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Toward understanding thalamocortical dysfunction in schizophrenia through computational models of neural circuit dynamics

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ABSTRACT

The thalamus is implicated in the neuropathology of schizophrenia, and multiple modalities of noninvasive neuroimaging provide converging evidence for altered thalamocortical dynamics in the disorder, such as functional connectivity and oscillatory power. However, it remains a challenge to link these neuroimaging biomarkers to underlying neural circuit mechanisms. One potential path forward is a "Computational Psychiatry" approach that leverages computational models of neural circuits to make predictions for the dynamical impact dynamical impact on specific thalamic disruptions hypothesized to occur in the pathophysiology of schizophrenia. Here we review biophysically-based computational models of neural circuit dynamics for large-scale resting-state networks which have been applied to schizophrenia, and for thalamic oscillations. As a key aspect of thalamocortical dysconnectivity in schizophrenia is its regional specificity, it is important to consider potential sources of intrinsic heterogeneity of cellular and circuit properties across cortical and thalamic structures.

1. Introduction

A key research challenge in biological psychiatry is to link systems-level biomarkers of a disorder to underlying alterations in neural circuits hypothesized to play a role in the pathophysiology. Schizophrenia (SCZ) is a disorder for which clinical neuroscience has leveraged a range of experimental modalities to discover systems-level neuroimaging markers based on the dynamics of neural activity in large-scale brain networks. These biomarkers can be observed noninvasively in patients using modalities such as functional magnetic resonance imaging (fMRI), electrocorticography (EEG), and magnetocorticography (MEG). Yet the mechanistic links between these emergent systems-level dynamics and underlying synaptic and neuronal processes are poorly understood. Mechanistic understanding of how synaptic or cellular pathologies can give rise to neuroimaging findings and clinical symptoms is a key step toward rational design of therapeutics acting at the synaptic level. This knowledge gap between mechanisms and biomarkers arises because of the need for ways to bridge the fine-grained neurophysiology of brain microcircuits and the properties of macrocircuits studied in clinical research using noninvasive neuroimaging.

One emerging approach to bridging this gap is to leverage advances in computational neuroscience to generate rigorous and testable hypotheses related to the neural bases of psychiatric pathophysiology (Anticevic et al. 2015c; Wang and Krystal 2014). More specifically, this "Computational Psychiatry" approach can harness computational models of neural systems that incorporate key neuronal and synaptic details, allowing mechanistic characterization of how cellular-level disruptions may propagate upward to produce systems-level dysfunction. Computational models of neural circuits models can therefore yield dissociable systems-level predictions for distinct synaptic-level perturbations, thereby allowing macroscopic measures in humans or animals to support inferences about microscopic pathophysiologies. This approach has translational potential, as it stands to inform the one-to-many mapping problem in neuroimaging research, i.e., the difficulty to map a statistical map from neuroimaging onto a given upstream cellular-level mechanism that may be 'driving' such an effect. Circuit models are developed and constrained by experiments in pre-clinical animal models at different levels, such as synaptic kinetics and spiking activity. By then examining which changes in the biologically interpretable model parameters map onto clinical findings, we can develop testable mechanistic hypotheses for specific circuit disruptions in the disease.

There is mounting evidence that SCZ can be characterized by widespread abnormalities of connectivity and interactions in brain circuits across a range of spatial scales, from microcircuits to large-scale networks. The thalamus is a critical node in large-scale brain networks, and thalamocortical interactions are emerging as a key component of "dysconnectivity" in SCZ. In this piece, we review recent experimental functional neuroimaging findings of altered dynamics of thalamocortical circuits in SCZ during task-free, spontaneous activity at rest or during sleep. We then describe biophysically-based computational modeling approaches that can be readily extended to study altered thalamocortical dynamics in SCZ. These computational approaches include models of large-scale resting-state networks, which are well

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suited to resting-state fMRI measurements, as well as biophysically-detailed models of neurons and microcircuits in the thalamus, which generate oscillatory activity that can be related to EEG/MEG measurements at timescales that fMRI cannot resolve. One salient aspect of thalamocortical dysconnectivity observed with fMRI is its regional specificity, implicating bidirectional changes in thalamic interactions with different cortical regions and preferentially more severe alterations in specific thalamic nuclei (e.g., the prefrontal-projecting thalamic nuclei). It is therefore critical to consider the heterogeneity of circuit properties across cortical areas and thalamic nuclei, which may contribute to the observed preferential disturbances arising from disease-related perturbations. Finally, we suggest future directions for computational and experimental research to probe the mechanistic basis of thalamocortical dysfunction in SCZ.

2. Recent experimental findings of thalamocortical dynamics in schizophrenia

Given the highly convergent and divergent connectivity between thalamus and cortex, it is important to characterize the topography of connectivity alterations across large-scale networks in SCZ. FMRI allows whole-brain measurement of the low-frequency blood oxygen level-dependent (BOLD) signal. Resting-state functional connectivity MRI (rs-fcMRI) has emerged as a powerful tool for characterizing the intrinsic functional architecture of brain network dynamics at rest. Its emerging use is built upon the hypothesis that neuropsychiatric conditions, such as SCZ, are brain disorders that affect computations across large-scale neural networks. Complementing fMRI, other noninvasive methods such as electroencephalography (EEG) and magnetoencephalography (MEG) can provide greater temporal resolution of neural dynamics. Because the thalamus is implicated in specific dynamical modes, such as oscillatory sleep spindles, these measures can relate specifically to thalamic function. In this section, we describe some recent studies revealing biomarkers of altered neural dynamics in SCZ, using fMRI, EEG, and MEG, which are particularly well suited to computational modeling.

2.1. Resting-state BOLD functional connectivity

In recent years, a number of independent rs-fcMRI studies have characterized thalamocortical connectivity in SCZ, converging on a robust set of alterations (Welsh et al. 2010; Woodward et al. 2012; Anticevic et al. 2014a, 2014b, 2015a; Woodward and Heckers 2015). Thalamocortical connectivity alterations in SCZ are bidirectional and regionally specific (Fig. 1A). Relative to controls, patients with SCZ exhibit lower connectivity between the thalamus and regions of prefrontal cortex, striatum, and cerebellum (Anticevic et al. 2014a). In contrast, in SCZ the thalamus is over-connected with sensory-motor cortex. There is a strong relationship between thalamic over- and under-connectivity across subjects. Specifically, there is a strong negative correlation between them, suggesting a common mechanism may underlie both the over- and under-connectivity patterns (Anticevic et al. 2014a, 2015a; Woodward and Heckers 2015).

Regional specificity of dysconnectivity extends to the thalamus as well. Thalamus is divided into multiple distinct nuclei with different input and output synaptic connection patterns with cortex. Of particular interest here is the mediodorsal (MD) nucleus, which is strongly interconnected with prefrontal cortex. The MD nucleus appears to preferentially drive the thalamocortical dysconnectivity pattern described above (Welsh et al. 2010; Anticevic et al. 2014a, 2014b) (Fig. 1B,C).

SCZ is a neurodevelopmental disorder with a complex illness progression. Neural biomarkers can alter dramatically across prodrome, early-stage, and chronic stages. Interestingly, this pattern—thalamic under-connectivity with prefrontal cortex and over-connectivity with sensorimotor cortex—appears to be present across illness stages. Woodward and Heckers (2015) found it to be present in both chronic and early-stage individuals with psychosis (SCZ/schizoaffective disorder and bipolar I disorder with psychotic features). Anticevic et al. (2015a) found this pattern to be present in young help-seeking individuals at clinically high risk for psychosis, and particularly strong for the subset of patients who converted to full-blown illness at a later time. These recent findings collectively indicate that the observed thalamic dysconnectivity is not consistent with typical confounds that emerge

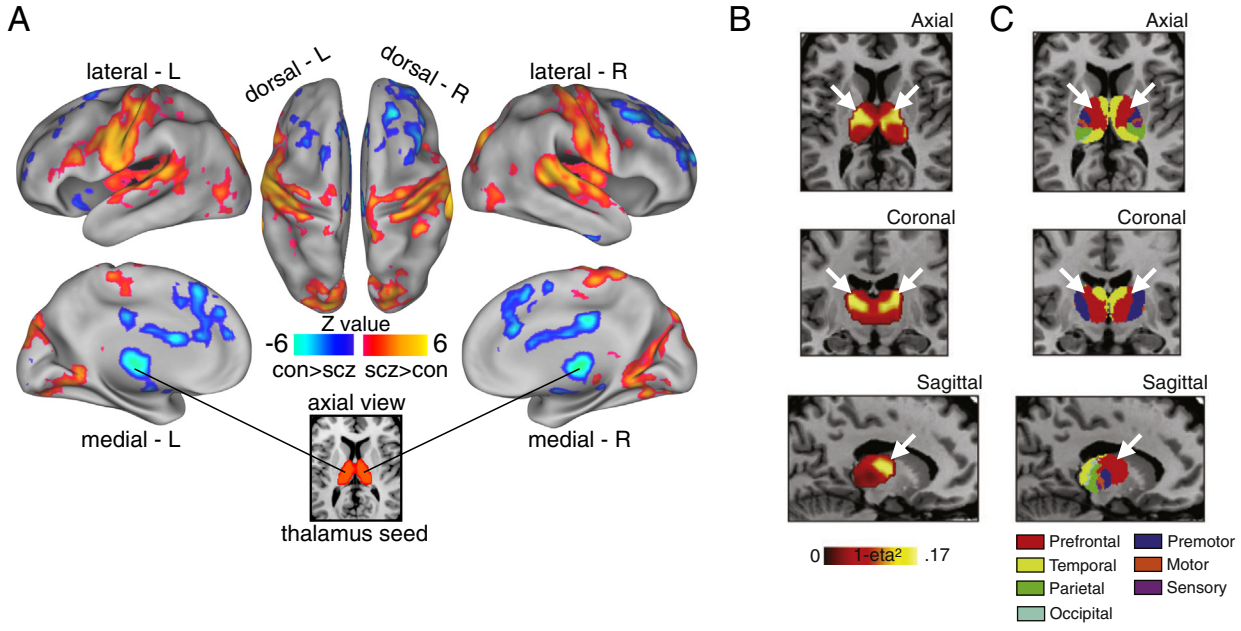

Fig. 1. Thalamic dysconnectivity in SCZ. (A) Significant whole-brain between-group differences in thalamic connectivity between healthy controls (CON) and individuals with schizophrenia (SCZ). Red-orange (blue) foci mark areas where patients exhibited stronger (reduced) thalamic coupling. (B) Intrinsic thalamic dysconnectivity pattern based on group dissimilarity. The brightest voxels are associated with highest between-group differences. (C) Thalamus subdivisions based on the FSL thalamic atlas, defined by their connectivity to different regions of cortex. White arrows indicate the correspondence between thalamic regions with greatest dysconnectivity in SCZ and thalamic subdivisions strongly connected with prefrontal cortex (red). Adapted from Anticevic et al. (2014a). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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