmonic basis functions for hierarchical brain activity (bottom).

(C) Complementary research has estimated the information flow in over 1,000 healthy participants using a novel method called normalized directed transfer entropy flow (Deco et al., 2019c). The figure shows the bidirectional matrix of information flow between regions. Summing these across rows and columns provides the total incoming (G_{in}) and outgoing (G_{out}) information for each brain region.

(D) The outgoing information flow corresponds well to the existing hierarchical information provided by the level of myelination of sensory regions, whereas the incoming information flow is found in integrative higher-order regions.

Other major challenges include the need to better characterize the structural connectome of the brain (ideally at the level of a single participant) with sufficient detail to capture the best features supporting the whole-brain model's emerging features. The proposed framework of estimating the effective connectivity is partially addressing these major challenges, but next-generation whole-brain models will need to be further validated by better structural imaging data, which could, for example, be provided by whole-brain multi-layer fMRI. Overall, the novel ideas put forward in this review are highly relevant for basic and clinical neuroscientists across many disciplines, potentially unifying and explaining a number of hitherto complex problems.

ACKNOWLEDGMENTS

M.L.K. is supported by the ERC Consolidator Grant CAREGIVING (615539); Center for Music in the Brain, funded by the Danish National Research Foundation (DNRF117); and Centre for Eudaimonia and Human Flourishing funded by the Pettit Foundation and Carlsberg Foundation. G.D. is supported by the Spanish Research Project (PID2019-105772GB-I00 AEI FEDER EU), funded by the Spanish Ministry of Science, Innovation and Universities (MCIU), State Research Agency (AEI), and European Regional Development Funds (FEDER); HBP SGA3 Human Brain Project Specific Grant Agreement 3 (grant agreement 945539), funded by the EU H2020 FET Flagship program; and SGR Research Support Group (2017 SGR 1545), funded by the Catalan Agency for Management of University and Research Grants (AGAUR).

AUTHOR CONTRIBUTIONS

M.L.K. and G.D. co-wrote and edited the review.

REFERENCES

Adhikari, M.H., Hacker, C.D., Siegel, J.S., Griffa, A., Hagmann, P., Deco, G., and Corbetta, M. (2017). Decreased integration and information capacity in

stroke measured by whole brain models of resting state activity. Brain *140*, 1068–1085.

Aerts, H., Schirner, M., Dhollander, T., Jeurissen, B., Achten, E., Van Roost, D., Ritter, P., and Marinazzo, D. (2020). Modeling brain dynamics after tumor resection using The Virtual Brain. Neuroimage *213*, 116738.

Autio, J.A., Glasser, M.F., Ose, T., Donahue, C.J., Bastiani, M., Ohno, M., Kawabata, Y., Urushibata, Y., Murata, K., Nishigori, K., et al. (2020). Towards HCP-style macaque connectomes: 24-channel 3T multi-array coil, MRI sequences and preprocessing. Neuroimage *215*, 116800.

Baars, B.J. (1989). A Cognitive Theory of Consciousness (Cambridge University Press).

Baker, A.P., Brookes, M.J., Rezek, I.A., Smith, S.M., Behrens, T., Probert Smith, P.J., and Woolrich, M. (2014). Fast transient networks in spontaneous human brain activity. eLife *3*, e01867.

Barttfeld, P., Uhrig, L., Sitt, J.D., Sigman, M., Jarraya, B., and Dehaene, S. (2015). Signature of consciousness in the dynamics of resting-state brain activity. Proc. Natl. Acad. Sci. USA *112*, 887–892.

Basser, P.J., and Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J. Magn. Reson. B *111*, 209–219.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system—a technical review. NMR Biomed. *15*, 435–455.

Bolton, T.A.W., Morgenroth, E., Preti, M.G., and Van De Ville, D. (2020). Tapping into multi-faceted human behavior and psychopathology using fMRI brain dynamics. Trends Neurosci. Published online July 15, 2020. https://doi.org/10.1016/j.tins.2020.06.005.

Breakspear, M. (2004). "Dynamic" connectivity in neural systems: theoretical and empirical considerations. Neuroinformatics *2*, 205–226.

Breakspear, M., Jirsa, V., and Deco, G. (2010). Computational models of the brain: from structure to function. Neuroimage *52*, 727–730.

Broca, M.P. (1861). Remarques sur le siége de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). Bull. Mém. Soc. Anat. Paris *6*, 330–357.

Cabral, J., Luckhoo, H., Woolrich, M., Joensson, M., Mohseni, H., Baker, A., Kringelbach, M.L., and Deco, G. (2014). Exploring mechanisms of spontaneous functional connectivity in MEG: how delayed network interactions lead to structured amplitude envelopes of band-pass filtered oscillations. Neuroimage *90*, 423–435.

Cabral, J., Vidaurre, D., Marques, P., Magalhães, R., Silva Moreira, P., Miguel Soares, J., Deco, G., Sousa, N., and Kringelbach, M.L. (2017). Cognitive performance in healthy older adults relates to spontaneous switching between states of functional connectivity during rest. Sci. Rep. *7*, 5135.

Carhart-Harris, R.L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., Tagliazucchi, E., Schenberg, E.E., Nest, T., Orban, C., et al. (2016). Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proc. Natl. Acad. Sci. USA *113*, 4853–4858.

Carhart-Harris, R.L., Roseman, L., Haijen, E., Erritzoe, D., Watts, R., Branchi, I., and Kaelen, M. (2018). Psychedelics and the essential importance of context. J. Psychopharmacol. (Oxford) *32*, 725–731.

Casali, A.G., Gosseries, O., Rosanova, M., Boly, M., Sarasso, S., Casali, K.R., Casarotto, S., Bruno, M.A., Laureys, S., Tononi, G., and Massimini, M. (2013). A theoretically based index of consciousness independent of sensory processing and behavior. Sci. Transl. Med. *5*, 198ra105.

Deco, G., and Jirsa, V.K. (2012). Ongoing cortical activity at rest: criticality, multistability, and ghost attractors. J. Neurosci. *32*, 3366–3375.

Deco, G., and Kringelbach, M.L. (2014). Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders. Neuron *84*, 892–905.

Deco, G., Jirsa, V., McIntosh, A.R., Sporns, O., and Kötter, R. (2009). Key role of coupling, delay, and noise in resting brain fluctuations. Proc. Natl. Acad. Sci. USA *106*, 10302–10307.

Deco, G., Jirsa, V.K., and McIntosh, A.R. (2011). Emerging concepts for the dynamical organization of resting-state activity in the brain. Nat. Rev. Neurosci. *12*, 43–56.

Deco, G., Jirsa, V.K., and McIntosh, A.R. (2013). Resting brains never rest: computational insights into potential cognitive architectures. Trends Neurosci. *36*, 268–274.

Deco, G., McIntosh, A.R., Shen, K., Hutchison, R.M., Menon, R.S., Everling, S., Hagmann, P., and Jirsa, V.K. (2014a). Identification of optimal structural connectivity using functional connectivity and neural modeling. J. Neurosci. *34*, 7910–7916.

Deco, G., Ponce-Alvarez, A., Hagmann, P., Romani, G.L., Mantini, D., and Corbetta, M. (2014b). How local excitation-inhibition ratio impacts the whole brain dynamics. J. Neurosci. *34*, 7886–7898.

Deco, G., Cabral, J., Woolrich, M.W., Stevner, A.B.A., van Hartevelt, T.J., and Kringelbach, M.L. (2017a). Single or multiple frequency generators in on-going brain activity: a mechanistic whole-brain model of empirical MEG data. Neuroimage *152*, 538–550.

Deco, G., Kringelbach, M.L., Jirsa, V.K., and Ritter, P. (2017b). The dynamics of resting fluctuations in the brain: metastability and its dynamical cortical core. Sci. Rep. *7*, 3095.

Deco, G., Cruzat, J., Cabral, J., Knudsen, G.M., Carhart-Harris, R.L., Whybrow, P.C., Logothetis, N.K., and Kringelbach, M.L. (2018). Whole-brain multimodal neuroimaging model using serotonin receptor maps explains non-linear functional effects of LSD. Curr. Biol. *28*, 3065–3074.e6.

Deco, G., Cruzat, J., Cabral, J., Tagliazucchi, E., Laufs, H., Logothetis, N.K., and Kringelbach, M.L. (2019a). Awakening: predicting external stimulation to force transitions between different brain states. Proc. Natl. Acad. Sci. USA *116*, 18088–18097.

Deco, G., Cruzat, J., and Kringelbach, M.L. (2019b). Brain songs framework used for discovering the relevant timescale of the human brain. Nat. Commun. *10*, 583.

Deco, G., Vidaurre, D., and Kringelbach, M.L. (2019c). Revisiting the global workspace: orchestration and hierarchical organization of the human brain. bioRxiv. https://doi.org/10.1101/859579.

Dehaene, S., and Changeux, J.P. (2011). Experimental and theoretical approaches to conscious processing. Neuron *70*, 200–227.

Dehaene, S., Kerszberg, M., and Changeux, J.P. (1998). A neuronal model of a global workspace in effortful cognitive tasks. Proc. Natl. Acad. Sci. USA *95*, 14529–14534.

de Pasquale, F., Della Penna, S., Sporns, O., Romani, G.L., and Corbetta, M. (2016). A dynamic core network and global efficiency in the resting human brain. Cereb. Cortex *26*, 4015–4033.

Donahue, C.J., Sotiropoulos, S.N., Jbabdi, S., Hernandez-Fernandez, M., Behrens, T.E., Dyrby, T.B., Coalson, T., Kennedy, H., Knoblauch, K., Van Essen, D.C., and Glasser, M.F. (2016). Using diffusion tractography to predict cortical connection strength and distance: a quantitative comparison with tracers in the monkey. J. Neurosci. *36*, 6758–6770.

Eickhoff, S.B., Constable, R.T., and Yeo, B.T.T. (2018a). Topographic organization of the cerebral cortex and brain cartography. Neuroimage *170*, 332–347.

Eickhoff, S.B., Yeo, B.T.T., and Genon, S. (2018b). Imaging-based parcellations of the human brain. Nat. Rev. Neurosci. *19*, 672–686.

Eslinger, P.J., and Damasio, A.R. (1985). Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. Neurology *35*, 1731–1741.

Ferrarelli, F., Massimini, M., Sarasso, S., Casali, A., Riedner, B.A., Angelini, G., Tononi, G., and Pearce, R.A. (2010). Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. Proc. Natl. Acad. Sci. USA *107*, 2681–2686.

Feynman, R.P., Leighton, R.B., and Sands, M. (2005). The Feynman Lectures on Physics Including Feynman's Tips on Physics: The Definitive and Extended Edition, Second Edition (Addison-Wesley).

Figueroa, C.A., Cabral, J., Mocking, R.J.T., Rapuano, K.M., van Hartevelt, T.J., Deco, G., Expert, P., Schene, A.H., Kringelbach, M.L., and Ruhé, H.G. (2019).

Altered ability to access a clinically relevant control network in patients remitted from major depressive disorder. Hum. Brain Mapp. *40*, 2771–2786.

French, B., Thomas, L., Leathley, M., Sutton, C., McAdam, J., Forster, A., Langhorne, P., Price, C., Walker, A., and Watkins, C. (2010). Does repetitive task training improve functional activity after stroke? A Cochrane systematic review and meta-analysis. J. Rehabil. Med. *42*, 9–14.

Freyer, F., Roberts, J.A., Ritter, P., and Breakspear, M. (2012). A canonical model of multistability and scale-invariance in biological systems. PLoS Comput. Biol. *8*, e1002634.

Frisch, U. (1995). Turbulence: The Legacy of A. N. Kolmogorov (Cambridge University Press).

Gervasoni, D., Lin, S.C., Ribeiro, S., Soares, E.S., Pantoja, J., and Nicolelis, M.A. (2004). Global forebrain dynamics predict rat behavioral states and their transitions. J. Neurosci. *24*, 11137–11147.

Ghosh, A., Rho, Y., McIntosh, A.R., Kötter, R., and Jirsa, V.K. (2008). Cortical network dynamics with time delays reveals functional connectivity in the resting brain. Cogn. Neurodyn. *2*, 115–120.

Gilson, M., Moreno-Bote, R., Ponce-Alvarez, A., Ritter, P., and Deco, G. (2016). Estimation of directed effective connectivity from fMRI functional connectivity hints at asymmetries of cortical connectome. PLoS Comput. Biol. *12*, e1004762.

Gilson, M., Zamora-López, G., Pallarés, V., Adhikari, M.H., Senden, M., Campo, A.T., Mantini, D., Corbetta, M., Deco, G., and Insabato, A. (2020). Model-based whole-brain effective connectivity to study distributed cognition in health and disease. Netw. Neurosci. *4*, 338–373.

Glomb, K., Kringelbach, M.L., Deco, G., Hagmann, P., Pearson, J., and Atasoy, S. (2019). Functional harmonics reveal multi-dimensional basis functions underlying cortical organization. bioRxiv. https://doi.org/10.1101/699678.

Gu, S., Betzel, R.F., Mattar, M.G., Cieslak, M., Delio, P.R., Grafton, S.T., Pasqualetti, F., and Bassett, D.S. (2017). Optimal trajectories of brain state transitions. Neuroimage *148*, 305–317.

Gu, S., Cieslak, M., Baird, B., Muldoon, S.F., Grafton, S.T., Pasqualetti, F., and Bassett, D.S. (2018). The energy landscape of neurophysiological activity implicit in brain network structure. Sci. Rep. *8*, 2507.

Hagmann, P., Cammoun, L., Gigandet, X., Gerhard, S., Grant, P.E., Wedeen, V., Meuli, R., Thiran, J.P., Honey, C.J., and Sporns, O. (2010). MR connectomics: principles and challenges. J. Neurosci. Methods *194*, 34–45.

Haken, H. (1988). Information and Self-Organization. A Macroscopic Approach to Complex Systems (Springer).

Hansen, E.C., Battaglia, D., Spiegler, A., Deco, G., and Jirsa, V.K. (2015). Functional connectivity dynamics: modeling the switching behavior of the resting state. Neuroimage *105*, 525–535.

Hashemi, M., Vattikonda, A.N., Sip, V., Guye, M., Bartolomei, F., Woodman, M.M., and Jirsa, V.K. (2020). The Bayesian Virtual Epileptic Patient: a probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model of epilepsy spread. Neuroimage *217*, 116839.

Honey, C.J., Kötter, R., Breakspear, M., and Sporns, O. (2007). Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proc. Natl. Acad. Sci. USA *104*, 10240–10245.

Huntenburg, J.M., Bazin, P.L., and Margulies, D.S. (2018). Large-scale gradients in human cortical organization. Trends Cogn. Sci. *22*, 21–31.

Hutchison, R.M., Womelsdorf, T., Allen, E.A., Bandettini, P.A., Calhoun, V.D., Corbetta, M., Della Penna, S., Duyn, J.H., Glover, G.H., Gonzalez-Castillo, J., et al. (2013). Dynamic functional connectivity: promise, issues, and interpretations. Neuroimage *80*, 360–378.

Jeurissen, B., Descoteaux, M., Mori, S., and Leemans, A. (2019). Diffusion MRI fiber tractography of the brain. NMR Biomed. *32*, e3785.

Jirsa, V.K., Jantzen, K.J., Fuchs, A., and Kelso, J.A. (2002). Spatiotemporal forward solution of the EEG and MEG using network modeling. IEEE Trans. Med. Imaging *21*, 493–504.

Johansen-Berg, H., and Rushworth, M.F. (2009). Using diffusion imaging to study human connectional anatomy. Annu. Rev. Neurosci. *32*, 75–94.

Johnson, M.W., Garcia-Romeu, A., and Griffiths, R.R. (2017). Long-term follow-up of psilocybin-facilitated smoking cessation. Am. J. Drug Alcohol Abuse *43*, 55–60.

Kahan, J., Urner, M., Moran, R., Flandin, G., Marreiros, A., Mancini, L., White, M., Thornton, J., Yousry, T., Zrinzo, L., et al. (2014). Resting state functional MRI in Parkinson's disease: the impact of deep brain stimulation on 'effective' connectivity. Brain *137*, 1130–1144.

Karahanoğlu, F.I., and Van De Ville, D. (2015). Transient brain activity disentangles fMRI resting-state dynamics in terms of spatially and temporally overlapping networks. Nat. Commun. *6*, 7751.

Kötter, R. (2004). Online retrieval, processing, and visualization of primate connectivity data from the CoCoMac database. Neuroinformatics *2*, 127–144.

Kringelbach, M.L., Jenkinson, N., Green, A.L., Owen, S.L.F., Hansen, P.C., Cornelissen, P.L., Holliday, I.E., Stein, J., and Aziz, T.Z. (2007). Deep brain stimulation for chronic pain investigated with magnetoencephalography. Neuroreport *18*, 223–228.

Kringelbach, M.L., Cruzat, J., Cabral, J., Knudsen, G.M., Carhart-Harris, R., Whybrow, P.C., Logothetis, N.K., and Deco, G. (2020). Dynamic coupling of whole-brain neuronal and neurotransmitter systems. Proc. Natl. Acad. Sci. USA *117*, 9566–9576.

Kucyi, A., and Davis, K.D. (2014). Dynamic functional connectivity of the default mode network tracks daydreaming. Neuroimage *100*, 471–480.

Lehmann, D., Strik, W.K., Henggeler, B., Koenig, T., and Koukkou, M. (1998). Brain electric microstates and momentary conscious mind states as building blocks of spontaneous thinking: I. Visual imagery and abstract thoughts. Int. J. Psychophysiol. *29*, 1–11.

Liu, X., and Duyn, J.H. (2013). Time-varying functional network information extracted from brief instances of spontaneous brain activity. Proc. Natl. Acad. Sci. USA *110*, 4392–4397.

Lord, L.D., Expert, P., Atasoy, S., Roseman, L., Rapuano, K., Lambiotte, R., Nutt, D.J., Deco, G., Carhart-Harris, R.L., Kringelbach, M.L., and Cabral, J. (2019). Dynamical exploration of the repertoire of brain networks at rest is modulated by psilocybin. Neuroimage *199*, 127–142.

Margulies, D.S., Ghosh, S.S., Goulas, A., Falkiewicz, M., Huntenburg, J.M., Langs, G., Bezgin, G., Eickhoff, S.B., Castellanos, F.X., Petrides, M., et al. (2016). Situating the default-mode network along a principal gradient of macroscale cortical organization. Proc. Natl. Acad. Sci. USA *113*, 12574–12579.

Markov, N.T., Vezoli, J., Chameau, P., Falchier, A., Quilodran, R., Huissoud, C., Lamy, C., Misery, P., Giroud, P., Ullman, S., et al. (2014). Anatomy of hierarchy: feedforward and feedback pathways in macaque visual cortex. J. Comp. Neurol. *522*, 225–259.

Massimini, M., Ferrarelli, F., Huber, R., Esser, S.K., Singh, H., and Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. Science *309*, 2228–2232.

Melozzi, F., Woodman, M.M., Jirsa, V.K., and Bernard, C. (2017). The Virtual Mouse Brain: a computational neuroinformatics platform to study whole mouse brain dynamics. eNeuro *4*, ENEURO.0111-17.2017.

Mesulam, M.M. (1998). From sensation to cognition. Brain *121*, 1013–1052.

Michel, C.M., and Koenig, T. (2018). EEG microstates as a tool for studying the temporal dynamics of whole-brain neuronal networks: a review. Neuroimage *180*, 577–593.

Northoff, G. (2013). What the brain's intrinsic activity can tell us about consciousness? A tri-dimensional view. Neurosci. Biobehav. Rev. *37*, 726–738.

Ozdemir, R.A., Tadayon, E., Boucher, P., Momi, D., Karakhanyan, K.A., Fox, M.D., Halko, M.A., Pascual-Leone, A., Shafi, M.M., and Santarnecchi, E. (2020). Individualized perturbation of the human connectome reveals reproducible biomarkers of network dynamics relevant to cognition. Proc. Natl. Acad. Sci. USA *117*, 8115–8125.

Pallarés, V., Insabato, A., Sanjuán, A., Kühn, S., Mantini, D., Deco, G., and Gilson, M. (2018). Extracting orthogonal subject- and condition-specific

signatures from fMRI data using whole-brain effective connectivity. NeuroImage *178*, 238–254.

Preti, M.G., and Van De Ville, D. (2019). Decoupling of brain function from structure reveals regional behavioral specialization in humans. Nat. Commun. *10*, 4747.

Preti, M.G., Bolton, T.A., and Van De Ville, D. (2017). The dynamic functional connectome: state-of-the-art and perspectives. NeuroImage *160*, 41–54.

Rorden, C., and Karnath, H.O. (2004). Using human brain lesions to infer function: a relic from a past era in the fMRI age? Nat. Rev. Neurosci. *5*, 813–819.

Saenger, V.M., Kahan, J., Foltynie, T., Friston, K., Aziz, T.Z., Green, A.L., van Hartevelt, T.J., Cabral, J., Stevner, A.B.A., Fernandes, H.M., et al. (2017). Uncovering the underlying mechanisms and whole-brain dynamics of deep brain stimulation for Parkinson's disease. Sci. Rep. *7*, 9882.

Shanahan, M. (2010). Metastable chimera states in community-structured oscillator networks. Chaos *20*, 013108.

Shen, K., Bezgin, G., Schirner, M., Ritter, P., Everling, S., and McIntosh, A.R. (2019). A macaque connectome for large-scale network simulations in TheVirtualBrain. Sci. Data *6*, 123.

Stark, E.A., Cabral, J., Riem, M.M.E., Van IJzendoorn, M.H., Stein, A., and Kringelbach, M.L. (2020). The power of smiling: the adult brain networks underlying learned infant emotionality. Cereb. Cortex *30*, 2019–2029.

Stevner, A.B.A., Vidaurre, D., Cabral, J., Rapuano, K., Nielsen, S.F.V., Tagliazucchi, E., Laufs, H., Vuust, P., Deco, G., Woolrich, M.W., et al. (2019). Discovery of key whole-brain transitions and dynamics during human wakefulness and non-REM sleep. Nat. Commun. *10*, 1035.

Tagliazucchi, E., and Laufs, H. (2014). Decoding wakefulness levels from typical fMRI resting-state data reveals reliable drifts between wakefulness and sleep. Neuron *82*, 695–708.

Tagliazucchi, E., Crossley, N., Bullmore, E.T., and Laufs, H. (2016). Deep sleep divides the cortex into opposite modes of anatomical-functional coupling. Brain Struct. Funct. *221*, 4221–4234.

Tognoli, E., and Kelso, J.A. (2014). The metastable brain. Neuron *81*, 35–48.

Tononi, G., Sporns, O., and Edelman, G.M. (1994). A measure for brain complexity: relating functional segregation and integration in the nervous system. Proc. Natl. Acad. Sci. USA *91*, 5033–5037.

Tu, C., Rocha, R.P., Corbetta, M., Zampieri, S., Zorzi, M., and Suweis, S. (2018). Warnings and caveats in brain controllability. NeuroImage *176*, 83–91.

Uhrig, L., Dehaene, S., and Jarraya, B. (2014). A hierarchy of responses to auditory regularities in the macaque brain. J. Neurosci. *34*, 1127–1132.

van Hartevelt, T.J., Cabral, J., Deco, G., Møller, A., Green, A.L., Aziz, T.Z., and Kringelbach, M.L. (2014). Neural plasticity in human brain connectivity: the effects of long term deep brain stimulation of the subthalamic nucleus in Parkinson's disease. PLoS One *9*, e86496.

van Hartevelt, T.J., Cabral, J., Møller, A., FitzGerald, J.J., Green, A.L., Aziz, T.Z., Deco, G., and Kringelbach, M.L. (2015). Evidence from a rare case study for Hebbian-like changes in structural connectivity induced by long-term deep brain stimulation. Front. Behav. Neurosci. *9*, 167.

Vidaurre, D., Smith, S.M., and Woolrich, M.W. (2017). Brain network dynamics are hierarchically organized in time. Proc. Natl. Acad. Sci. USA *114*, 12827–12832.

Vidaurre, D., Hunt, L.T., Quinn, A.J., Hunt, B.A.E., Brookes, M.J., Nobre, A.C., and Woolrich, M.W. (2018). Spontaneous cortical activity transiently organises into frequency specific phase-coupling networks. Nat. Commun. *9*, 2987.

Wernicke, C. (1874). Der Aphasische Symptomencomplex. Eine Psychologische Studie auf Anatomischer Basis (Cohn & Weigert).