

Control of Dynamics in Brain Networks

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The ability to effectively control brain dynamics holds great promise for the enhancement of cognitive function in humans, and the betterment of their quality of life. Yet, successfully controlling dynamics in neural systems is challenging, in part due to the immense complexity of the brain and the large set of interactions that can drive any single change. While we have gained some understanding of the control of single neurons, the control of large-scale neural systems—networks of multiply interacting components—remains poorly understood. Efforts to address this gap include the construction of tools for the control of brain networks, mostly adapted from control and dynamical systems theory. Informed by current opportunities for practical intervention, these theoretical contributions provide models that draw from a wide array of mathematical approaches. We present intriguing recent developments for effective strategies of control in dynamic brain networks, and we also describe potential mechanisms that underlie such processes. We review efforts in the control of general neurophysiological processes with implications for brain development and cognitive function, as well as the control of altered neurophysiological processes in medical contexts such as anesthesia administration, seizure suppression, and deep-brain stimulation for Parkinson’s disease. We conclude with a forward-looking discussion regarding how emerging results from network control—especially approaches that deal with nonlinear dynamics or more realistic trajectories for control transitions—could be used to directly address pressing questions in neuroscience.

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I. INTRODUCTION

The brain displays a wealth of complex dynamics across various spatial and temporal scales (Betzel and Bassett, 2016; Kopell *et al.*, 2014). From 302 neurons in the nematode worm *C. elegans* (Bentley *et al.*, 2016;

Varier and Kaiser, 2011) to some 86 billion neurons in the adult human (von Bartheld *et al.*, 2016; Herculano-Houzel *et al.*, 2007), the units that drive brain function are large in their number but even more complicated in their interactions. Far from the canonical models in statistical mechanics stemming from either crystalline or random structure, the brain displays a heterogeneous pattern of interconnections (Bassett and Bullmore, 2016; Castellana and Bialek, 2014; Fraiman *et al.*, 2009) that fundamentally constrains the propagation of activity. Understanding these dynamics remains of primary interest in the field of neurophysics (Gao and Ganguli, 2015; Scott, 1977). An emerging and intriguingly tractable avenue for understanding the mechanisms of these dynamics lies in the notion of control, or how to effectively guide neural dynamics. How are brain dynamics controlled intrinsically in the awake, behaving animal? Can we harness natural principles of control in neural systems to better guide therapeutic interventions?

The increase in available experimental neurotechnologies (Chang, 2015; Nag and Thakor, 2016; Patil and Thakor, 2016), as well as more sophisticated computational tools (Glaser and Kording, 2016; Marblestone *et al.*, 2016) and theoretical models (Giusti *et al.*, 2016), has recently made it possible to tackle this question from fundamentally new angles. While at present there is no comprehensive theory of control in the brain that we can refer to, the pursuit of such a theory remains critically important, having pervasive implications for our understanding of healthy neurophysiological processes, and our ability to intervene when those healthy processes go awry in neurological disease and psychiatric disorders (Bassett and Khambhati, 2017; Chen *et al.*, 2014; Johnson *et al.*, 2013). Several recent models propose new ways to control neural activity and neural rhythms, and further provide mechanistic insights into the rules by which brain dynamics are (and can be) guided. Hence, it is timely to discuss these emerging developments, and to seek to tie them together into a meaningful theoretical field that can be used to tackle current open questions in neuroscience and medicine.

Motivated by recent progress in understanding brain function from the perspective of interacting networks (Bassett and Bullmore, 2006, 2009; Bullmore and Sporns, 2012; Kaiser, 2011), we focus on systems-level control of either local neural circuits or whole-brain connectomes (Fornito and Bullmore, 2015; Sporns *et al.*, 2005). Here we use the term “network” in the sense that is common in network science (Newman, 2010). A *brain network* is a graph whose nodes represent units of the brain that perform a specific function, like vision or audition (Bullmore and Bassett, 2011). At the large-scale, these units may be several centimeters of tissue, while at the small scale, these units may be individual neurons. In structural brain graphs, the edges can represent structural links such as fiber bundles at the large scale (Bassett

et al., 2011; Hagmann *et al.*, 2008) or synapses at the small scale. In functional brain graphs, the edges represent synchronized dynamics that form functional links (Achard *et al.*, 2006; Stam, 2004) between these units. Our choice to focus on the control of brain networks enables us to build a theoretical understanding regarding biological processes and associated dynamics that occur across spatially distributed systems in neural tissue. Should the reader instead be searching for an excellent treatment of various control methods for single neurons or for ensembles of neurons, we direct them to the recent textbook by Schiff (2012), and to references therein. For further details on emerging control technologies in the brain—especially invasive electrical and optical stimulation at rapid timescales (milliseconds or below)—and associated modelling approaches, please see the recent review by Ritt and Ching (2015).

The remainder of this Colloquium is organized as follows. In Sec. II we draw inspiration for understanding control of brain networks by considering how the brain itself enacts intrinsic control. In particular, we briefly discuss important computational paradigms of cognitive control, a basic ability that each of us has to control our neural activity and by extension our behavior. This discussion motivates the introduction of network control theory in Sec. III, which offers a useful theoretical framework in which to probe control in brain networks constructed from neuroimaging data. We next turn in Sec. IV to detailing a few examples of how we can use network control theory, or its extensions, to understand healthy brain function. In Sec. V, we describe the utility of network control in targeting interventions when healthy brain function goes awry. We next turn in Sec. VI to modeling the controlled *versus* uncontrolled trajectories of neural dynamics, and we close in Sec. VII by outlining emerging frontiers at the intersection of dynamical systems theory, control theory, and complex systems. Throughout, we keep neuroscience jargon to a minimum, although some terminology specific to the technique or context remains unavoidable. Our goal is to stimulate discussion and encourage further work from physicists, control theorists, practitioners and others in this exciting and rapidly developing field.

II. HOW DOES THE BRAIN CONTROL ITSELF?

While there may be many ways of tackling the question of how to control brain dynamics, arguably one of the simplest is to ask how the brain controls itself. Perhaps by understanding intrinsic mechanisms of control in the brain, we could harness that knowledge to inform therapeutic interventions for people with mental illness. In considering this idea, it is useful to distinguish between external control, which is enacted on the system from the outside, and internal control, which is a feature of

the system itself. In the brain, internal control processes include phenomena as conceptually diverse as homeostasis, which refers to processes that maintain equilibrium of dynamics (Nelson and Turrigiano, 2008; Nelson and Valakh, 2015), and cognitive control, which refers to processes that exert top-down influence to drive the system between various dynamical states (Botvinick and Braver, 2015; Heatherton and Wagner, 2011).

Here we focus on cognitive control because it is conceptually akin to the idea of extrinsic control: driving dynamics from one type to another. What can we learn from cognitive control that might help us to develop a theory for external control? To answer that question, we begin by turning to history. An early computational model that explained the production of decisions based on a given set of inputs was the perceptron (Freund and Schapire, 1999; Rosenblatt, 1958), a simple artificial neural network (Bishop, 1995; McCulloch and Pitts, 1943). The perceptron and associated notions were developed by proponents of connectionism (Medler, 1998), which suggests that cognition is an emergent process of interconnected networks. The complexity of the connection architecture in these models was thought to support a complexity of brain dynamics, such as the separation of parallel neural processes and distributed neural representations propounded by the parallel distributed processing (PDP) model (Rumelhart *et al.*, 1986).

Notably, the PDP model offers conceptual explanations for the processes characteristic of cognitive control (Botvinick and Cohen, 2014). These ideas are built on the notion that the development of control systems in the brain (Chai *et al.*, 2017) can be seen as responding to the structure of naturalistic tasks, and therefore that control can be defined as the optimal parameterization of task processing. Within such a parameterization, two specific features of cognitive control appear particularly critical: (i) its remarkable flexibility, which supports diverse behaviors, and (ii) its clear constraints, which limit the number of control-demanding behaviors that can be executed simultaneously. Addressing these two features, models inspired by the PDP approach allow for cognitive control as instantiated in processes of selection from competing inputs or adaptation based on reward (Fig. 1).

These and related computational models emphasize the role of specific brain areas in cognitive control, including prefrontal cortex, anterior cingulate, parietal cortex, and brainstem. Yet, studying any of these areas in isolation will likely provide an impoverished understanding of the system's function. Indeed, Eisenreich *et al.* (2016) argue that control in the brain is not localized to small regions or modules, but is instead very broadly distributed, enabling versatility in both information transfer and executive control. Such a distributed – and even perhaps overlapping – network architecture can also offer usefully fuzzy boundaries between controllers and proce-

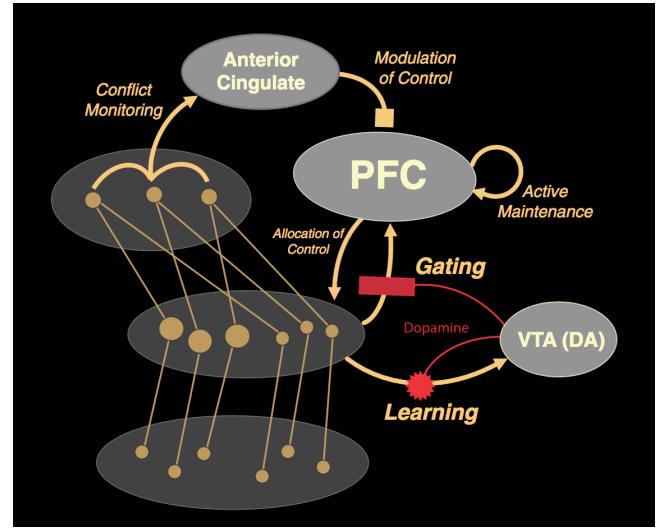


FIG. 1 Model for adaptive cognitive control showing distinct mechanisms between different brain regions. Schematic of a neural network connecting the prefrontal cortex, which executes much of the “top-down” control actions, to other brain regions. Another part of the brain – the anterior cingulate cortex – serves as a conflict monitoring mechanism that modulates the activity of control representations, while an adaptive gating mechanism regulates the updating of control representations in prefrontal cortex through dopaminergic projections. From Botvinick and Cohen (2014).

sors (Eisenreich *et al.*, 2016; Haykin and Fuster, 2014). How exactly information is processed on these distributed systems remains an open question, but some promising modeling approaches include those that use Bayesian inference, sparse-coding, and information entropy to characterize control (Haykin and Fuster, 2014). Specifically, a few recent efforts draw heavily from the idea of probabilistic reasoning to formulate a model for risk control – posited to be an overarching function of the prefrontal cortex – characterized by a closed-loop feedback structure describing executive attention.

To briefly summarize, previous computational models of cognitive control have included the eclectic notions of neural networks, regional localization, distributed processing, and information theory. Collectively, these notions motivate the construction of a model or theory that explicitly builds on the emerging capability to measure the brain’s true network structure to better understand control. In the next section, we will describe recent developments in dynamical systems and control theory as applied to complex networks, whose application to the brain may offer explanatory mechanisms of neural dynamics and provide insights into the distributed nature of cognitive control.

III. NETWORK CONTROL THEORY

Conceptually, it is interesting to ask the question whether and to what degree cognitive control (as defined by neuroscientists) is similar to network control (as defined by physicists, mathematicians, and engineers). To address this interesting question, we must first define what it is that we mean by network control. Controllability of a dynamical system refers to the possibility of driving the current state of the system to a specific target state by means of an external control input, see Kalman *et al.* (1963). Developments in engineering and physics have recently extended these ideas to the control of networks, as we describe in more detail below.

A. Control of linear dynamics

We begin by describing a general framework for the control of linear dynamics on a complex network. Consider a network represented by the directed graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$, where \mathcal{V} and \mathcal{E} are the vertex and edge sets, respectively. Let a_{ij} be the weight associated with the edge $(i, j) \in \mathcal{E}$, and define the *weighted adjacency matrix* of \mathcal{G} as $\mathbf{A} = [a_{ij}]$, where $a_{ij} = 0$ whenever $(i, j) \notin \mathcal{E}$. We associate a real value (*state*) with each node, collect the node states into a vector (*network state*), and define the map $\mathbf{x} : \mathbb{N}_{\geq 0} \rightarrow \mathbb{R}^n$ to describe the evolution (*network dynamics*) of the network state over time. A simple way to begin is to describe the network dynamics by a discrete time, linear, and time-invariant recursion

$$\mathbf{x}(t+1) = \mathbf{Ax}(t). \quad (1)$$

Let a subset of nodes $\mathcal{K} = \{k_1, \dots, k_m\}$ be independently controlled, and let

$$\mathbf{B}_{\mathcal{K}} := [e_{k_1} \ \dots \ e_{k_m}] \quad (2)$$

be the *input matrix*, where e_i denotes the i -th canonical vector of dimension n . The network with control nodes \mathcal{K} reads as

$$\mathbf{x}(t+1) = \mathbf{Ax}(t) + \mathbf{B}_{\mathcal{K}} \mathbf{u}_{\mathcal{K}}(t), \quad (3)$$

where $\mathbf{u}_{\mathcal{K}} : \mathbb{N}_{\geq 0} \rightarrow \mathbb{R}$ is the control signal injected into the network via the nodes \mathcal{K} (see Fig. 2). The network (3) is controllable in T steps by the nodes \mathcal{K} if, for every state \mathbf{x}_f , there exists a control input $\mathbf{u}_{\mathcal{K}}$ such that $\mathbf{x}(T) = \mathbf{x}_f$ with $\mathbf{x}(0) = \mathbf{0}$ (Kailath, 1980).

Controllability of this type of system can be ensured by different structural conditions (Kailath, 1980; Reinschke, 1988). For instance, let $\mathbf{C}_{\mathcal{K}, T}$ be the *controllability matrix* defined as

$$\mathbf{C}_{\mathcal{K}, T} := [\mathbf{B}_{\mathcal{K}} \ \mathbf{AB}_{\mathcal{K}} \ \dots \ \mathbf{A}^{T-1}\mathbf{B}_{\mathcal{K}}].$$

The network (3) is controllable in T steps by the nodes \mathcal{K} if and only if $\mathbf{C}_{\mathcal{K}, T}$ is of full row rank, where T is typically taken to be at least as large as the system size n .

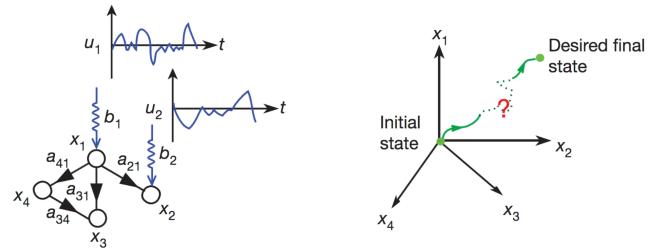


FIG. 2 **Controlling a simple network.** This small network can be controlled by an input vector $\mathbf{u}_{\mathcal{K}} = (u_1(t), u_2(t))^T$ (left), allowing us to move the network within the state space, from its initial state to some desired final state (right). From Liu *et al.* (2011).

B. Key driver nodes

Recent work from Liu *et al.* (2011) demonstrated that the analytical framework described in the previous section could be used to study large, complex networks. In that study, the authors explored common patterns in a wide variety of networks from biological to man-made and social. Under certain conditions in these weighted and directed networks, the set of driver nodes capable of guiding the dynamics of the entire system could be directly estimated from the degree distribution. Since that study, others have shown that under other conditions and in other networks, the degree distribution alone may not provide enough information to adequately determine the set of driver nodes. Instead, that knowledge regarding the network's structure must be complemented with an understanding of the network's dynamics, or the state equations at each node (Cowan *et al.*, 2012).

In these studies, networks are allowed to contain real-valued weights on each edge. However, for some real-world networks, knowledge of the edge weights is uncertain. For such scenarios, a complementary framework is provided by structural controllability which evaluates the controllability of binary networks (Kailath, 1980; Reinschke, 1988). By studying the underlying “structure”, i.e. distinguishing merely between which edges are absent (zero) *versus* present (non-zero), these methods allow the identification of minimal structures or control points that allow for full controllability of the network. Recent efforts have extended these ideas to large-scale systems, and to the problem of identifying the minimum number of nodes that need to be driven in order to achieve structural controllability (Pequito *et al.*, 2016a).

In recent work, Pequito *et al.* (2016b) extended the notion of structural controllability to situations in which edges evolve dynamically, and they identified the minimum number of driven nodes for full controllability of the system. Their methods would appear particularly relevant in situations like those observed in Khambhati *et al.* (2015), who studied dynamic functional connectiv-

ity in epileptic patients, and found that the edges within seizure-generating areas are almost constant over time, whereas the edges outside these areas exhibit higher variability over time. An important potential goal of control would then be to steer function on these edges away from pathological regimes (Pequito *et al.*, 2016b).

While network control and structural controllability are particularly relevant concepts for brain network control, many other key contributions have been made to the study of control in complex networks, which lie outside the scope of this article. We wish to point interested readers to the following reviews that focus entirely on network control tools. For a review of methods to identify control points to affect particular dynamics such as synchrony, see Chen (2014). For more general background and detail on network control in complex systems, the recent review by Liu and Barabási (2016) provides an excellent summary of the latest developments.

C. Control energy and metrics

Another important area of work lies in the development of metrics that characterize different control strategies for real networks. Classic results in control theory ensure that controllability of the network (3) from the set of network nodes \mathcal{K} is equivalent to the controllability Gramian $\mathbf{W}_{\mathcal{K}}$ being invertible, where

$$\mathbf{W}_{\mathcal{K}} = \sum_{\tau=0}^{\infty} \mathbf{A}^{\tau} \mathbf{B}_{\mathcal{K}} \mathbf{B}_{\mathcal{K}}^{\top} \mathbf{A}^{\tau} \quad (4)$$

and for \mathbf{A} satisfying Schur stability. In practical applications, controllable networks featuring small Gramian eigenvalues cannot be steered to certain states because the control energy is limited. This fact motivated Pasqualetti *et al.* (2014) to propose certain control strategies and associated metrics based on minimizing the control energy; these include average, modal, and boundary controllability.

To define these control metrics, we first let the network be controllable in T steps, and let $\mathbf{x}_f = \mathbf{x}(T)$ be the desired final state in time T , with $\|\mathbf{x}_f\|_2 = 1$. Define the energy of the control input $\mathbf{u}_{\mathcal{K}}$ as

$$E(\mathbf{u}_{\mathcal{K}}, T) = \|\mathbf{u}_{\mathcal{K}}\|_{2,T}^2 = \sum_{\tau=0}^T \|\mathbf{u}_{\mathcal{K}}(\tau)\|_2^2, \quad (5)$$

where T is the control horizon. The unique control input that steers the network state from $\mathbf{x}(0) = \mathbf{0}$ to $\mathbf{x}(T) = \mathbf{x}_f$ with minimum energy is (Kailath, 1980)

$$\mathbf{u}_{\mathcal{K}}^*(t) = \mathbf{B}_{\mathcal{K}}^T (\mathbf{A}^T)^{T-t-1} \mathbf{W}_{\mathcal{K},T}^{-1} \mathbf{x}_f \quad (6)$$

with $t \in \{0, \dots, T-1\}$. Then it can be seen that

$$E(\mathbf{u}_{\mathcal{K}^*}, T) = \sum_{\tau=0}^{T-1} \|\mathbf{u}_{\mathcal{K}}^*(\tau)\|_2^2 = \mathbf{x}_f^T \mathbf{W}_{\mathcal{K},T}^{-1} \mathbf{x}_f \leq \lambda_{\min}^{-1}(\mathbf{W}_{\mathcal{K},T}), \quad (7)$$

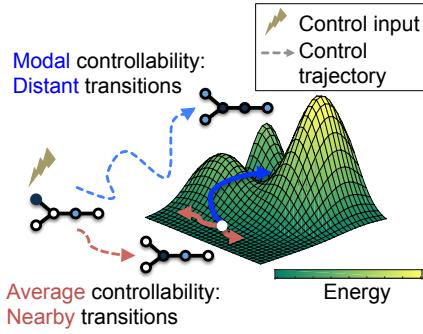


FIG. 3 **Energetic costs of controllability metrics.** Pasqualetti *et al.* (2014) propose realistic control strategies that include the energetic costs of control (7). Average controllability describes transitions nearby on an energy landscape, while modal controllability describes transitions distant on this landscape.

where equality is achieved whenever \mathbf{x}_f is an eigenvector of $\mathbf{W}_{\mathcal{K},T}$ associated with $\lambda_{\min}(\mathbf{W}_{\mathcal{K},T})$.

Average controllability identifies network nodes that, on average, can steer the system into different states with little effort (i.e., input energy), see Fig. 3. The average controllability in a network—formally defined as $\text{Trace}(\mathbf{W}_{\mathcal{K}}^{-1})$ —equals the average input energy from a set of control nodes and over all possible target states (Marx *et al.*, 2004; Shaker and Tahavori, 2012). This is motivated by the relation $\text{Trace}(\mathbf{W}_{\mathcal{K}}^{-1}) \geq N^2 / \text{Trace}(\mathbf{W}_{\mathcal{K}})$ (Summers and Lygeros, 2014), and the fact that $\mathbf{W}_{\mathcal{K}}$ is close to singularity even for networks of small cardinality. It should be noticed that $\text{Trace}(\mathbf{W}_{\mathcal{K}})$ encodes a well-defined control metric, namely the energy of the network impulse response or, equivalently, the network H_2 norm (Kailath, 1980). Intuitively, network nodes with high average controllability are most influential in the control of network dynamics over all possible target states.

Modal controllability identifies network nodes that can push the network activity into difficult-to-reach states, which are those that require substantial input energy. To quantify modal controllability, we first note that the behavior of a dynamical system is fully determined by the eigenvalues (modes) and eigenvectors of its system matrix. Regarding controllability, the Popov-Belovich-Hautus test ensures that a system with matrix \mathbf{A} is controllable by an input matrix \mathbf{B} if and only if all its modes are controllable or, equivalently, if and only if there exists no left eigenvector of \mathbf{A} orthogonal to the columns of \mathbf{B} (Kailath, 1980). In particular, the i^{th} mode is controllable by the matrix \mathbf{B} if and only if $\mathbf{w}_i \mathbf{B} \neq 0$, where \mathbf{w}_i is a left eigenvector of \mathbf{A} associated with its i^{th} mode. Intuitively, network nodes with high modal controllability are able to control all of the dynamic modes of the network, and hence to drive the dynamics towards hard-to-reach configurations.

Boundary controllability identifies network nodes that

lie at the boundaries between network communities, as defined across all possible levels of hierarchical modularity in a network, and thus intuitively measures the ability to control the integration and segregation of network modules. This metric depends on the choice of a method for detecting boundary control points, for which an algorithm is proposed in Pasqualetti *et al.* (2014). This algorithm can be altered as needed for the physical system under study, e.g., to enhance the accuracy in estimating an initial partition of the network into communities, and to sharpen or loosen the boundary point criteria. Intuitively, network nodes with high boundary controllability are able to gate information between different communities, across topological scales in the network.

Overall, these three metrics provide useful estimates for real systems especially when considering dynamics over the whole network. Further work could be done to investigate other scenarios such as dynamics in just parts of the network, or how different patterns of community structure change the resulting controllability. These and more general questions about the relationship between network topology and the resulting dynamics remain open areas of study, which we discuss in more detail at the end of this article.

D. Application to brain networks

To use these methods to answer questions in neuroscience, we must begin by constructing networks based on our knowledge of brain connectivity. At the large scale, network nodes in the brain are often defined based on regional differences in cellular architecture (Brodmann, 1909; Glasser *et al.*, 2016) or local gradients in fine-scale functional connectivity (Power *et al.*, 2011; Yeo *et al.*, 2011). Connectivity between these nodes can be estimated with emerging neurotechnologies. In humans, one particularly powerful non-invasive probe of connectivity uses magnetic resonance imaging (MRI) to infer structural pathways in the brain (Wedgeen *et al.*, 2012) by exploiting molecular resonances of water molecules as they diffuse along white-matter tracts (Basser *et al.*, 1994; Makris *et al.*, 1997), see Fig. 4. By reconstructing the pathways that exist between brain regions and by estimating the strengths of those pathways, a brain network (weighted, symmetric graph) is obtained where the network edges are given by the inter-regional connection strengths (Bassett *et al.*, 2011; Hagmann *et al.*, 2008). Similar techniques can be used in rodents, cats, dogs, and non-human primates by way of a small-bore magnet (Duong, 2010). Of course, tract-tracing techniques and other invasive methods are also a powerful way to image structural pathways in non-human animals (Markov *et al.*, 2011; Okano and Mitra, 2015).

Recently, Gu *et al.* (2015) applied network control theory to such whole-brain structural networks in humans.

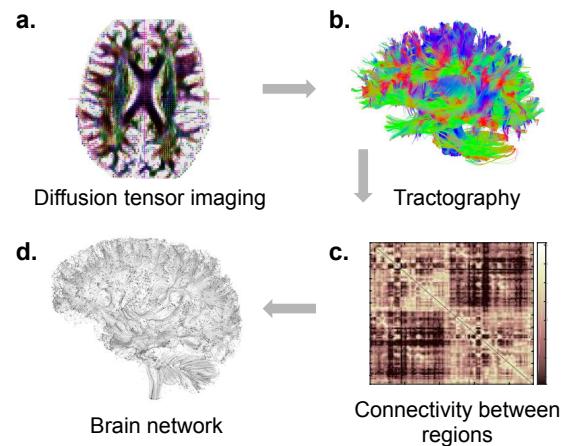


FIG. 4 Construction of a human brain structural network. (a) Diffusion imaging measures the direction of water diffusion in the human brain. (b) From these data, white matter streamlines can be reconstructed that connect brain regions. (c) Adjacency matrix representation of the structural connectivity: entries denote the estimated strength of white matter connectivity between brain regions. (d) Resulting brain network where nodes are brain regions and edges are the connection strengths between them.

Using networks composed of between 83 and 1015 nodes, the authors study the three controllability metrics of average, modal, and boundary controllability (Pasqualetti *et al.*, 2014) discussed in the previous section. While these techniques have not yet been ubiquitously applied to non-human imaging (Badhwar and Bagler, 2015; Tang *et al.*, 2012), the mathematics is generalizable to any estimate of structural connectivity in a neural system. Conceptually, this approach supports the general study of the kinds of dynamics predicted by the constraints of structural connectivity, particularly for the scenario in which a given brain region is acting as a control point for the rest of the network.

IV. UNDERSTANDING HEALTHY BRAIN FUNCTION THROUGH CONTROL THEORY

In this section, we explore the utility of network control theory for offering mechanisms of cognitive control, providing explanations for individual differences in cognitive control across people, and capturing the evolution of control as we grow from children to adults. We close this section by discussing open questions in cognitive neuroscience that appear particularly amenable to extensions of network control theory.

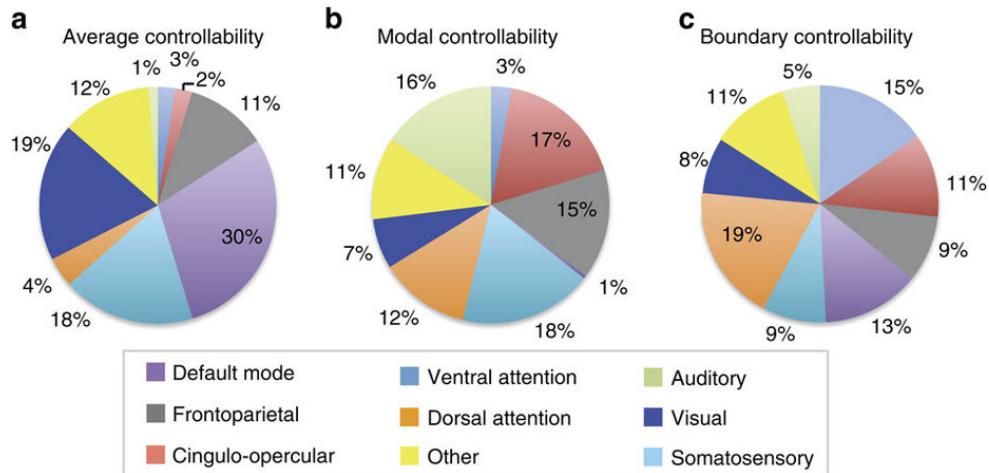


FIG. 5 Cognitive control hubs are differentially located across cognitive systems. (a) Hubs of average controllability are preferentially located in the default mode system. (b) Hubs of modal controllability are predominantly located in cognitive control systems, including both the frontoparietal and cingulo-opercular systems. (c) Hubs of boundary controllability are distributed throughout all systems, with the two predominant systems being ventral and dorsal attention systems (Gu *et al.*, 2015).

A. Network control as a partial mechanism for cognitive control

A simple question to ask about any theory is whether or not it offers predictions of observed processes. One particularly straightforward and testable hypothesis is that the common control strategies studied in control and dynamical systems theory are strategies that the brain uses to control its own intrinsic dynamics. In a recent study, Gu *et al.* (2015) addressed this hypothesis by first calculating the controllability strengths for each brain region, and then by identifying the preferences of each brain region for different types of control. The authors found that strong average controllers, strong modal controllers, and strong boundary controllers were located in quite different areas of the brain, see Fig. 5.

Intriguingly, the different sorts of controllers appeared to map on to the types of function that each brain region is thought to perform. For example, strong average controllers were disproportionately located in the default mode system, which is a spatially distributed set of brain regions that are particularly active when a person is simply resting (Raichle, 2015). This is particularly interesting because it suggests that areas of the brain that are active in the “ground state” are also areas that are structurally predicted to optimally push the system into many local easily-reachable states, close by on the underlying energy landscape. Furthermore, strong modal controllers were disproportionately located in cognitive control systems, including both the frontoparietal and cingulo-opercular systems. This is particularly interesting because it suggests that the areas of the brain that are active during tasks that demand high levels of cognitive control or task switching (Botvinick and Braver,

2015) are structurally predicted to optimally push the system into distant states, far away on the underlying energy landscape. Lastly, strong boundary controllers were disproportionately located in regions implicated in attention (Corbetta and Shulman, 2002), supporting their predicted role in gating (Eldar *et al.*, 2013; Womelsdorf and Everling, 2015) information between network communities.

This study offers a possible mechanistic explanation for how the brain might move between cognitive states that depends fundamentally on white matter microstructure. The work suggests that structural network differences between the default mode, cognitive control, and attentional control systems dictate their distinct roles in brain network function. While the results need to be validated in other species and data sets, the broad trends indicate the relevance of control theory for capturing canonical concepts in cognitive control.

B. Network control and cognitive performance

In the previous section, we reviewed evidence that notions from network control applied to neuroimaging data can provide insight into the roles that brain regions may play in the control of neural dynamics. Here we ask the more specific question of whether the brain in one person (or animal) might be optimized for a different type of control than the brain in another person. That is, can controllability metrics explain why cognitive performance differs across individuals?

While still a very open question, two recent studies suggest that indeed each brain displays a different profile of control, and differences across people are corre-

lated with differences in their cognitive capacities. In one study in healthy adult humans, Medaglia *et al.* (2016) compare the predictions from network control theory applied to individual brain images to the performance of these same individuals on traditional cognitive control tasks. More specifically, the authors calculate modal and boundary controllability (see III.C) on brain networks obtained from diffusion imaging, and they also test the performance of subjects in cognitive control tasks that measure the inhibition of behavior, the shifting of attention, vigilance, and working memory capacity. The study reports key regional controllers in the brain whose controllability strength is correlated with task performance measures across individuals, thus providing a second line of evidence that network control may be a partial mechanism for cognitive control in humans.

Turning from adults to children, Tang *et al.* (2016) evaluated the controllability strength of brain regions as well as more general cognitive performance (not specific to cognitive control) in a community-based sample of 882 healthy youth that ranged in age from 8 to 22 years. The authors found that the relative strength of average controllers in subcortical *versus* cortical regions (which are the earliest evolving and latest evolving brain areas, respectively) is an important predictor of improved cognitive performance. This relationship held true even when accounting for differences in age across the cohort, suggesting that it is a fundamental characteristic of human brain structure and dynamics.

C. Evolution of network control in development

The identification of age-invariant relationships between controllability metrics and cognitive function begs the question of whether controllability metrics of brain networks change with age, either in their magnitude or in their spatial distribution. To address this question, Tang *et al.* (2016) studied the controllability metrics of average controllability and modal controllability in 882 healthy youth from 8 to 22 years, and quantified a single value of controllability for a person as given by the average of controllability strengths across all brain regions. This coarse-graining of the data enabled the authors to study how brain networks are facilitate energetically easy transitions (average controllability) as well as energetically costly ones (modal controllability).

They found that brain networks are highly optimized to support a diverse range of possible dynamics (as compared with randomized versions of the networks) and that this range of supported dynamics increases with age, see Fig. 6. Seeking to investigate structural mechanisms that support these changes, the authors simulate network evolution with a set of growth rules, to find that all brain networks – from child to adult – become increasingly structured in a manner highly optimized for

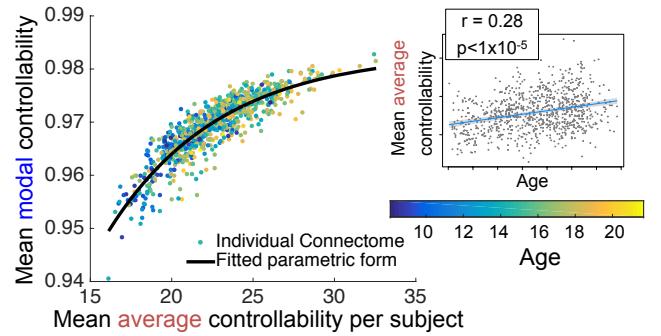


FIG. 6 Controllability metrics are positively correlated with age, with older youth displaying greater average and modal controllability than younger youth. Each data point represents the average strength of controllability metrics calculated on the brain network of a single individual, in a cohort of 882 healthy youth from ages 8 to 22. Brain networks were found to be optimized to support energetically easy transitions (average controllability) as well as energetically costly ones (modal controllability). The color bar denotes the age of the subjects, illustrating a significant correlation between age and the ability to support this diverse range of dynamics (Tang *et al.*, 2016).

network control. These results suggest key neurophysiological changes that may be occurring during development, driving the system towards an increasing capability to traverse a larger surface of the energy landscape. It would be interesting in future to assess whether these metrics are altered in youth with neuropsychiatric disorders, or whether they could be used to predict transition to psychosis.

D. Open questions in control and cognition

It is important to note that linear models of neural dynamics (Fernández Galán, 2008; Honey *et al.*, 2009) for use in network control theory have both advantages and disadvantages. Their advantage is that one has access to a wide array of theoretical observations that can offer intuitions about the system's (controlled) dynamics, particularly around an operating point (Gu *et al.*, 2015). The disadvantage is that they cannot speak to neural processes that transition from one dynamical regime (limit cycles, fixed points, attractors) to another (Deco and Jirsa, 2012; Golos *et al.*, 2015; Muldoon *et al.*, 2016a). In these cases, developing additional methods for control of nonlinear systems may be necessary.

One simple scenario in which limit cycles – or transitions between them – may be particularly important for processes of cognitive control is that of human decision-making (Chand and Dhamala, 2016; Chand *et al.*, 2016). For example, oscillatory activity in specific brain regions has been linked to rational *versus* irrational decision-making in a task that requires financial judgements (akin

to gambling). Sacré *et al.* (2016) studied a group of human subjects in which multiple depth electrodes were implanted in deep brain structures as a part of routine presurgical evaluation for medically refractory epilepsy. By recording the local field potentials at each of these electrodes, the authors were able to monitor the activity of neuronal ensembles in the precuneus and show that high-frequency activity (70–100 Hz) increased when irrational decisions were made. This and similar studies in other areas of higher-order cognitive function that depend upon synchronized oscillatory activity in neuronal ensembles (Bassett *et al.*, 2009; Kopell *et al.*, 2000) suggest the possibility that control strategies could be devised that use brain stimulation to alter the frequency of neuronal synchrony to modulate cognitive processes. Such a possibility will depend on accurately extending linear control models to nonlinear ones, isolating the dynamics relevant for the cognitive process of interest, and localizing the region that is most impacted.

V. TARGETING THERAPEUTIC INTERVENTIONS TO MAXIMIZE BENEFICIAL OUTCOMES TO PATIENTS

In this section, we broaden our focus from linear models of network control in order to more generally discuss emerging engineering approaches for the control of brain dynamics in the context of clinical medicine. We separate our discussion into methods for modulating consciousness via anesthesia administration, methods for ongoing monitoring and treatment of Parkinson’s disease, methods for non-invasive stimulation, and methods for the control of transient epileptic seizures. These topics are in no way meant to be comprehensive of the field, but simply to highlight important directions of clinical relevance. Where appropriate, we point out connections to the network control literature, and opportunities for further synergies between medicine and control theory.

A. Anesthesia titration

Anesthesia is used in medical institutions to modulate consciousness through drugs during surgery, potentially by altering distributed circuitry (Crone *et al.*, 2016). Accurately titrating the levels of anesthetic for each person, and at each time point during the surgery, is critically important for the health and survival of the patient. Recent efforts seek to optimize this titration using a closed-loop system (Ching *et al.*, 2013), where the challenge is to maintain a medically-induced coma by delivering propofol via an intravenous catheter or pump. Using a computer to control this delivery system, precise amounts of anesthetic can be chosen, administered, and adapted in a time-dependent manner, potentially reducing the incidence of propofol overdose which is accompanied by

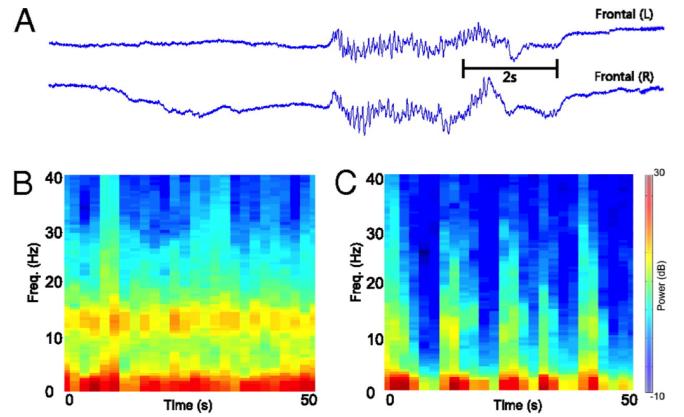


FIG. 7 Burst suppression phenomenology. (a) A typical recording of burst suppression from a human subject anesthetized with propofol – a type of general anesthesia. The bursts manifest concurrently across the scalp (here, shown for left and right frontal electrodes). (b) Spectrogram for a frontal electrode during deep, but not burst-suppression, general anesthesia. (c) At a deeper level of general anesthesia, burst suppression is achieved (the spectrogram clearly displays epochs of quiescence). From Ching *et al.* (2012b).

debilitating side effects.

Building on their earlier biophysical model, Ching *et al.* (2013) suggest the real-time computation of the brain’s burst suppression state from the electroencephalogram (see Fig. 7), which indicates a state of highly reduced electrical and metabolic activity (Ching *et al.*, 2012b). This is done using an on-line parameter estimation procedure and proportional-integral controller. The technique has already been validated in rodents, where it can be used to successfully monitor and control the burst suppression state. Translating this work into humans will require more extensive computational estimation of model parameters and empirical validation over periods of several hours.

B. Deep-brain stimulation for Parkinson’s disease

High-frequency deep brain stimulation (DBS), commonly used to treat Parkinson’s disease, is one of the oldest examples of successful dynamical manipulation of brain function to alleviate clinical symptoms. Yet, it remains unclear exactly how and why it works so well. Control and systems theory approaches are useful for modelling the underlying circuitry to understand the mechanisms by which deep-brain stimulation affects behavioral phenotypes (Santaniello *et al.*, 2015; Tass *et al.*, 1998; Wilson and Moehlis, 2016).

Recent work has highlighted the network-level mechanisms of the diseased dynamics, and the control necessary to treat them. For example, Santaniello *et al.* (2015) move from localized functions to the relevant circuitry, positing that DBS increases the regularity of firing pat-

terns in the basal ganglia, thereby decreasing symptoms of Parkinson's disease (Chiken and Nambu, 2014). The authors suggest that high-frequency stimulation of 130 Hz in DBS is effective because it is a resonant frequency of the overall cortico-basal ganglia-thalamo-cortical loop. The authors explore the effects of different stimulation conditions by simulating hundreds of biophysically realistic neurons from different regions of the circuitry that are thought to have very different functions. Their results suggest a loop-based reinforcement model, where DBS proximally or distally does not individually account for resulting pattern changes, but instead relies on a combined impact across the circuit. This observation could inform the choice of stimulation frequency and location when using DBS clinically (Johnson *et al.*, 2013).

While identifying the resonant frequency of a critical circuit may provide a useful target for control, other mechanisms may also exist, and it is possible that interventions targeting more than one mechanism could be more effective than targeting one mechanism alone. Other candidate mechanisms include coupling between peripheral tremor rhythms, and the phase locking of the activity of primary and secondary motor areas. For example, Tass *et al.* (1998) propose two techniques to identify the relative phase locking between two MEG signals, thereby detecting synchronization of neuronal activity and mapping its relationship to peripheral tremors. Other attempts to uncover mechanisms include the investigation of entrainment and desynchronization dynamics, both seen in populations of neurons, as a result of DBS. Wilson and Moehlis (2016) study a population of model neurons and the effects of stimulation, to observe underlying low-dimensional patterns that can illuminate collective processes in spiking neurons. The simplicity of that particular model affords theoretical insight into a potential mechanism that governs DBS.

Once the optimal mechanism(s) have been identified, a tantalizing goal is the use of control theory to create a closed-loop system for more effective treatment. Holt and Netoff (2014) identify their goal for DBS as the suppression of pathological frequencies that occur during Parkinson's disease. They simulate the physiology of the basal ganglia to create a mean-field model of the closed-loop system, which allows for the tuning of stimulation parameters based on patient physiology. This setup provides significant advantages over the current method of trial-and-error tuning, which is based on the clinician's past experience. If such a model can be empirically validated, it would be an important step towards improving the efficacy of DBS for patients with Parkinson's disease.

C. Non-invasive transcranial stimulation

While such invasive monitoring and stimulation paradigms are not accessible to most humans, other non-

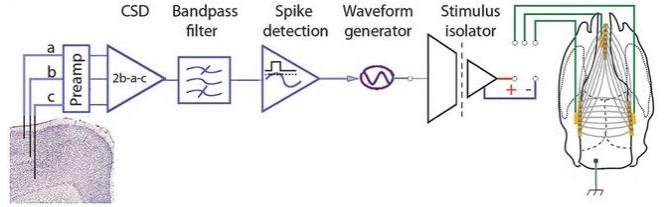


FIG. 8 Closed-loop stimulation for seizure suppression in a rat. Recordings from channels *a*, *b* and *c* in the cortex are filtered for spike detection, where signals exceeding the predetermined amplitude threshold are detected. These thresholded signals are used to trigger transcranial electric stimulation, which is applied through the scalp. From Berényi *et al.* (2012).

invasive methods of brain stimulation are becoming increasingly feasible. The most common is that of transcranial magnetic (electric) stimulation, which is the application of a magnetic (electric) field through the scalp for a short period of time (Bikson *et al.*, 2016). While the effects of transcranial stimulation tend to be diffuse, they have demonstrated utility in treating depression and other neurological and psychiatric disorders (Kedzior *et al.*, 2016). Indeed, the ubiquitous use of non-invasive stimulation makes it critical to build mechanistic models that provide a deeper understanding of the effects of stimulation (Johnson *et al.*, 2013), and rules by which stimulation parameters and location can be optimized to enhance beneficial impacts, and mitigate detrimental ones.

One study directly bridges mathematical models of nonlinear neural dynamics and the predictions of network control theory in the context of such exogenous stimulation. Muldoon *et al.* (2016b) consider the effects of electrical stimulation to a specific brain region using a model of non-linear oscillators connected by a coupling matrix estimated from actual diffusion imaging data (Fig. 4). By simulating dynamics in this network of Wilson-Cowan oscillators, they can test for different regimes of desired functional outcomes supported by the network—if the effects of stimulation remain focal or spread globally—and compare these with the predictions from network control theory using the controllability metrics described in III.C. Importantly, their results validate linear network control predictions over eight subjects and more generally provide a model that can be used or tested in clinical settings, in order to strengthen the connection between theory and clinical practice.

D. Seizure suppression in epilepsy

Both invasive and non-invasive stimulation methods have been considered for the treatment of medically intractable epilepsy. Both types of interventions would seem to be preferable to the current clinical practice of re-

secting large sections of neural tissue thought to cause the seizure, although of course this statement is speculative (Stacey and Litt, 2008). Instead, stimulation may have the potential to suppress seizures (Berényi *et al.*, 2012; Ching *et al.*, 2012a), particularly if tailored to the underlying brain connectivity (Taylor *et al.*, 2015), and/or its associated dynamics (Khambhati *et al.*, 2016). In a recent practical demonstration, work from the group of Berényi *et al.* (2012) shows the efficacy of brain stimulation in seizure suppression, in a rat model for epilepsy (see Fig. 8). Application of transcranial electrical stimulation using a closed-loop system reduces seizure duration, on average, by 60%. These results show great promise for the development of closed-loop stimulation that leaves other aspects of brain function unaffected, and paves the way for the use of such therapies in humans.

A particularly poignant example of more theoretical work considering control in brain networks for seizure suppression is the work by Ching *et al.* (2012a), which employs a grid of stimulating electrodes that act as actuators to help stem and direct the propagation of electrical activity. To model mesoscale cortical dynamics, they use a network of Wilson-Cowan oscillators, with both diffusive and synaptic coupling. By modelling the placement of several actuators, they demonstrate the ability to limit pathological activity (the spreading of electrical activity across a patch). By slowing the spread of activity, their method can be used in conjunction with pharmacological agents, or allow time for other self-correcting mechanisms in the brain. Naturally, their method would depend on how well the actuators contact and target the underlying tissue, as well as on accurate monitoring of seizure activity and the ability to control in real time. An alternative approach is put forth by Taylor *et al.* (2015), whose model covers a larger spatial area and uses connectivity derived from patient MRI to facilitate personalization of stimulation. A simple dynamical model describes regional activity including epileptic spike wave dynamics, and a pseudospectral method generates time-varying stimuli to halt simulated seizures.

When thinking about translating some of these techniques to the clinic, it is useful to contrast them with existing clinical procedures. Generally speaking, clinical interventions for epilepsy can come in the form of (i) carefully modifying neural structure and dynamics, (ii) entirely quieting dynamics over short periods of time, or (iii) removing tissue to ensure silence over a lifetime. Khambhati *et al.* (2016) study methods to treat epilepsy via either short term “lesioning” (meaning quieting dynamics using stimulation) or long term “resection” (actually surgically removing the tissue). They develop methods for the identification of suitable lesion points, that affect the ability of the network to sustain synchronous activity associated with the occurrence of a seizure (see Fig. 9). These inferences are based on a measure of syn-

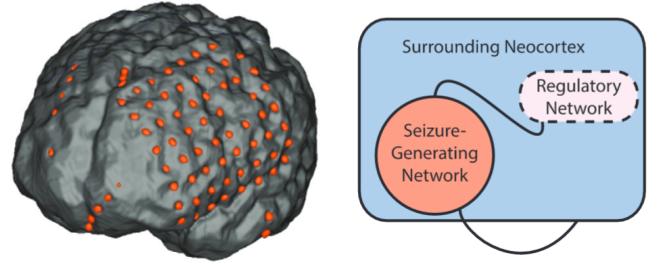


FIG. 9 Schematics of patient electrophysiology and epileptic model. *Left:* Intracranial electrophysiology of patients with neocortical epilepsy. Each sensor (red) can be treated as a node within a functional network that uses magnitude squared coherence between sensors as network edges. *Right:* Model of epileptic network, comprised of a seizure-generating system and a hypothesized regulatory system that controls the spread of pathologic seizure activity (Khambhati *et al.*, 2016).

chronizability of the network – the ratio of the largest and smallest eigenvalues of the graph Laplacian (Barahona and Pecora, 2002). Virtual resection of individual brain regions *in silico* can pinpoint control regions that strongly synchronize or desynchronize network dynamics, while revealing a principle of push-pull antagonism that provides a possible explanation for why seizures spread. Further work that clarifies the translational verity of this approach could improve methods for surgical resection in patients with medically refractory epilepsy.

VI. CONTROL OF SPECIFIC NEURAL DYNAMICS OR PATHWAYS

The example contexts in clinical medicine that we discuss in the previous sections highlight the great diversity of neural network dynamics in both health and disease. In this section, we focus on two specific types of network dynamics for which simple mathematical models can be studied, and for which control strategies can be examined analytically. The first context is that of neural synchrony, or rhythmic oscillations of neural ensembles. The second context is state transitions, where the activation profile of the brain moves from one pattern to another. We conclude the section by describing a few empirical tools that can be used to modulate these dynamics, and to test predictions from network control theory.

A. Synchrony of neural populations

1. Dynamical characteristics and clinical relevance

When considering the control of specific dynamics, a natural place to start in neural systems is synchrony, which occurs when populations of neurons or brain regions exhibit the same dynamics $s(t)$, i.e. $x_1(t) = \dots =$

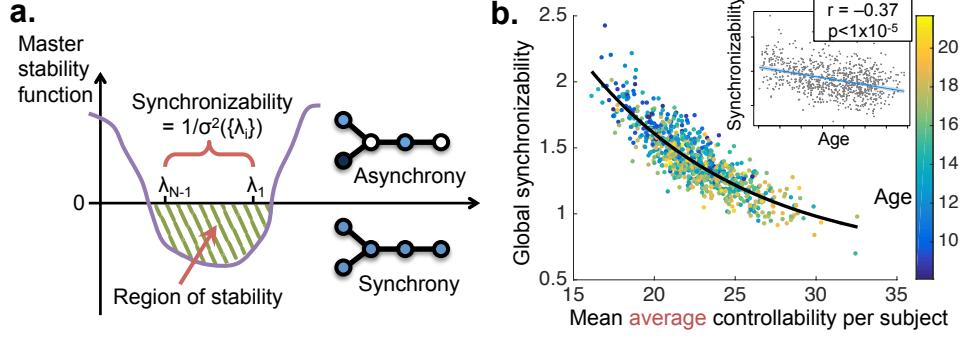


FIG. 10 Synchronizability of structural brain networks and a negative correlation with age. (a) Schematic of a master stability function (MSF) for a generic network of oscillators, which gives the perturbative stability of a globally synchronous state (Pecora and Carroll, 1998). Such a state is stable when the MSF is negative for all positive eigenvalues of the graph Laplacian, hence the inverse spread of the Laplacian eigenvalues $1/\sigma^2(\{\lambda_i\})$ provides an estimate of synchronizability (or stability under synchrony), see Nishikawa and Motter (2010). (b) Synchronizability in structural brain networks estimated from diffusion imaging in a large cohort of 882 youth is found to be anti-correlated with mean average controllability, as well as with age (Tang *et al.*, 2016).

$x_n(t) = s(t)$ (see Fig. 10a). In many organisms, synchrony manifests as strong time-locked patterns, such as circadian rhythms and gait regularity. Moreover, the transition between synchrony and desynchrony has implications for treating epilepsy (Jirsa *et al.*, 2014), Parkinson's disease, or other pathological conditions. Hence the propensity towards synchrony or the ease of transitioning in and out of a synchronous state is of great interest – both in local neuronal ensembles (Davison *et al.*, 2016; Nabi and Moehlis, 2011) and in distributed whole-brain networks (Tang *et al.*, 2016).

While this field is too large to do justice to in this small space, we highlight the work of Nabi and Moehlis (2011) as an excellent example describing the process of desynchronization in two models of coupled units (Kuramoto and a reduced phase Hodgkin-Huxley with electrotonic coupling), through the dynamic programming of inputs to a single neuron in the population. This work offers a possible mechanism for deep-brain stimulation in Parkinson's disease, where stimulation represents a single input that can affect desynchronization. Importantly, the model includes global (all-to-all) coupling between neurons, and therefore the use of more heterogeneous couplings that are characteristic of empirically measured brain networks could be an interesting future direction.

While understanding desynchronization processes is critically important, another relevant question pertains to the conditions under which synchrony can occur. While some efforts seek to address this question through the analysis of Lyapunov functions (Davison *et al.*, 2016), the bounds are often of limited value as they are far from the regime in which we expect neural dynamics to take place. Alternatively, perturbative methods on synchronizability can be used to describe more realistic regimes.

2. Structural drivers of synchrony: Graph architecture and symmetries

One framework to study the perturbative stability of a synchronous state takes an explicitly structural approach. In particular, Pecora and Carroll (1998) proposed the master stability function (MSF) to analyze the stability of this state on a network of oscillators. A schematic of this function for a generic network of identical oscillators is given in Fig. 10a. Within this framework, linear stability depends on the positive eigenvalues $\{\lambda_i\}, i = 1, \dots, N - 1$ of the graph Laplacian \mathbf{L} defined by $L_{ij} = \delta_{ij} \sum_k A_{ik} - A_{ij}$, where \mathbf{A} is the network adjacency matrix defined in III.A. More specifically, stability under perturbations exists when this function is negative for all positive eigenvalues of the Laplacian matrix.

Without detailed specification of the properties of the dynamical units, typically a larger spread of Laplacian eigenvalues will make the system more difficult to synchronize than a smaller spread. Therefore, one natural measure of global synchronizability is the inverse variance $1/\sigma^2(\{\lambda_i\})$, as proposed by Nishikawa and Motter (2010):

$$\sigma^2 = \frac{\sum_{i=1}^{N-1} |\lambda_i - \bar{\lambda}|^2}{d^2(N-1)}, \quad \text{where } \bar{\lambda} := \frac{1}{N-1} \sum_{i=1}^{N-1} \lambda_i \quad (8)$$

and $d := \frac{1}{N} \sum_i \sum_{j \neq i} A_{ij}$, the average coupling strength per node, which effectively normalizes the overall network strength.

Tang *et al.* (2016) used this metric of global synchronizability to study the brain networks of 882 typically developing youth from the ages of 8 to 22. They found that brain networks that are more synchronizable tend to display lower average controllability (Fig. 10b) as well as lower modal controllability. While no known relationship between synchronizability and controllability exists, the

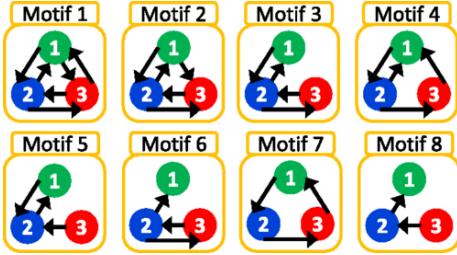


FIG. 11 Motif structures that occur within networks. The motif structures studied by Whalen *et al.* (2015), through simulations of non-linear biophysical neuronal models and their resulting controllability.

correlation is intuitive in that it suggests that individuals who are theoretically predicted to more easily transition into a variety of dynamical states are less susceptible to having many regions locked in synchrony. Interestingly, the relationship between synchronizability and controllability is partially explained by age: synchronizability decreases as children age (inset of Fig. 10b). These results suggest that as the brain matures, its network architecture supports a larger range of dynamics (from nearby to distant states) perhaps necessary for the adult repertoire of cognitive functions, and is less able to support globally synchronized states which are instead characteristic of pathological conditions such as epilepsy.

When considering structural constraints on the control of synchrony in brain networks, it is important to consider the role of structural symmetries. Indeed, critical work from Whalen *et al.* (2015) demonstrates that symmetries and motifs in the network structure have a nontrivial impact on the potential to control the system's dynamics. Their work addressing three-node motifs (see Fig. 11) explores the possibility of introducing a group-theoretic component to the existing algebra of control theory. They conduct simulations of the motifs using biophysical neuronal models characterized by non-linear dynamics as described by the Fitzhugh-Nagumo equations, which comprise a general representation of excitable neuronal membranes. They explore several dynamical regimes including chaotic, pulsed limit-cycle, and constant input limit-cycle, to see how different types of symmetries (such as rotational or mirror) affect the resulting controllability. Further work is needed to determine whether these effects on controllability generalize to scenarios in which the same 3-node motifs are embedded in a larger network, or in which the model of dynamics is changed from a cellular-level model to a macro-scale model of neuronal activity.

B. The cost of controlling specific trajectories

While the control metrics defined earlier (III.C) consider the cost of control, they necessarily coarse-grain

over many different state transitions: average controllability measures the ability to move the system to (all) local states on the energy landscape, while modal controllability measures the ability to move the system to (all) distant states on the energy landscape. However, there are circumstances in real world networks – and particularly in brain networks – in which we would like to understand how to move the system from a specified initial state to a specified target state. In this general scenario, we might like to be able to compare the shape of different trajectories within state space, thereby providing intuitions regarding the feasibility of a specific transition and the accessibility of certain final states.

In the context of the linear network system described earlier (Eq. 3), one proposed solution to this problem considers the trajectory from an initial state \mathbf{x}_0 (one pattern of regional activation) to a target state \mathbf{x}_T (another pattern of regional activation), see Fig. 12. Our goal is to infer a control input function $\mathbf{u}(t)$ that minimizes the energy of the transition and the distance of the current state from the target (final) state:

$$\begin{aligned} \min_{\mathbf{u}} \quad & \int_0^T ((\mathbf{x}_T - \mathbf{x}(t))^T (\mathbf{x}_T - \mathbf{x}(t)) + \rho \mathbf{u}(t)^T \mathbf{u}(t)) dt, \\ \text{s.t.} \quad & \dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t), \\ & \mathbf{x}(0) = \mathbf{x}_0, \\ & \mathbf{x}(T) = \mathbf{x}_T, \end{aligned} \quad (9)$$

where T is the control horizon, $\rho \in \mathbb{R}_{>0}$, and $(\mathbf{x}_T - \mathbf{x}(t))$ is the distance between the state at time t and the target state.

Using this formulation, Gu *et al.* (2016) study the energy landscape of finite-time control trajectories from the brain's baseline activation state to states with heightened activity in cortex devoted to vision, audition, and motor function. Interestingly, they observe that the most

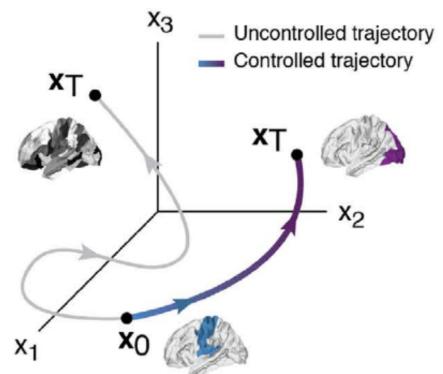


FIG. 12 Example trajectory through state space. With external input (control signals), the system at state \mathbf{x}_0 is driven into the desired target state \mathbf{x}_T ; without input the system's passive dynamics leads to another state \mathbf{x}_T' where random brain regions are more active than others.

efficient drivers of these transitions were nodes in the network (or regions of the brain) with high communicability to the target state, indicating the importance of long-distance walks on the network for efficient control. Moreover, by studying changes in the energetic impact of nodes on certain control actions, they also find that patients with mild traumatic brain injury show a loss of specificity in the putative control processes that their brain networks support. This work sheds light on the mechanisms that drive brain state transitions in healthy cognition and their alteration following injury.

In a similar vein, Betzel *et al.* (2016) simulate control trajectories among states characterized by the activation of various cognitive systems in the brain: systems devoted to visual, auditory, motor, baseline, cognitive control, salience, and attention-related functions. The goal was to compare energetic costs of these transition and to determine how this cost depends on the number of controllers used. The authors identify the brain regions that contribute most strongly to changes in energetic cost, and compare these with predictions from network control theory. In particular, they identify a group of control regions that are located in the rich club: a set of high-degree nodes that tend to also connect to one another (Colizza *et al.*, 2006). Notably, these rich-club hubs acting as control regions most altered energetic outcomes when the brain's rich club organization was destroyed by simulated lesioning, an increasingly common model of neurodegenerative disease (Alstott *et al.*, 2009).

Within this modeling framework, a choice of which trajectories to be simulated has to be made. Further work remains to identify the most useful trajectories for simulation that can reveal actual brain dynamics, thereby increasing biophysical relevance.

C. Empirical tools for control of specific neural dynamics or pathways

In the previous few subsections, we outlined theoretical frameworks and computational methods to model and interrogate the control of neural synchrony and brain state transitions. In each of these cases, it is and will remain important to inform and validate theories and models with empirical data, using experimental tools for control. Earlier in this report, we highlighted several of these tools in the form of brain stimulation, which have proven especially relevant for therapeutic interventions. However, in addition to these relatively large-scale tools, that are already being linked to control theory, there also exist fine-scale tools for the manipulation of single neuronal cell types (Lee *et al.*, 2010), which could benefit from additional theoretical work.

Arguably one of the most powerful recently-developed tools for the manipulation of single cell types is optogenetics. Optogenetics offers millisecond-scale optical con-

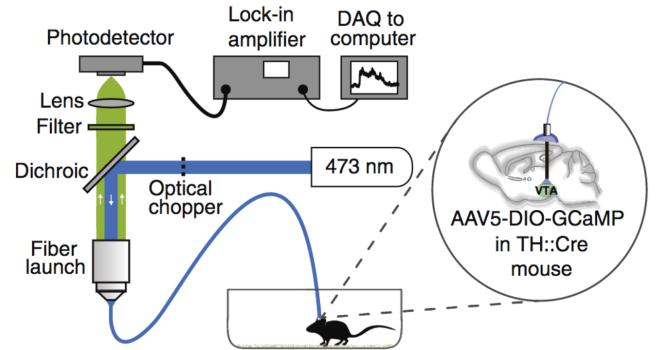


FIG. 13 Setup for optogenetic control in a rat. *Left:* Fiber photometry setup showing light path for fluorescence excitation and emission through a single 400 micron fiber optic implanted in the ventral tegmental area (VTA). *Right:* Recombinase-dependent viral targeting of GCaMP5 to VTA dopamine neurons. From Grosenick *et al.* (2016).

trol of neural activity in defined cell types during animal behavior (Grosenick *et al.*, 2016). Its incredible precision, in some cases at single-cell resolution, allows the possibility to guide activity in awake animals and provide a causal investigation of neural circuitry, see Fig. 13. While mostly used in rodents, these techniques are increasingly being used in primates as well to probe basic principles of neural function, and to test strategies for therapeutic interventions such as the interruption of seizures.

Meanwhile, technologies for simultaneously recording cell activity and targeting stimulation are constantly improving, and hence now allow the possibility for closed-loop control in animals. The very specificity of the stimulation and the targeted cells, means that at present specific design choices about intended outcomes have to be made. For instance, the same stimulation that evokes gamma oscillations (> 60 Hz) at the circuit level using a relatively slow opsin variant ChR2(H134R) cannot always reliably drive individual pyramidal cells at such frequencies. Still, the ability to use such stimulation to direct behavior in animals, suggests tremendous potential for closed-loop optogenetics to reveal mechanisms for cognition.

VII. EMERGING CONTROL METHODS WITH POTENTIAL UTILITY IN NEUROSCIENCE

Many of these recently introduced theoretical frameworks to model the control of brain activity rest on linear or simplified models of dynamics. While they already provide useful conceptual insights and analytical descriptions for controlling neural activity, the large repertoire of dynamics in the brain requires more flexible models to capture its complexity. To close this review, we focus on two broad directions of advances in network control

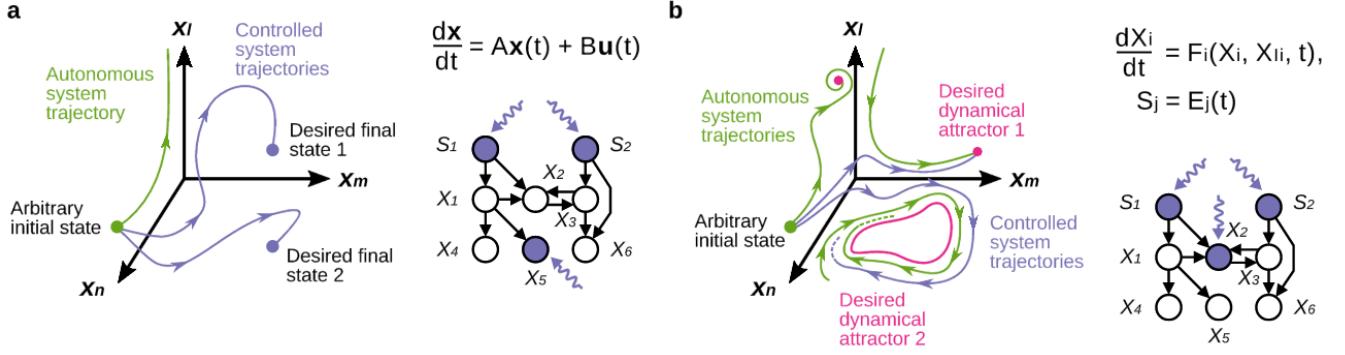


FIG. 14 Comparison between structural controllability and control using feedback vertex sets. (a) In structural controllability, the objective is to drive the network from an arbitrary initial state to any desired final state by acting on the network with an external signal $u(t)$. The dynamics are considered to be well-approximated by linear dynamics. (b) In feedback vertex set control the objective is to drive the network from an arbitrary initial state to any desired dynamical attractor (e.g., a fixed point) by overriding the state of certain nodes. From Zañudo *et al.* (2016).

theory that appear particularly relevant for addressing this gap. The first is the extension of network control theory to describe a broader range of dynamical regimes – such as non-linear dynamics or time-dependent control – or the study of control metrics to estimate the feasibility of control trajectories. The second examines new approaches in network control theory that exploit specific properties of the problem to better achieve desired targets, which may well differ based on the problem at hand. These include the use of perturbations, stochasticity in the system, or aspects of the network topology, to design control strategies.

A. Broader control regimes

1. Non-linear dynamics

Brain activity is highly nonlinear, which can be seen especially at the level of single neurons or small groups of neurons. A recent analytical development that is mathematically exact for a broad range of nonlinear dynamics is that of feedback vertex sets (FVS) (Fiedler *et al.*, 2013). It only requires a few conditions (e.g. continuous, dissipative, and decaying) that are typically satisfied by many real systems. This formalism identifies the set of nodes in a directed network that can control all the dynamics of the network and can steer it to the desired trajectories. Open-loop control applied to the nodes of an FVS allow for switching the dynamics of the whole system from one attractor to some other attractor.

Zañudo *et al.* (2016) provide an instructive discussion of the differences between structural controllability and control using FVS, as illustrated in Fig. 14. The authors use the FVS formalism to study several real networks. By comparing its predictions to those of classical structural controllability, they identify the topological characteristics that underlie the observed differences. In addition,

they apply the FVS formalism to study dynamic models of gene regulation, in which directed networks can be used to model gene interactions.

In cases where both the function and structure of the network are known, one can use simplified dynamical models to identify stable motifs that can control the dynamics of the network. Indeed, Zañudo and Albert (2015) demonstrate that such an approach need only be applied transiently for the network to reach and remain in the desired state. The authors illustrate this method using a leukemia signaling network and a network for cell differentiation, giving rise to several predicted interventions that are supported by experiments.

2. Time-dependent control

Given a possible lack of full information about the network, which is usually the case when one is estimating a brain network from empirical data, it is possible to identify strategies based on available data to define an uncertainty set containing all networks that are coherent with empirical observations. Indeed, Han *et al.* (2015) propose a method to control the spread of a viral epidemic, taking place in a directed contact network with unknown contact rates. They assume that they have access to time series data describing the evolution of the spreading process, and propose a data-driven optimization framework to find the optimal allocation of protection resources. This method is illustrated using partial data about the dynamics of a hypothetical epidemic outbreak over a finite period of time—paving the way for inferring control strategies based on limited observational data over finite periods of time. These or similar methods may be particularly relevant for the control of seizure spread in the human brain given that the “resource” of brain stimulation is limited by the fact that too much stimulation causes heating of the tissue and eventual cell

death.

Indeed, the question of cost and limited resources is further investigated by Li *et al.* (2016), who point out the possibility to take advantage of dynamically changing edges in a network to inform time-dependent control strategies, that may actually reach controllability faster than time-independent control strategies. This idea is based on the premise of energy savings in such strategies, by exploiting the changing topology to avoid energetically costly directions. For instance, they exert control towards the desired final state when the topology renders the energy cost acceptable, and pause when the topology makes the cost prohibitive. While suggestive of new designs for time-dependent control strategies that may prove more effective than static strategies, further work is needed to examine their relevance and feasibility in real neural systems.

3. Realistic control trajectories

Sun and Motter (2013) investigate the control of dynamical trajectories in practice and what determines their energetics or feasibility. In particular, they point to the condition number of the controllability Gramian (4) as crucial for understanding control in practice, even if the corresponding Kalman's controllability matrix is well conditioned. Furthermore, they point out that numerical control fails even for linear systems if the Gramian is ill conditioned, and that control trajectories are generally nonlocal in the phase space (see Fig. 15). Futher, they provide a condition for the numerical success rate of control strategies that depends on the number of control inputs, which they term the numerical controllability transition. Their work points towards additional criteria that would be relevant when considering the practicality of various control strategies in real systems.

B. Exploiting system properties

1. Compensatory perturbations or noise

It is important to note that the study of control of brain network dynamics could also benefit from other methods that target neither nodes nor edges but instead identify effective parameters to design new strategies for control. The advantage of such approaches is their applicability for realistic regimes including nonlinear dynamics or stochastic systems. One such method proposed by Cornelius *et al.* (2013) uses compensatory perturbations to steer the system to desired states: that is, perturbations to state variables that bring the system to the basin of attraction of the desired target state. The authors present methods to iteratively identify such compensatory perturbations, through consideration of the

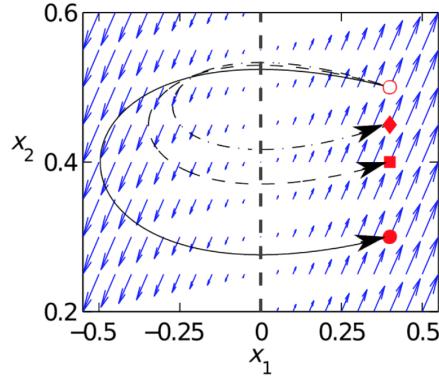


FIG. 15 Two-dimensional example of nonlocal trajectories. Example system $\dot{x}_1 = x_1 + u_1(t)$, $\dot{x}_2 = x_1$, where the curves indicate minimal-energy control trajectories for the given initial state (open symbol) and target states (solid symbols). Background arrows indicate the vector field in the absence of control. From Sun and Motter (2013).

physically admissible perturbations, and through nonlinear optimization on this space of possible changes. Their approach is effective in bringing the system to a desired target state even when this state is not directly accessible, as they demonstrated through the mitigation of cascading failures in a power grid and the identification of drug targets in a cancer signaling network.

Another such method identifies interventions that can reshape the topography of the underlying quasipotential in a desired way (Wells *et al.*, 2015). This is achieved by determining the minimum action paths—those followed by the likely noise-induced transition trajectories—and the corresponding transition rates between all pairs of stable states. By optimizing these transition rates, the authors effectively alter quasipotential barriers between different stable states, which could be achieved biologically through, for example, a genome editing approach. This proposal exploits the response of biological systems to noise to induce a desired cell state, and thereby to predict and control noise-induced switching in genetic networks. While this method is demonstrated on models of cell differentiation, it is potentially useful for control in other classes of noisy complex networks.

2. Network topology

Finally, understanding control in brain networks could benefit greatly from a better understanding of which topological features and symmetries determine the controllability of a network. Recent work on this front has been pioneered by Bianchin *et al.* (2015), who study the controllability degree of complex networks as a function of the network diameter and the weights. By examining the energy required by a group of nodes to control the network to a desired state, the authors find that networks

with a long diameter and anisotropic weights are easier to control than networks with a short diameter or isotropic weights. Here weights are defined to be isotropic if they allow a (control) signal to propagate equally in all directions, and to be anisotropic otherwise.

Separately, Ruths and Ruths (2014) discuss control profiles in real networks, by identifying topological features of the network (such as sources and sinks) that correlate with control properties. Building on these ideas, Campbell *et al.* (2015) show that the number of source and sink nodes, the form of the in- and out-degree distributions, and local complexity (e.g., cycles) shape the control profile in empirical networks. Other work by Pósfai *et al.* (2013) examines the effects of clustering, modularity and degree correlations on the minimal number of driver nodes required to control a network (similar to the problem posed by Liu *et al.* (2011)). They find that under certain conditions, only degree correlations have a discernible effect.

Lastly, DeVille and Lerman (2015) investigate analytical relationships between network modularity or symmetries, and the resulting dynamics. They show that continuous time network dynamics can be decomposed into collections of interacting local control systems — and that a class of maps called *graph fibrations* give rise to conjugate dynamical systems. Their work provides a robust mathematical formalism to generalize existing understanding such as the relationship between symmetries and synchrony, through the broad notion of modularity.

VIII. CONCLUSION

We have discussed many new developments in the exciting field of controlling brain network dynamics and more importantly, tried to highlight some of the many remaining open questions. This is an exciting time that has seen rapid theoretical and technological progress in methods of brain network control, or innovations that could be useful for brain network control. By outlining the potential in this young and emerging field, we hope to entice new practitioners and further efforts towards this important goal of controlling brain network dynamics, that has great implications for the bettering of our health and cognitive function.

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