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Beyond The Connectome: The Dynome

N. Kopell[1], **H. J. Gritton**[2], **M. A. Whittington**[3], and **M. A. Kramer**[1]

[1]Department of Mathematics and Statistics, Boston University

[2]Department of Biomedical Engineering, Boston University

[3]The Hull York Medical School, University of York

Abstract

The human connectome will provide a detailed mapping of the brain's connectivity, with fundamental insights for health and disease. However, further understanding of brain function and dysfunction will require an integrated framework that links brain connectivity with brain dynamics, as well as the biological details that relates this connectivity more directly to function. In this Perspective, we describe such a framework for studying the brain's "dynome" and its relationship to cognition.

It may seem ill-timed to be discussing post-connectome science just when connectomics has become a major initiative within neuroscience. Understanding the connectome presents many technical and theoretical challenges, which will deliver novel insights into brain function and dysfunction. However, it is already clear what some of the limitations of connectomics will be. Furthermore, the connectome can be - and indeed needs to be - studied at a very wide range of spatial scales, making any endpoint seem very far in the future. We will argue here that the neuroscience community needs to be thinking now about how to extend the insights that will emerge from the kinds of work highlighted in this special issue to incorporate additional features of brain dynamics and physiology; this is needed to address function and dysfunction of cognition. A shape for such a research program is already emerging in the study of fast time scale (~millisecond) brain processes, which is especially important when considering rapid changes in brain activity (e.g., during cognition) and to supplement the static observations and slower times scales available by other measurements (e.g., fMRI).

In general, connectomics refers to a comprehensive structural description of the human brain, rendered as a network (Sporns, 2013). These networks consist of two fundamental components: nodes and edges. A node is usually identified with a region of the brain, often taken in principled ways from knowledge of brain anatomy and function, and can vary in size and specificity, from the scale of a microscopic single neuron to a macroscopic brain

Corresponding author: Nancy Kopell, nk@math.bu.edu.

region; in general, how to best define a node remains an active research topic (Stanley *et al.*, 2013). An edge represents a connection between two nodes. In a *structural network*, an edge represents an anatomical connection between two brain elements. In a *functional network*, an edge represents the statistical association between activities recorded from separate brain elements (Park & Friston, 2013). The description of the anatomical connections (in some versions) is often called the "connectome", while the dynamic networks associated with brain activity during a particular brain state (such as attention or rest; Greicius *et al.*, 2003; Fox *et al.*, 2005; Bullmore & Sporns, 2009; Bressler & Menon, 2010) represents a "functional connectome".

In this essay, we emphasize that connections, even functional connections, do not provide information critical to understanding how the brain produces cognition. What is needed is not only what is connected, but how and in what directions regions of the brain are connected: what signals they convey and how those signals are acted upon as part of a neural computational process. As we describe below, the "how" is important for understanding the ways in which various parts of the brain combine their particular computations to support cognitive function. Indeed, we argue that how the brain generates temporal structure is critical to the ways in which signals are routed, combined and coordinated. We note that this viewpoint overlaps with the philosophy of (Bargmann & Marder, 2013), although we focus here more directly on observations from the vertebrate brain and rhythms.

Brain dynamics are hugely complicated, in ways that we are just beginning to chart. Measurements from EEG, MEG, ECoG, local field potentials, and single-unit recordings (both intra- and extra-cellular) are documenting complex temporal structures that are far from random and are both reproducible and specific to classes of cognitive activities (Engel *et al.*, 1997; Wang, 2010). Some of this structure is usually called "brain rhythms", which typically are broadly distributed across a frequency band. In the analysis of brain electric and magnetic field activity, standard peak frequencies range from somewhat below 1 Hz to well over 100 Hz (Buzsaki & Draguhn, 2004). Many sophisticated tools exist to characterize rhythms; however care must be taken to distinguish true brain rhythms from analysis artifacts (Kass *et al.*, 2005; R.E. Kass *et al.*, 2014). Individual neurons can fire (somewhat) coherently with the temporal structure of neuronal population activity (Fries *et al.*, 2007; Womelsdorf *et al.*, 2007), or not (Senior *et al.*, 2008; Manning *et al.*, 2009), in ways that can depend on the behavioral condition and the neuron type.

The existence of this specific and reproducible temporal structure motivates the search for a kind of functional connectome that relates directly to it. Statistical associations between the spatially averaged "activity" in separate brain areas typically do not provide insight into the mechanisms that support these associations. That is, functional connectomics can provide very insightful summary statistics describing how large-scale brain networks correspond to cognitive states and how they change with learning or disease processes, but this framework is typically not suited to describing or explaining the intricate cellular processes that take part in producing what we call cognition, or even suggesting mechanisms by which regions are coordinated.

More specifically, the description of the brain as nodes and edges de-emphasizes the questions of what signals get sent over the edges and how those signals are processed. Also, distinctions that are clear in such a network framework (nodes versus edges) can be unclear in brain tissue. For example, the local field potential (LFP), measured at a point in space, depends both on "node" activity that is local to the measurement and also nonlocal synaptic input along "edges" targeting that point in space; the LFP measurements do not distinguish these components, though clues can be obtained by current source density measurements or other techniques. We contend that, to understand the nature of a functional connection requires a more detailed look at the local dynamics of the nodes (that is, not considering them as points with "activity", but acknowledging more detailed physiological and dynamical structure), to understand how local processing is done, how it is regulated by neuromodulators, and how the language of signals coordinates multiple parts of the brain in cognitive tasks.

This expanded description of brain activity is what we call the "dynome". The dynome is the collection of experimental and modeling observations having to do with dynamical structure (and its physiological and pathophysiological implementation) in the brain and its relationship to cognition. It includes what is usually known as the functional connectome, but expands the notion to go beyond statistical associations to the mechanisms involved in producing and processing signals within the brain. In the dynome context, "understanding" brain activity means uncovering the functions and dysfunctions provided by the brain's temporal dynamics. Like the connectome, the dynome proposes a framework for a broad research program. Yet, the dynome does not have to be constructed *de novo*: there is already a body of work on which further efforts can be based, and in the next part of this essay we describe some of it. However, we note that, though much cognitively important dynamical structure has been uncovered, the field is still in its infancy.

What constitutes the dynome?

In this section we discuss a framework for constructing the dynome, along with examples of such work. Dynomics involves charting the dynamical structure of local and global networks, studied mainly *in vitro* and *in vivo* respectively, and connecting those dynamics to biophysical mechanisms and cognitively important computations via modeling of detailed neuron and network biophysics. This complements other approaches, including dynamical causal modeling, which tends to focus on more abstract, neural mass models (e.g., Kiebel *et al.*, 2009; Moran *et al.*, 2013), which may not reflect the biophysical properties critical to some neural computations. We focus, as invited, on brain rhythms, which reflect and influence spiking activity; however, dynamic processes can also happen in the absence of rhythmic brain activity (Ecker *et al.*, 2010; Renart *et al.*, 2010; Ainsworth *et al.*, 2012; Histed & Maunsell, 2014) and the dynome includes other temporal structures as well (Larson-Prior *et al.*, 2013).

Local temporal structure

By "local", we mean a network whose components are physically close and which participate in similar computations, as described by functional anatomy. This could be a single cortical column or a larger but related group of columns (e.g., hypercolumns in visual

cortex). This is similar to the idea of a “node”, but encompasses all the anatomical and physiological structure within the local network, including cortical layers, distinct neuronal populations, intrinsic currents, local synaptic connectivity, and responses to neuromodulation.

The dynamics within such a local network can be extremely complex. *In vitro* and *in vivo* preparations reveal the intrinsic properties of these local networks. The amount of reproducible temporal structure is astonishing, and the task of charting such structure is by no means finished. Structure found *in vitro* includes: Multiple mechanistically different versions of a rhythm in the same frequency band (Roopun *et al.*, 2010); Multiple mechanistically different rhythms in the same cortical region (Ainsworth *et al.*, 2011); Different rhythms appearing simultaneously in different cortical layers (Oke *et al.*, 2010; Ainsworth *et al.*, 2012); Different effects of neuromodulators on rhythms in different brain areas (Middleton *et al.*, 2008; Roopun *et al.*, 2008a); Switches in temporal structure with changes in activation (Roopun *et al.*, 2008b); Fast rhythms nested inside slower rhythms (Gloveli *et al.*, 2005; Carracedo *et al.*, 2013); Faster intrinsic rhythms suppressed by slower ones (Pietersen *et al.*, 2014). Some of this structure observed *in vitro* has also been found *in vivo*. For example, the properties of gamma rhythms as interactions of excitation and inhibition (Atallah & Scanziani, 2009; Cardin *et al.*, 2009), and laminar differences in rhythms (Buffalo *et al.*, 2011). Understanding the substrates and mechanisms that support these rhythms, their interactions, and their function, is one goal of dynomics.

In vivo, brain rhythms are rarely seen in isolation. Indeed, a widespread motif is that faster rhythms are nested in slower rhythms (Chrobak & Buzsaki, 1998; Lakatos *et al.*, 2005; Palva & Palva, 2007; Colgin *et al.*, 2009). Experiments and modeling have begun to illuminate the possible mechanisms of cross-frequency coupling, including an important role for inhibition (Wulff *et al.*, 2009). However, major challenges remain in detecting and understanding cross-frequency coupling. Quantitative characterization of cross-frequency coupling from *in vivo* recordings is fraught with difficulties (e.g., due to complicated, non-sinusoidal nature of brain activity (Kramer *et al.*, 2008b). Moreover, a meaningful understanding of cross-frequency coupling – beyond a biomarker of brain dynamics – requires knowledge of the biological mechanisms that support the observed activity in the different frequency bands expressed.

It remains to establish which aspects of *in vitro* dynamics manifest meaningfully *in vivo*, especially in the context of cognitive tasks. This is difficult, partly because *in vivo* recordings with behavior require the entire brain, which necessarily introduces uncertainty regarding important features that shape the observed dynamics (e.g., the neuromodulatory state of the area of interest, the nature of the inputs to the area, etc). *In vitro* experiments, on the other hand, sacrifice a direct link with behavior to allow controlled observations of the dynamics produced by a physically isolated area of interest. Though all spectral bands that are seen *in vitro* appear with remarkable consistency *in vivo*, we generally still do not know the underlying mechanisms of the *in vivo* rhythms. Moreover, the variety of mechanisms that support the same rhythm *in vitro* means that we cannot assume from the frequency of an observed rhythm the underlying physiology without, for example, local pharmacological

manipulation or carefully designed, neuron subtype-specific optogenetic/pharmacogenetic interference.

In order to address the issues of how dynamic structure affects cognitive computations, it is necessary to understand how the physiology of local regions gives rise to local rhythms and their interactions. The most thoroughly studied rhythms are the class of gamma (30–90 Hz) rhythms (Whittington *et al.*, 2000; Buzsaki & Wang, 2012). Though there are many subtleties to the underlying mechanisms and their consequences for spatiotemporal interactions of this set of rhythms, the basic phenomenon involves feedback inhibition from fast-spiking cells, notably parvalbumin-positive (PV+) cells, to pyramidal cells (in Pyramidal Interneuron Network Gamma or "PING") or to the inhibitory cells themselves (Interneuron Network Gamma or "ING"): The decaying feedback inhibition provides a window of opportunity for cells to fire, and the decay time of the inhibition is central in determining the period of the rhythms. Other slower brain rhythms appear to depend more on voltage-dependent intrinsic currents, especially M-currents (outward currents suppressed by activation of muscarinic receptors) (Roopun *et al.*, 2006) and h-currents (inward currents activated by hyperpolarization) (Luthi & McCormick, 1998). Both of these currents are sensitive to inhibition on fast time scales, so feedback inhibition from fast-spiking PV+ cells (with fast decay times) and somatostatin-positive (SOM+) cells (with synaptic decay kinetics several times slower than that of PV+ cells), can affect multiple intrinsic currents, leading to complex local dynamics in which the intrinsic time scales of the activation and deactivation of the currents - combined with synaptic input - shape the period. At still lower frequencies (< 4 Hz), even slower inhibition ($GABA_B$ receptor-mediated) and metabolic/metabotropic effects can support the slower timescales. Modeling has been done for many of the above frequencies to illuminate the roles of the various currents and the effects of neuromodulators in supporting and disrupting neuronal rhythms (Whittington *et al.*, 2000; Destexhe & Sejnowski, 2003; Rotstein *et al.*, 2005; Tort *et al.*, 2007; Kramer *et al.*, 2008a; Vierling-Claassen *et al.*, 2010; Skinner, 2012; Lee *et al.*, 2013; Cannon *et al.*, 2014).

These observations only partially illustrate the tremendous complexity in local brain dynamics. However, this complexity is not arbitrary. There is structure to the complexity induced by neurobiology, as there is in the connectome, with much of that structure left to be uncovered.

Temporal structure and cognition

There is now a large and growing literature documenting the different electrophysiological rhythms associated with distinct cognitive operations, occurring across different spatiotemporal scales, and within broadly and narrowly defined anatomical regions (for reviews see Engel *et al.*, 2001; Womelsdorf & Fries, 2006; Siegel *et al.*, 2012). Studies over the last two decades have revealed that rhythms can support a variety of cognitively-relevant functions from enhancing thalamocortical inputs locally (Le Masson *et al.*, 2002; Lakatos *et al.*, 2008) to enabling two or more different regions to be bound together through coherence, thus enhancing feature discrimination or memory encoding (Fries, 2005; Sejnowski & Paulsen, 2006; Buffalo *et al.*, 2011; Igarashi *et al.*, 2014). Cognitive tasks often encompass a multitude of discrete processes that co-occur simultaneously in different brain regions.

Dynomics focuses on understanding these processes, how they are coordinated, and the consequences of their disruption. Despite the complexity of these questions, some progress has been made, revealing insight into the dynamics of cognition, as we describe in the examples below.

Cognitive processes often begin with the presentation of multimodal task-relevant stimuli, and rhythms seem to play a key role in the integration of these signals (Senkowski *et al.*, 2008; Hipp *et al.*, 2011). This process is dependent on specialized regions being actively engaged during task performance, and studies from humans have revealed that large-scale networks are recruited and synchronized at a particular frequency band(s) in a region specific manner (Senkowski *et al.*, 2008). The brain rhythm proposed to be most instrumental to task-based functional connections between neuronal populations in different brain areas is the set of beta (12–30 Hz) rhythms (Donner & Siegel, 2011). This set is also the most mysterious: there appear to be a large number of mechanistically different versions of these rhythms, produced in different parts of the nervous system (Cannon *et al.*, 2014). These rhythms may involve different classes of cells, and use synaptic excitation and/or inhibition, as well as intrinsic currents (Roopun *et al.*, 2006; Kopell *et al.*, 2011). Other slower frequency ranges have also been found to be important for macroscale interactions. Most notably, low frequency delta rhythms (1–4 Hz) are known to coordinate large portions of the brain (Fujisawa & Buzsaki, 2011; Nacher *et al.*, 2013). Some of this coordination is done through subcortical structures, notably the thalamus and the basal ganglia (Amzica & Steriade, 1998; Lopez-Azcarate *et al.*, 2013; Antzoulatos & Miller, 2014).

Faster rhythms are generally thought to play a prominent role in localized processing, usually within a particular region or even within a cortical column; again, the most well studied oscillations are gamma rhythms associated with attention. Gamma oscillations play a prominent role in stimulus detection locally by modulating spike timing relative to a specific phase of the local field potential (Fries *et al.*, 2001; Bichot *et al.*, 2005). This process is thought to improve signal discriminability by elevating firing rates to near saturation levels and by decreasing spike-count variability (Masuda & Doiron, 2007; Mitchell *et al.*, 2007). In addition to local processing, gamma rhythms support cross-regional coupling, particularly as it relates to attentional and working memory networks. For example, as demands on attention increase, different association areas also show strongest coupling between one another at gamma frequencies (Gregoriou *et al.*, 2009) and demands on attention can also recruit other frequency bands that interact with gamma oscillations through cross-frequency coupling (Lakatos *et al.*, 2008).

Other frequency bands are often coordinated or coupled between regions during cognitive tasks and the strength of coupling at a given frequency band between two regions can be modulated by task conditions (Buschman & Miller, 2007). In this sense, multiple networks, all associated with different frequency bands, may contribute to the same task at task-relevant time points through different rhythms (Palva *et al.*, 2010). Brain rhythms also appear in cortical and subcortical structures whose coordination is essential for certain types of sensory perception and learning. Multiple frequency bands can contribute to this process, and the level of synchronization across large scale networks can be predictive of both sensory perception and task performance (Hipp *et al.*, 2011). Functional connectivity

between the striatum and prefrontal cortex, for example, has been shown to strengthen as rules associated with categories are acquired in a category-specific manner (Antzoulatos & Miller, 2011; 2014). This coupling, particularly in the beta frequency range, seems to be important for selecting task rules and dissociating ensembles associated with rule relevant behavior from overlapping neuronal populations (Buschman *et al.*, 2012). These examples suggest that rhythms are dynamically modulated by task demands and they can change over the course of learning. Furthermore, cross-frequency coupling across structures important for different aspects of task performance may set the stage for cooperation among neuronal ensembles that are recruited depending on task conditions (Tort *et al.*, 2008).

While some rhythms may be better suited to enable change during learning, other rhythms may be important for stability once learning has occurred. Studies from hippocampal slices reveal that calcium entry through NMDA receptors or voltage-gated calcium channels provide the basis for both LTP and LTD depending on the frequency with which the input arrives (Bear & Malenka, 1994), and recent studies have revealed that the nesting of gamma rhythms in hippocampal theta rhythms support memory encoding and retrieval depending on the phase of the theta cycle (Colgin *et al.*, 2009; Tort *et al.*, 2009; Igarashi *et al.*, 2014). Modeling work has suggested that the interaction of gamma and theta rhythms are important for promoting spike-timing dependent plasticity through NMDA receptors (Lee *et al.*, 2009). Just as importantly, other rhythms have been suggested to promote stabilization and the continuation of on-going processes, the most prominent being beta oscillations in theories where beta is important for maintaining the status quo (Engel & Fries, 2010).

The ubiquity of brain rhythms, their specificity, and their dynamic nature strongly suggest their importance in cognition and behavioral outcome. The question then remains: through what mechanism can rhythms be regulated with the specificity to support and coordinate discrete aspects of cognitive operations both temporally and spatially? We suggest that part of the answer to this question must involve the primary neuromodulator systems. Neuromodulators can act locally or globally in ways that have profound influences on overall network function. Widespread regulation by neuromodulators is most evident in conditions of sleep onset or sleep transitions, where specific rhythms come to characterize these states (McGinty & Harper, 1976; Kayama *et al.*, 1992; Carter *et al.*, 2012). Neuromodulators, however, can also function to convey information in a very discrete and targeted way by communicating information about task relevant stimuli to some regions of neocortex and not others (Parikh *et al.*, 2007; Howe *et al.*, 2013) and by promoting oscillations at specific frequency bands in a region specific manner (Roopun *et al.*, 2010).

As described above, by changing physiology, neuromodulators change dynamics which, in turn, changes the processing of inputs. Hence, an important function of neuromodulators may be to change what regions are “on-line”; emerging evidence suggests that neuromodulators effectively regulate what inputs a region can “hear “ (Disney *et al.*, 2007; Lee *et al.*, 2013). Slice physiology experiments combined with modeling have elucidated a mechanism by which cholinergic mediated changes in signaling can support different cognitive functions through rhythm modulation; for example, pharmacology experiments in visual cortex first noted that cholinergic signaling has the potential to regulate the direction of information flow within cortical columns based on differences in muscarinic and nicotinic

receptor expression across two classes of inhibitory (LTS and FS) interneurons (Xiang *et al.*, 1998). Modeling built upon this finding provides a functional mechanism through which the emergence of deep layer beta-oscillations, associated with periods of top-down attention, could be explained by the enhanced excitability of slow-inhibitory interneurons in the presence of acetylcholine (Lee *et al.*, 2013). Other modeling studies have also offered insight into the details of stimulus competition where neuromodulators are essential to recruiting interneuron networks to promote gamma rhythmicity (Borgers *et al.*, 2008) or to promote synaptic weakening (Lee *et al.*, 2009). Future insight into cognitive function will depend on understanding the mechanisms by which neuromodulators change physiological processes in a way that recruits or alters rhythms during cognition.

Bridging the scales: physiology and modeling

Most of the work that has been done so far on fast temporal structure (such as brain rhythms) has focused on two categories: either finding the biophysical bases of brain rhythms or charting the association of cognitive activity with rhythms. By contrast, there has been much less work attempting to understand how, or even if, the physiological properties underlying fast dynamics are used in cognitive computations. This section describes some of that work and the kinds of questions that need to be addressed.

A central question concerns how the signals that are transmitted along the anatomy of the connectome are heard (or not), and how these transmitted signals interact with local dynamics to transform and coordinate local activity. The investigation of that question is often done via modeling. For example, we know that unpatterned input can give rise to gamma rhythms (Borgers & Kopell, 2005) and that gamma rhythms are ideal for the creation of cell assemblies (Harris *et al.*, 2003) and their protection against distractors (Olufsen *et al.*, 2003; Borgers *et al.*, 2005; 2008). The ability of gamma rhythms to facilitate such a computation through competition comes directly from the physiological properties of the gamma rhythm: it is the feedback inhibition underlying its formation that allows the most activated cells to fire in unison and suppress activity of other cells via the feedback inhibition. Another rhythm whose physiology is important to transmission and coordination is a form of the beta 1 rhythm: In rodent association cortex *in vitro*, the superficial layers produce a gamma rhythm in the presence of the glutamate receptor agonist kainate, and the deep layers produce a beta 2 (25 Hz) rhythm; when the kainate is partially removed by an antagonist after a period in which plasticity takes place, the gamma and beta 2 rhythms are replaced in all layers by a beta 1 oscillation (15 Hz) (Roopun *et al.*, 2008b). In this rhythm, the activation is passed back and forth between the superficial and deep layers via inhibitory rebound. Modeling has shown that such a temporal pattern of activity has the ability to maintain a representation of an input beyond the duration of a stimulus, and coordinate cells assemblies from earlier and later inputs (Kramer *et al.*, 2008a; Kopell *et al.*, 2011); this maintenance is not possible in computational models when gamma-mediated cell assemblies are coordinated only by common inhibition in the superficial layers (Borgers *et al.*, 2005; 2008). Furthermore, relationships exist between the gamma and beta frequency bands; for example, signals that are transmitted at beta frequency can be transformed to produce higher power in the gamma frequency, leading to gain control of input. (Lee *et al.*, 2013). In general, the physiology of brain rhythms, especially connected with feedback inhibition, is

believed to be important for creating the right phase relationship for coordination (Fries, 2005; Cannon *et al.*, 2014) and therefore supportive of cognitive computations (Roopun *et al.*, 2010).

The above question is centrally involved in the relationship between a network's structural connectivity and the dynamic functional connectivity associated with a cognitive process (Honey *et al.*, 2010; Woolrich & Stephan, 2013). In addressing that relationship, a natural approach is to simplify, for example, by examining simple oscillator models embedded in a network. However, an oscillator model typically consists of only one degree of freedom for the oscillator, its phase, which is manipulated by temporal input. For oscillations produced by the brain's networks, there are myriad internal degrees of freedom, including participation of any given cell on a given cycle and the state of all the conductances of each cell at any given time. Thus, the literature on responses of simple oscillators to temporal input can give some direction, but not a complete picture. Therefore, to understand the relationship between the brain's functional and structural networks, more biophysically realistic models are required. In that direction, one approach is to simulate neural population activity on a static anatomical network. This modeling approach has been used, for example, to suggest important contributions of general features (such as signal transmission delays and noise) to the organization of dynamic resting state functional networks (Deco *et al.*, 2011). An even more complex modeling approach is to utilize detailed biophysical models of neural activity, embedded in an anatomical network. This approach requires much greater computational effort but may be essential to examine the effects on functional connectivity that arise from the actual biological dynamics of cognitive function.

The available modeling and physiology is just the beginning of investigations under the framework of the dynome. For example, it is not known why there are so many different forms of beta rhythm, but reasonable conjectures include that a) regions that produce - or resonate to - a given frequency can respond in a stronger way to input from a similar frequency (Lee *et al.*, 2013); b) the kinds of computations done in the various regions are facilitated best by different biological implementations of the same rhythm; c) the various rhythms can be independently modulated, leading to flexibility in computation (Somogyi *et al.*, 2003) and d) different mechanisms impart different phase sensitivities to input, so a set of beta rhythm generators may all have statistically identical frequencies, but respond very differently to a shared spectral profile of input. To understand if this is correct requires knowledge of how each region responds to its temporally patterned input. A critical feature is that the impact of an input on a brain region is not generic; the signal traveling along axons to some region can have effects on the target that would not occur if the same input went to a different region. To understand the impact of a neuronal input, we need to know features of the targeted region, including: what classes of cells are targeted, the time scales and nature (excitatory or inhibitory) of the synaptic currents, the intrinsic currents of the target cells, the state of the extracellular environment at the target, and the neuromodulators present.

Interdependence of dynamics and connectomics

We have emphasized the importance of dynamics - and the physiological implementation of these dynamics - in understanding the cognitive computations performed by the brain. The signals created and routed throughout the brain are carried by physical pathways that are studied by connectomics. However, the consideration of the more extensive notion of "functional connection" provided by dynomics – a notion that includes an understanding of the physiology that supports dynamic coordination - helps to clarify what sorts of connectomics information might be most useful. A very detailed anatomical description of a piece of tissue that does not specify the kind of information needed to understand the effect of neuronal input (see end of last section) cannot be used to address the kinds of questions posed in the dynome. We need to be able to add physiological knowledge and functional significance to the anatomical results. This situation is complicated by the interrelationship between physical connectivity and network dynamics. For example, as highlighted above, some dynamics are closely related to neuronal plasticity underlying memory (Tort *et al.*, 2009; Igarashi *et al.*, 2014), and both the frequency and timing of neuronal events is critical for expression of this (e.g., Bear & Malenka, 1994; Bi & Poo, 1998). As such, plasticity induces structural changes in neuronal connectivity (Bailey & Kandel, 1993), so changes in temporal structure are very likely to change the connectome.

In 'non-plastic' model systems the close interrelationship between connectivity and dynamics can also be readily observed. Even random connectivity graphs have discrete dynamic signatures associated with activity propagating within them (Traub *et al.*, 2001) and different dynamic signatures appear to be correlated with different conduction delays (Kopell *et al.*, 2000; Tort *et al.*, 2007; Deco *et al.*, 2009). This is one reason why the study of the dynome needs to be engaged in parallel with that of the connectome. Like connectomics, this program involves a daunting amount of work, but that work is well specified, and any addition to our knowledge driven by investigator initiated research consistent with this program is likely to have immediate implications for understanding how coordination happens within the nervous system.

As new technology has supported construction of the connectome, so will new technology facilitate continuing study of the dynome. Emerging technologies for the observation of the brain's dynamic activity include high-density electrode recordings (Viventi *et al.*, 2011), optogenetic tools (Chow *et al.*, 2010; Klapoetke *et al.*, 2014), and large-scale three-dimensional imaging of single neuron activity (Prevedel *et al.*, 2014). These technologies make now an opportune time to study the dynome. To do so will also require the development and application of data analysis tools to characterize activity (R.E. Kass *et al.*, 2014) including interacting rhythms across temporal and spatial scales (Tort *et al.*, 2010), as well as principled approaches to link neuronal data with computational models (Huys & Paninski, 2009; Meng *et al.*, 2014).

Dynamics and diseases

Finally, many neurological diseases involve dysregulation of brain rhythms (Whittington *et al.*, 2011; McCarthy *et al.*, 2012; Uhlhaas & Singer, 2012). For some of these, there are also

pathological changes in structural and functional connectivity that come under the purview of connectomics (Kramer & Cash, 2012; McCarthy *et al.*, 2012; Anticevic *et al.*, 2013). However, the relationship between the anatomical changes and the cognitive changes in neurological disease remains unclear. By contrast, dynomics provides a path to explanation that may engender new interventions driven by the neurobiology. The path has the following form: 1) changes in physical and anatomical properties (via genetically-related neurodevelopmental changes, post-birth insults, or neurodegenration later in life) produce changes in local brain dynamics; 2) changes in local dynamics change the profile of interactions between brain regions; 3) such changes are pathological for producing the kinds of computations important for cognitive functioning. A working example of this approach can be found in attempts to link primary pathology with cognitive deficit in schizophrenia: Many markers for function of fast spiking interneurons are dysregulated in this disorder (Lewis *et al.*, 2012). As a consequence local network dynamics – particularly gamma rhythms - are disrupted in specific brain regions (Cunningham *et al.*, 2006; Pafundo *et al.*, 2013); Gamma rhythms are mediators of mainly local functional interactions (see above) and their disruption in schizophrenia is associated with selective loss of short-range functional connections in patients with cognitive deficit (Alexander-Bloch *et al.*, 2013).

The promise of such a view of neurological disease is that it can suggest ways to change the dynamics even when underlying disease etiology is not currently understood or able to be changed. In this case, therapy directly affects the dynamical brain pathology. A very promising technology for such interventions is deep brain stimulation, which has become a standard treatment option for medication resistant Parkinson's disease symptoms. Brain stimulation is also being investigated for a variety of other diseases such as depression (Holtzheimer & Mayberg, 2011; Holtzheimer *et al.*, 2012), obsessive compulsive disorder (de Koning *et al.*, 2011), and epilepsy (Leuchter *et al.*, 2012). The understanding of how such interventions could work will depend on a description of how the dynamics are being perturbed in these technologies. In particular, if the region of the brain being stimulated is a hub, the stimulation is apt to effect regions of the brain in ways that depend on hub dynamics and connectivity.

Can we "understand" the brain without studying the mechanisms of its (fast) dynamics?

It might be argued that the sorts of details we are describing above are important only for the implementation of principles supported by the brain, and these principles can be described in terms of networks of nodes and edges. The above examples suggest that this is unlikely. First of all, in understanding what might support a computation involved in cognition, we need to know what the "wetware" is capable of. Secondly an immersion in the physiology supporting temporal dynamics suggests mechanisms that would not be obvious if one were thinking abstractly about "computation" and rhythms; as discussed above, different mechanisms may support the same rhythm, and therefore respond to input, or changes in neuromodulation, in different ways.

Indeed, the functional connectome (as described in a graph) is known to be dynamic (Bassett *et al.*, 2011; Chu *et al.*, 2012). However, it largely remains to be understood how the rich diversity of observed functional network dynamics are regulated. Here fast temporal

dynamics can provide essential cues. As discussed above, the details of the local dynamics can be essential to how a signal is “heard” and processed, both locally at a node, and non-locally throughout the network. Thus, all modulations that change fast time scale dynamics impact not only the statistically related activities captured in functional networks, but also details of how signals are routed, combined and coordinated over the brain’s “wires”. Since cognitive outcomes depend on stages of processing that can happen in tens to hundreds of milliseconds, we need a framework that allows assessment of information at this timescale to be considered. The dynome is exactly such a framework.

We are not advocating implementation of the dynome framework as a mega-project to be addressed on a highly condensed time scale. Rather, we propose continued efforts to balance the research activity of the neuroscience community, in which brain dynamics (including fast dynamics such as rhythms, as well as other non-oscillatory dynamics) are studied along with connectivity to reveal how such dynamics facilitate the flexible and dynamic coordination of brain regions. Further understanding the brain’s “dynome” would benefit from larger-scale consortium projects, and individual investigator-driven projects to advance our knowledge and understanding of brain processing. We have given some details about what research already exists and what areas could benefit from more attention. To understand the brain’s dynome, knowledge of the biological details that support the brain’s dynamics remains critical. However, we do not propose solely a bottom-up approach focused only on these biological details. Instead, we envision a feedback loop between: (i) observations of large-scale neurological phenomena *in vivo*, (ii) implementation of the basic elements of these phenomena in experimental laboratory models in vitro, and (iii) analytical and predictive computational models that feed back into experimental models to assess their validity against the large-scale observations. Like connectomics (and unlike the original aims of genomics), the goals are open-ended and the progress from many specific research projects will be of use.

There is another aspect of dynomics that makes this framework different from that of connectomics: the study of brain dynamics has the potential to bridge insights across levels of function. Studying how genes affect anatomy and physiology leads naturally to the study of small network dynamics; any information we have about small network activity provides the basis for further understanding how networks interact to produce meso- and macro-level behavior. Interactions of large networks are critical to understanding cognition and pathologies of cognition. We do not think this work needs to (or can) be finished through a linear progression of stages, from molecules to behavior; rather, work must occur at multiple levels simultaneously. We have employed the “omics” label here to emphasize the inclusive nature of this framework to understand brain dynamics. We propose that coordination of efforts to understand the mechanisms of brain dynamics across spatial and temporal scales will drive new understanding of brain function and dysfunction in cognition.

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