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EDITORIAL

# Thalamus as a "hub" to predict outcome after epilepsy surgery

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The role of the thalamus in mediating seizure activity has been investigated for decades.[1] In 1952, Penfield[2] proposed "centrencephalic" interactions as an integral part not only of generalized but also of focal automatisms. The dynamic integration between the centrencephalic system and cerebral cortex was hypothesized as pivotal for normal brain function, as well as a mechanism for seizure propagation. The concept was later hotly debated, and generalized seizures with 3-Hz spike wave discharges were considered mainly centrencephalic.[1]

Recently, the thalamus has again gained increased importance in focal epilepsy. Intermittent stimulation of the anterior nucleus of the thalamus decreases the seizure frequency in focal epilepsy.[3] Since Penfield's time, we have made tremendous progress in imaging the brain. However, our concepts of epileptic seizures and epilepsy may not have progressed at the same pace.

In this issue of *Neurology*®, He et al.[4] present a study using resting-state MRI to predict the outcomes of epilepsy surgery. They apply graph theory to measure the "hubness" of 45 nodes per hemisphere and their integration into the global network. They compare seizure-free with not seizure-free patients after epilepsy surgery and with normal controls. All patients had similar temporal lobectomies. One significant finding is that not seizure-free patients had a greater number of and more important connections in the ipsilateral and contralateral thalamus, while seizure-free patients were equivalent to normal controls. No differences were found in other examined regions, including the contralateral temporal lobe. Nodes in seizure-free and not seizure-free patients differed in the richness of connections (degree centrality) and in the influence of the node on the network (eigenvector centrality) but not in modulating signals between nodes (between centrality). Thalamic nodes played a more important role in network integration in not seizure-free patients compared to seizure-free patients, as measured by global efficiency. This demonstrates that patients are less likely to be seizure-free if the thalamus, ipsilateral and contralateral, is integrally part of the epileptic network and functions as a major "hub."

Because graph theory measures are theoretical constructs, the authors confirmed their findings with an additional analysis in the supplementary materials. Graph theory measures do not necessarily reflect anatomic connections. It remains to be discussed which one of the interthalamic structures is most relevant to the maintenance or recurrence of seizures and at least theoretically would be the most advantageous target for stimulation approaches for the treatment of epilepsy.

This work nicely complements animal studies in which thalamocortical connections are necessary to sustain seizure activity in a cortical injury model of epilepsy, a well-defined model of focal epilepsy.[5] In addition, seizures in the injury model could be controlled by optogenetically modulating thalamocortical pathways in a closed-loop paradigm.[5] Other rodent studies found that involvement of thalamic structures correlated with seizure severity in a kindling model of seizures.[6]

In the work of He et al., thalamic measures of hubness and network integration predicted outcome after epilepsy with greater accuracy than routine clinical measures (74% vs 56%). Another recent study focused on volumetric and diffusion tensor imaging and correlated it to surgical outcome.[7] In that study, only pulvinar and dorsomedial thalamic volume compared to volumes of any other structures (including volume of resection) correlated with outcome after surgery.[7] Thalamic and subcortical structures are involved in secondary generalization of focal seizures.[8] As a clinical measure, a history of secondary generalization is a negative predictor of outcome of seizures. It is possible that if generalization occurs, larger networks are involved in the maintenance of seizures. Along these lines, resting-state fMRI measures and clinical variables may nicely complement each other.

In addition to clinical measures, the study by He et al. may give us another tool to predict outcome after epilepsy surgery.[9] It seems that network models of epilepsy increasingly substitute for purely focal models of epilepsy.[10] We could imagine a model of epilepsy in

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which seizures would be divided into seizures with larger and smaller networks to predict outcome after epilepsy surgery. In clinical practice, it seems premature not to proceed to surgery if such measures of increased hubness in the thalamus are present. However, additional predictive measures could prove helpful in counseling patients. In the past, MRI was mainly predictive insofar as whether a lesion was present or not; additional resting-state MRI may give us more precise predictive measures.[9]

Furthermore, the He et al. study supports the concept of treating seizures with stimulation of thalamic targets after unsuccessful surgery. In the limited experience with stimulation of the anterior thalamic nucleus after unsuccessful epilepsy surgery, stimulation decreased seizure frequency to an extent similar to that of patients without previous surgery.[3]

As Penfield[2] already suggested 65 years ago, the thalamus and thalamocortical connections are of great importance even in focal or temporal lobe epilepsy. Thalamocortical connections play a larger role in the epileptic network than previously assumed, and they are certainly worthy of further investigation.

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