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Commentary

Converging Evidence for Abnormal Thalamic Oscillations in Schizophrenia

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The thalamic nuclei are subcortical structures that are thought to play a key role in integrated brain activity. Reciprocal thalamocortical and corticothalamic projections provide the circuitry that could underlie cortical oscillations that integrate and coordinate brain function, whereby control exerted at the thalamus could influence activity across the cortex (1). Such a role has been postulated for the thalamic reticular nucleus (TRN). Receiving afferents from both thalamocortical and corticothalamic projections, it sends inhibitory gamma-aminobutyric acidergic projections to other thalamic nuclei but no projections to the cortex, in contrast to all other thalamic nuclei. This permits the TRN to control oscillations across large sectors of cortex, which might underlie major state changes in brain function, such as sleep. Indeed, sleep spindles—powerful, brief 12- to 15-Hz oscillations around 1 second in duration, a defining characteristic of stage 2 sleep—have been localized to TRN generators. Sleep spindles have also been linked to memory consolidation, suggesting an important role in complex behavior (2).

As centrally located, subcortical structures involved in the integration of brain activity, the thalamic nuclei have long been implicated in schizophrenia, a disorder with diverse manifestations and notable impairments in cognition, emotion regulation, and psychomotor function (3). Postmortem studies of the thalamus have reported reduced cell counts, including abnormalities of the TRN, such as reduction in the perineuronal nets and the parvalbumin-positive inhibitory interneurons that these nets surround (4). Neuroimaging studies have reported reductions in thalamic size (although not consistently), reduced task-induced activation, and more recently, altered patterns of connectivity between the thalamus and cortex (5). Given the critical role that the thalamus is thought to play in oscillatory activity, resting-state studies of connectivity may provide an important window on this aspect of dysfunction. However, a weakness of resting-state functional connectivity magnetic resonance imaging (rsfcMRI) is that the low-frequency fluctuations measured in these studies (0.1–0.01 Hz) have an unclear relationship with the oscillatory activity measured in typical electrophysiological studies, which is typically in the range of 1 to 80 Hz. In general, there have been few links made between these two modalities of measurement, and many questions remain about the functional role of the altered thalamocortical connectivity patterns identified in schizophrenia.

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Baran *et al.* (6) report results from a multimodal study of brain function that provides an important link between thalamic connectivity and electrophysiology. Baran *et al.* (6) conducted a polysomnographic study to measure sleep spindle activity in 26 patients with schizophrenia as well as rsfcMRI studies in these same patients to measure thalamocortical connectivity. The published literature shows that patients with schizophrenia exhibit a variety of disturbances in sleep architecture, and more recent work, including studies performed by this group, has shown that patients with schizophrenia exhibit a reduction in sleep spindle counts. Although the published literature is not entirely consistent, spindle counts have been related to positive symptoms and cognitive dysfunction, and they do not appear to be affected by medication status. In addition, at least one report has identified reduced spindle counts in relatives of patients with schizophrenia, suggesting that the finding may constitute an endophenotype that is linked to the liability to schizophrenia (7). Baran *et al.* (6) replicate previous findings of reduced spindle density in patients with schizophrenia, which adds to this growing literature.

Baran *et al.*'s (6) key finding was that spindle counts exhibited an inverse relationship with thalamocortical connectivity. Healthy subjects typically exhibit a negative correlation between the thalamus and the sensorimotor cortex, whereas patients with schizophrenia exhibit positive "hyperconnectivity" of thalamocortical connectivity to the sensorimotor cortex, which Baran *et al.* (6) replicate here. An important aspect of their finding is that this relationship—lower spindle counts correlating with greater thalamocortical connectivity—was found in both patients and the unmedicated, healthy control subjects (n = 29 available for analysis), suggesting that the relationship between spindle generators in the TRN may be a part of the mechanism whereby the thalamus controls connectivity with parts of the cortex in rsfcMRI. As Baran *et al.* (6) point out, parvalbumin-positive interneurons are concentrated in the part of the TRN projecting to the sensorimotor cortex, and the correlation they find with thalamocortical connectivity appeared in the left sensorimotor cortex (as well as the left superior temporal gyrus). Their findings provide some evidence that the oscillatory function of the TRN may also be related to the low-frequency fluctuations in the rsfcMRI signal, which reveals thalamocortical hyperconnectivity with the sensorimotor cortex.

Although this is an important finding, it is, as Baran *et al.* (6) acknowledge, only one report from a relatively small sample that needs replication. We still have more questions than answers about how these oscillations—at both time scales of sleep electroencephalography and rsfcMRI—work to organize complex brain function. It is tempting to speculate that the hyperconnectivity between the thalamus and the sensorimotor cortex represents a lack of the normal inhibition the TRN might

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exert on thalamic nuclei. While this is one plausible interpretation, the hyperconnectivity may reflect an absence of the normal negative correlation between the thalamus and the sensorimotor cortex. Negative correlations, also called anticorrelations, can be strong correlations with a 180° phase shift. They are poorly understood phenomena of rsfcMRI studies, and they can also be artificially inflated by preprocessing steps, such as global signal regression [which Baran *et al.* (6) did not use]. In the context of the present findings, it may be that the TRN interneurons are capable of inhibition but with impaired timing, leading to weak spindles and reduced capacity to set up the anticorrelated, low-frequency oscillations measured by rsfcMRI.

Another finding from their study may shed some light on the role of the negative correlations in the healthy control subjects. Baran *et al.* (6) found that the larger the negative correlation, the greater the degree of positive correlation in the cortex (confined to the region of group differences between patients and control subjects). There was no such relationship in the patients with schizophrenia. This finding—a relatively novel analysis—is consistent with the idea that the normal, anticorrelated relationship of the thalamus to the sensorimotor cortex works to facilitate correlations within that sector of cortex—a coordinating relationship that is absent in schizophrenia. They did not report any relationship of spindle density with cortical intracorrelation, and the meaning of this particular metric is open to other interpretations. However, it is an easy enough analysis to test in other data sets, with both the thalamus and any other seed, to see if this is a general network property in rsfcMRI or something specific to the thalamus.

What Baran *et al.* (6) did not replicate were reports of hypoconnectivity between the thalamus and the prefrontal cortex (8,9). At least one of these previous reports (9) used a thalamic seed centered on the medial dorsal nucleus, which comprises the bulk of the thalamocortical projections to the prefrontal cortex, whereas Baran *et al.* (6) used a larger seed at the center of the thalamic nuclei. In the unthresholded connectivity maps, one can see a reduced positive correlation signal in medial frontal regions of the schizophrenia patients, which did not reach the threshold for significant group differences. Given the poor reliability of rsfcMRI signals, they may have been underpowered to detect hypoconnectivity. The important point here is that the story with the thalamocortical connectivity in schizophrenia probably comprises both hyper- and hypoconnectivity.

As the majority of putative endophenotypes and disease biomarkers seem not to respect DSM boundaries, Baran *et al.*'s (6) findings raise the question as to the specificity of their results. Although this group has not found sleep spindle deficits in nonpsychotic psychiatric disorders, such deficits have been reported in a range of neurodevelopmental and neurodegenerative disorders (7). An intriguing hypothesis is that parvalbumin-positive interneurons—fast-spiking, metabolic-demanding neurons—are especially vulnerable to oxidative stress, and damage to these interneurons may constitute a common etiopathophysiology of serious neuropsychiatric disorders (4). Alternatively, gene pathways that are concentrated in the thalamus may lead to errors in neural dynamics and timing, which may set up a vulnerability for multiple psychiatric conditions (10). The findings reported here, focusing on the TRN, add to a growing body of literature that should stimulate additional research to address these possibilities in schizophrenia and other neuropsychiatric disorders.

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Article Information

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