



# The energy landscape underpinning module dynamics in the human brain connectome<sup>☆</sup>



Arian Ashourvan<sup>a,b</sup>, Shi Gu<sup>a,c</sup>, Marcelo G. Mattar<sup>a,d</sup>, Jean M. Vettel<sup>a,b,f</sup>, Danielle S. Bassett<sup>a,e,\*</sup>

<sup>a</sup> Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104, USA

<sup>b</sup> U.S. Army Research Laboratory, Aberdeen Proving Ground, MD 21005, USA

<sup>c</sup> Applied Mathematics and Computational Science Graduate Program, University of Pennsylvania, Philadelphia, PA 19104, USA

<sup>d</sup> Department of Psychology, University of Pennsylvania, Philadelphia, PA 19104, USA

<sup>e</sup> Department of Electrical & Systems Engineering, University of Pennsylvania, Philadelphia, PA 19104, USA

<sup>f</sup> Department of Psychological & Brain Sciences, University of California, Santa Barbara, CA 93106, USA

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## ABSTRACT

Human brain dynamics can be viewed through the lens of statistical mechanics, where neurophysiological activity evolves around and between local attractors representing mental states. Many physically-inspired models of these dynamics define brain states based on instantaneous measurements of regional activity. Yet, recent work in *network neuroscience* has provided evidence that the brain might also be well-characterized by time-varying states composed of locally coherent activity or functional modules. We study this network-based notion of brain state to understand how functional modules dynamically interact with one another to perform cognitive functions. We estimate the functional relationships between regions of interest (ROIs) by fitting a pairwise maximum entropy model to each ROI's pattern of allegiance to functional modules. This process uses an information theoretic notion of energy (as opposed to a metabolic one) to produce an energy landscape in which local minima represent attractor states characterized by specific patterns of modular structure. The clustering of local minima highlights three classes of ROIs with similar patterns of allegiance to community states. Visual, attention, sensorimotor, and subcortical ROIs are well-characterized by a single functional community. The remaining ROIs affiliate with a putative executive control community or a putative default mode and salience community. We simulate the brain's dynamic transitions between these community states using a random walk process. We observe that simulated transition probabilities between basins are statistically consistent with empirically observed transitions in resting state fMRI data. These results offer a view of the brain as a dynamical system that transitions between basins of attraction characterized by coherent activity in groups of brain regions, and that the strength of these attractors depends on the ongoing cognitive computations.

## Introduction

The human brain is a complex dynamical system comprised of billions of neurons that continuously communicate with one another. Although the vast number of processing units challenges exact prediction of single neuron activity, recently developed statistical models reveal a characteristic meso-scale structure whereby sets of larger-scale brain regions display coherent activity at rest. These sets form putative functional modules characterized by locally dense functional connectivity, and include the default mode, salience, attention, fronto-parietal, cingulo-opercular, motor, visual, auditory, and subcortical systems (Salvador et al., 2005; Meunier et al., 2009; Yeo et al., 2011; Power

et al., 2011). Interestingly, although within-module functional connectivity is in general higher than between-module functional connectivity, these patterns fluctuate dynamically over short periods of time (Ma et al., 2014; Kiviniemi et al., 2011; Watanabe et al., 2013), both at rest and during task performance (Cole et al., 2014; Mattar et al., 2015; Bassett et al., 2011, 2013b, 2015; Braun et al., 2015).

The existence of functional modules – as measured using graph theory – was first reported nearly a decade ago (Salvador et al., 2005; Meunier et al., 2009), and these initial reports were swiftly corroborated by studies using complementary methodologies ranging from co-activation analysis to independent components analysis. A natural question following the observation of these modules was “What do they

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\* Corresponding author at: Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104, USA.  
E-mail address: [dsb@seas.upenn.edu](mailto:dsb@seas.upenn.edu) (D.S. Bassett).

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do? And how are they recruited as we go through life performing a variety of functions?" To address these questions, dynamic community detection methods were developed and applied to neuroimaging data, revealing the fact that modules reconfigure in support of working memory (Braun et al., 2015, 2016), reinforcement learning (Gerraty et al., 2016), visuo-motor learning (Bassett et al., 2011, 2013b, 2015), and linguistic processing (Chai et al., 2017; Doron et al., 2012a). Module reconfiguration at rest has also been reported as a marker of aging and development (Betzel et al., 2015). These studies collectively demonstrate that module reconfiguration is a hallmark of healthy brain function (Telesford et al., 2016), and recent evidence suggests that it is a marker that is altered in psychiatric disease, even providing an intermediate phenotype of schizophrenia (Braun et al., 2016).

Despite the extensive work demonstrating the presence and cognitive utility of dynamic module reconfiguration, fundamental insights into the mechanisms or rules by which modules interact with one another over time have remained elusive (Mattar et al., 2015; Khambhati et al., 2016). Evidence suggests that module reconfiguration may be driven by glutamatergic signaling (Braun et al., 2016), affect and arousal (Betzel et al., 2016a), and may provide a substrate for cognitive control (Khambhati et al., 2016), supporting a delicate balance between domain-general and domain-specific function (Fedorenko and Thompson-Schill, 2014a). Although these observations support the biophysical relevance of the phenotype, they do not provide computational theories for its existence. Indeed, the development of a theory explaining and predicting module dynamics would be particularly important in informing studies of its cognitive specificity, transmitter-level drivers, and role in psychiatric disease.

One potential route towards a mechanistic theory of brain network dynamics is to consider probabilistic models that were originally developed in the field of statistical mechanics. Pair-wise maximum entropy models (MEM), for example, have proven very useful in estimating and predicting spiking activity in neurons (Shlens et al., 2006), local field potentials from neuronal assemblies (Tang et al., 2008), and blood oxygen level dependent signals (BOLD) from brain regions using functional magnetic resonance imaging (fMRI) (Watanabe et al., 2013, 2014b, 2014c). When a pair-wise MEM accurately fits empirical data, it implies that the observed activation pattern can be described as a combination of each unit's independent activation rate plus the units' joint activation rates. When a pair-wise MEM does not accurately fit empirical data, it implies that higher order interactions (such as triplets) or nonlinearities contribute to the observed dynamics. Importantly, pair-wise MEMs can be used to infer an *energy* landscape of brain activity during task performance. Here the term energy is used in an information theoretic sense, and it does not have a direct relation to metabolic energy or to a formal Hamiltonian. The energy landscape is characterized by basins of attraction representing common brain states, as well as the paths or trajectories along which the brain moves as it transitions from one basin to another. The architecture of this energy landscape has proven useful in predicting individual differences in human perception and behavior (Watanabe et al., 2014c).

In traditional applications of MEMs to neurophysiological data, a brain state is defined as a pattern of activity across brain regions (or similarly, a neural state is defined as a pattern of activity across neurons). However, these notions of brain state are agnostic to the patterns of communication or synchronization linking brain regions, and therefore are unable to address the question of how one pattern of coherent activity could evolve into another pattern of coherent activity. To address this question, we explicitly define a *network* state as the pattern of module allegiance across brain regions, and we use this definition to examine transitions between network states. We test the hypothesis that mesoscale structure in dynamic functional connectivity patterns is well explained by pairwise interactions between communities. The null hypothesis that we seek to reject is that such patterns cannot be explained without contributions from higher-order interac-

tions between communities. To test this hypothesis, we construct a time-dependent network by linking 10 regions of interest by the low frequency (0.06–0.19 Hz) wavelet coherence between their time series in a given time window. We use a community detection algorithm to identify groups of brain regions that show stronger coherence with one another than they do to other groups. We refer to these groups as network communities, and we fit the MEM to each ROI's time series of the state of co-occurrence in the same community with other ROIs. This approach enables us to identify network states that form local energy minima, as well as features of the energy landscape surrounding these minima. More generally, this approach highlights the dynamic functional roles that different ROIs play in network states and the transitions between them.

Our results reveal the presence of local minima on the energy landscape, many of which are characterized by the activation of a single community. Interestingly, different ROIs show different patterns of membership to these single community states. Visual, attention, sensorimotor, and subcortical ROIs tend to form a single functional community (Class-I). The remaining ROIs form the putative executive control network (Class-II) and the putative default mode and salience network (Class-III). To further study these dynamics, we modeled the transitions of single community states over the landscape of the states' energy via a random walk process. Our numerical simulations of basin transitions using an MCMC random walk predict empirical frequencies and probabilities of state transitions with high fidelity for Class-I and Class-III ROIs, and with lower fidelity for executive control (Class-II) ROIs. In addition, empirically the executive control ROIs also display higher entropy energy landscapes, linking diverse state classes, and utilizing uniform transition probabilities across basins. These features support the unique role of executive control regions in diversifying the brain's dynamic functional repertoire across many cognitive processes via their rich and flexible dynamic functional fingerprint.

## Results

### *Distillation of drivers of resting state dynamics*

Maximum entropy models are optimally constructed to fit patterns of interactions between *relatively few* brain regions. We therefore sought to distill the drivers of resting state dynamics to a few well-chosen regions of interest. Specifically, in resting state fMRI data acquired from 20 healthy adult individuals in a multiband imaging sequence, we extract 10 regions of interest in a data-driven fashion as centroids of independent components (see Methods). These regions include the cuneus, precuneus, dorsomedial gyrus, caudate, right and left rostral middle frontal cortex, precentral prefrontal cortex, medial orbitofrontal cortex, and *pars triangularis* (see Table 1). We use these regions as proxies of their respective cognitive systems, spanning visual, dorsal attention, sensorimotor, basal ganglia, executive control, dorsomedial prefrontal cortex, default mode, and salience systems, respectively. For explicit maps of each independent component, and the representative region chosen, see SI3.

**Table 1**  
Regions of interest and their corresponding ICN.

ICN	Lausanne ROI (scale 125)
1. Visual	189 Cuneus.1
2. Dorsal Attention (Attn)	184 Precuneus.1
3. Sensory/Motor (SM)	147 Precentral.3
4. Basal Ganglia/Thalamus (BG)	228 Caudate
5. Left Executive Control Network (LECN)	128 Rostral middle frontal.2
6. Right Executive Control Network (RECN)	15 Rostral middle frontal.2
7. Rostral Middle Frontal Cortex (rmFC)	130 Rostral middle frontal.4
8. Dorsomedial Prefrontal Cortex (dMPFC)	135 Superior frontal.3
9. Default Mode Network (DMN)	122 Medial orbitofrontal.1
10. Salience	124 Pars triangularis.1

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