Epilepsy Currents
2020, Vol. 20(3) 130-131

DOI: 10.1177/1535759720909336
journals.sagepub.com/home/epi
SAGE

# When the Brakes Fail: Basal Ganglia and Seizure Generalization

**Disrupted Basal Ganglia–Thalamocortical Loops in Focal to Bilateral Tonic-Clonic Seizures**

He X, Chaitanya G, Asma B, et al. *Brain*. 2020;143(1):175-190. doi:10.1093/brain/awz361.

Focal to bilateral tonic-clonic seizures are associated with lower quality of life, higher risk of seizure-related injuries, increased chance of sudden unexpected death, and unfavorable treatment outcomes. Achieving greater understanding of their underlying circuitry offers better opportunity to control these seizures. Toward this goal, we provide a network science perspective of the interactive pathways among basal ganglia, thalamus and cortex, to explore the imprinting of secondary seizure generalization on the mesoscale brain network in temporal lobe epilepsy. Specifically, we parameterized the functional organization of both the thalamocortical network and the basal ganglia–thalamus network with resting state functional magnetic resonance imaging in 3 groups of patients with different focal to bilateral tonic-clonic seizure histories. Using the participation coefficient to describe the pattern of thalamocortical connections among different cortical networks, we showed that, compared to patients with no previous history, those with positive histories of focal to bilateral tonic-clonic seizures, including both remote (none for $>1$ year) and current (within the past year) histories, presented more uniform distribution patterns of thalamocortical connections in the ipsilateral medial-dorsal thalamic nuclei. As a sign of greater thalamus-mediated cortico-cortical communication, this result comports with greater susceptibility to secondary seizure generalization from the epileptogenic temporal lobe to broader brain networks in these patients. Using interregional integration to characterize the functional interaction between basal ganglia and thalamus, we demonstrated that patients with current history presented increased interaction between putamen and globus pallidus internus, and decreased interaction between the latter and the thalamus, compared to the other 2 patient groups. Importantly, through a series of "disconnection" simulations, we showed that these changes in interactive profiles of the basal ganglia–thalamus network in the current history group mainly depended upon the direct but not the indirect basal ganglia pathway. It is intuitively plausible that such disruption in the striatum-modulated tonic inhibition of the thalamus from the globus pallidus internus could lead to an under-suppressed thalamus, which in turn may account for their greater vulnerability to secondary seizure generalization. Collectively, these findings suggest that the broken balance between basal ganglia inhibition and thalamus synchronization can inform the presence and effective control of focal to bilateral tonic-clonic seizures. The mechanistic underpinnings we uncover may shed light on the development of new treatment strategies for patients with temporal lobe epilepsy.

## Commentary

Most people in medicine or the neurosciences have some familiarity with basal ganglia circuitry. The outputs of the direct and indirect pathways, including projections from globus pallidus interna (GPi), exert tonic inhibitory influence onto the ventral anterior and ventral lateral thalamus, essentially "putting the brakes" on cortical input that may lead to exaggerated or unintentional motor activity.[1] Dysfunction of basal ganglia circuitry plays an important role in movement disorders and certain neuropsychiatric disorders. However, the potential role of basal ganglia in epilepsy, and specifically seizure propagation, has received far less attention.

In the highlighted work by He and colleagues,[2] the authors posit that impaired inhibitory interactions between basal ganglia and thalamus may contribute to abnormal cortico-thalamic synchronization that leads to secondary seizure generalization in temporal lobe epilepsy (TLE). To test this hypothesis, they performed a resting-state functional magnetic resonance imaging (fMRI) study of 96 patients with drug-resistant TLE, including individuals with a recent, distant, or absent history of focal to bilateral tonic-clonic seizures. The investigators then used a network analysis approach to estimate cortico-thalamic and basal ganglia–thalamic interactions between patient groups and matched controls. They observed relatively high participation coefficient values across thalamic nuclear groups in all TLE patients, but notably higher values in the ipsilateral medial dorsal thalamus in patients with a remote or recent history of generalized seizures compared to those

without such a history. This may suggest a greater propensity for thalamocortical synchronization ipsilateral to the seizure focus in individuals having generalized seizures. Interregional integration of the basal ganglia–thalamus network was then explored, revealing abnormally increased connectivity between the striatum and GPi, and reduced interactions between GPi and thalamus in patients with recent seizure generalization. This observation suggests increased inhibition within the direct pathway of the basal ganglia associated with decreased inhibition of the basal ganglia upon the thalamus, which may thus increase the propensity for seizure propagation in patients.

One method to highlight in this study is the use of community detection-based statistics, which while not necessarily novel in the study of complex networks, has been underutilized in the epilepsy literature. The authors point out that while pairwise measurements of functional connectivity between basal ganglia and thalamus did not reveal clear differences between patient subgroups, network-based analysis helped uncover abnormal interregional integration involving these key regions. In addition, the authors utilized a relatively novel approach involving simulated disconnection to better define which basal ganglia pathway is aberrant in patients with generalized seizures. In this analysis, connectivity values between basal ganglia structures in the direct or indirect pathway were systematically set to zero prior to reapplying community detection, revealing that connections involving the direct pathway, but not indirect pathway, contribute to the detected GPi integration differences.

One factor to consider in the highlighted study is that subcortical connectivity differences between patients group may be confounded by other disease-related factors beyond seizure generalization. For instance, patients without generalized seizures in this study were less likely to have normal anatomical MRI and had a somewhat shorter duration of epilepsy than those with any history of seizure generalization grouped together. Fortunately, the authors did account for these and other potential confounders using regression. It is also notable that the segmentation methods for regions of interest varied in the study, whereas independent component analysis was used to segment functionally independent regions in the striatum and thalamus, while smaller structures such as GPi and the subthalamic nuclei were defined anatomically. However, this is unlikely to markedly influence the findings observed.

Overall, the work by He and colleagues builds upon prior fMRI studies by this group which revealed larger perturbations in bilateral thalamocortical connectivity in TLE patients with generalized seizures compared to those with focal seizures alone.[3] Other fMRI studies in TLE patients have also demonstrated functional connectivity abnormalities in seizure propagation networks involving the anterior thalamic nuclei as well as thalamic arousal nuclei with broad neocortical projections such as central lateral nucleus and pulvinar.[4,5] The basal ganglia has received much less attention than thalamus in this field, but one study using single photon emission computed tomography did uncover increased cerebral blood flow during seizure generalization that was most consistent in both thalamus and basal ganglia.[6] Furthermore, basal ganglia atrophy has been described in epilepsy patients with generalized seizures,[7] and cortico-striatal synchronization has been noted in stereo-electroencephalographic recordings during focal seizures.[8] While thalamic nuclei are often targeted for neurostimulation in drug-resistant epilepsy,[9,10] one may contemplate whether basal ganglia pathways might be explored as neuromodulation targets to prevent seizure propagation when seizure cessation is not possible. What is clear from the study by He et al, however, is that given the key role of the basal ganglia as the "brakes" of the brain, its circuits warrant greater attention in the study of epilepsy and seizure generalization.

*By Dario J. Englot*


## ORCID iD

Dario J. Englot https://orcid.org/0000-0001-8373-690X


## References


1. DeLong M, Wichmann T. Changing views of basal ganglia circuits and circuit disorders. *Clin EEG Neurosci*. 2010;41(2):61-7.
2. He X, Chaitanya G, Asma B, et al. Disrupted basal ganglia-thalamocortical loops in focal to bilateral tonic-clonic seizures. *Brain*. 2020;143(1):175-190.
3. He X, Doucet GE, Sperling M, Sharan A, Tracy JI. Reduced thalamocortical functional connectivity in temporal lobe epilepsy. *Epilepsia*. 2015;56(10):1571-1579.
4. Gonzalez HFJ, Chakravorti S, Goodale SE, et al. Thalamic arousal network disturbances in temporal lobe epilepsy and improvement after surgery. *J Neurol Neurosurg Psychiatry*. 2019;90(10):1109-1116.
5. Morgan VL, Rogers BP, Abou-Khalil B. Segmentation of the thalamus based on BOLD frequencies affected in temporal lobe epilepsy. *Epilepsia*. 2015;56(11):1819-1827.
6. Blumenfeld H, Varghese GI, Purcaro MJ, et al. Cortical and subcortical networks in human secondarily generalized tonic-clonic seizures. *Brain*. 2009;132(pt 4):999-1012.
7. Yang L, Li H, Zhu L, et al. Localized shape abnormalities in the thalamus and pallidum are associated with secondarily generalized seizures in mesial temporal lobe epilepsy. *Epilep Behav*. 2017;70(Pt A):259-264.
8. Aupy J, Wendling F, Taylor K, Bulacio J, Gonzalez-Martinez J, Chauvel P. Cortico-striatal synchronization in human focal seizures. *Brain*. 2019;142(5):1282-1295.
9. Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology*. 2015;84(10):1017-1025.
10. Warren AEL, Dalic LJ, Thevathasan W, Roten A, Bulluss KJ, Archer J. Targeting the centromedian thalamic nucleus for deep brain stimulation. *J Neurol Neurosurg Psychiatry*. 2020:jnnp-2019-322030.