Towards causal mechanisms in large-scale brain function

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Overview

With the advent of neuroimaging and, more recently, the generation of high- resolution imaging and stimulation technology through the NIH BRAIN Initiative, neuroscience now has access to a plethora of tools to study brain activity at multiple levels. However, most human neuroimaging studies continue to focus on identifying correlations, and multiple barriers need to be addressed to advance the field towards causal mechanisms.

Recently, a new research sub-field has begun to take shape – developing and testing theoretical computational models of regional and whole-brain function to understand fundamental neural mechanisms and dysfunction in brain disorders. By then introducing pharmacological, neurostimulation-based, or physiological state manipulations, such mechanistic models can then be afforded richer empirical context and move close towards validation. For example, a recent study developed a whole brain computational model of serotonergic function, by combining structural and functional connectivity measures with a 5HT2A receptor availability map using PET imaging. LSD administration was then used to test the impact of pharmacological manipulation on brain dynamics the energy landscape in the brain.

For human studies, such approaches offer the potential to advance the field towards causal mechanistic models of brain function and an opportunity to study complex neuropsychiatric disorders for which animal models may be inadequate. In this session, we will highlight speakers who have applied novel theoretical modeling tools combined with experimental manipulations towards a mechanistic understanding of brain and behavior at the network level.

Lecture 1: *The multi-scale impacts of the ascending arousal system on complex, adaptive neural dynamics*
Mac Shine Presenter

To effectively interact with the brain requires an appreciation of the multi-scale organisation of the nervous system. Changes in cognitive function do not arise directly from the modulation of individual neurons, but are mediated by population dynamics in mesoscopic neural ensembles. Understanding this multiscale mapping is an important but nontrivial issue. In my talk, I will bridge microscopic and macroscopic levels of description using computational models that map classic neuromodulatory processes onto systems-level models of neural activity. I will highlight recent work that used spontaneous functional magnetic resonance imaging data to study phasic bursts in two key hubs within

the ascending arousal system – namely, the noradrenergic locus coeruleus and cholinergic basal forebrain – and linked these subcortical dynamics to low-dimensional energy landscapes, network topology, and spatiotemporal travelling waves. I will then compare these approaches to dynamic network-signatures of optogenetic stimulation of the locus coeruleus in anaesthesized mice. These results highlight the cross-scale effects of the ascending arousal system on the dynamic network architecture of the brain.

Lecture 2: *Psychedelics acutely flatten the brain's energy landscape*
Amy Kuceyeski Presenter

Psychedelics like lysergic acid diethylamide (LSD) and psilocybin offer a powerful method with which to perturb human brain activity patterns and explore causal mechanisms. The RElaxed Beliefs Under Psychedelics (REBUS) model postulates that 5-HT2a receptor agonism allows the brain to explore its dynamic landscape more readily, as suggested by more diverse (entropic) brain activity in the acute stages directly after administration of these substances. Formally, this effect is theorized to correspond to a reduction in the energy required to transition between different brain-states, i.e. a "flattening of the energy landscape." However, this hypothesis remains thus far untested. Here, we leverage network control theory to map the brain's energy landscape, by quantifying the energy required to transition between recurrent brain states using previously acquired functional magnetic resonance imaging data under LSD, psilocybin, and placebo. In accordance with the REBUS model, we show that LSD and psilocybin reduce the energy required for brain-state transitions, and, furthermore, that LSD's reduction in energy correlates with more frequent state transitions and increased entropy of brain-state dynamics. Through network control analysis that incorporates the spatial distribution of 5-HT2a receptors, we demonstrate the specific role of this receptor in flattening the brain's energy landscape. This work validates fundamental predictions of the REBUS model of psychedelic action. More broadly, by combining receptor-informed network control theory with pharmacological modulation, this work highlights the potential of this approach in studying the impacts of targeted neuropharmacological manipulation on brain activity dynamics.

Lecture 3: *Why do we think of consciousness as a scalar magnitude?*
Enzo Tagliazucchi Presenter

The human brain is an incredibly complex system of interacting nonlinear units. Among the multiple functions of the brain, consciousness is frequently considered the pinnacle of this complexity. In spite of its suspected origin as an emergent from this complexity, however, consciousness seems to be organized alongside a suspiciously simple unidimensional continuum. Both in clinical and basic research, we speak of "levels of consciousness" and we compare them across several different brain states. But why does this approximation work? In this talk we argue that consciousness appears to be scalar only because global brain activity can be compressed into a one dimensional manifold that can be parametrized by a single scalar. Using whole-brain modeling combined with methods from deep learning, we will provide evidence supporting this hypothesis by showing that such a manifold exists and can be retrieved from fMRI data.

Lecture 4: *How Brain Circuits Function in Health and Disease: Understanding Brain-Wide Current Flow*
Kanaka Rajan Presenter

Dr. Rajan and her lab design neural network models based on experimental data, and reverse-engineer them to figure out how brain circuits function in health and disease. They recently developed a powerful framework for tracing neural paths across multiple brain regions— called Current-Based Decomposition (CURBD). This new approach enables the computation of excitatory and inhibitory input currents that drive a given neuron, aiding in the discovery of how entire populations of neurons behave across multiple interacting brain regions. Dr. Rajan's team has applied this method to studying the neural underpinnings of behavior. For example, CURBD has been used to explore the underlying biology driving adaptive and maladaptive behaviors in the face of stress. With this framework Dr. Rajan's team probes for mechanisms at work across brain regions that support both healthy and disease states - as well as identify key divergences from multiple different nervous systems, including zebrafish, mice, non-human primates, and humans.