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Thalamus and Seizures—Here We Come Again…

Thalamus and Focal to Bilateral Seizures: A Multiscale Cognitive Imaging Study.

Caciagli L, Allen AL, He X, et al. *Neurology*. 2020;95(17):e2427-e2441. doi:10.1212/WNL.0000000000010645

Objective: To investigate the functional correlates of recurrent secondarily generalized seizures in temporal lobe epilepsy (TLE) using task-based functional magnetic resonance imaging (fMRI) as a framework to test for epilepsy-specific network rearrangements. Because the thalamus modulates propagation of temporal lobe onset seizures and promotes cortical synchronization during cognition, we hypothesized that occurrence of secondarily generalized seizures, that is, focal to bilateral tonic-clonic seizures (FBTCS), would relate to thalamic dysfunction, altered connectivity, and whole-brain network centrality. Methods: Focal to bilateral tonic-clonic seizures occur in a third of patients with TLE and are a major determinant of disease severity. In this cross-sectional study, we analyzed 113 patients with drug-resistant TLE (55 left/58 right), who performed a verbal fluency fMRI task that elicited robust thalamic activation. Thirty-three (29%) patients had experienced at least one FBTCS in the year preceding the investigation. We compared patients with TLE-FBTCS to those without FBTCS via a multiscale approach, entailing analysis of statistical parametric mapping (SPM) 12–derived measures of activation, task-modulated thalamic functional connectivity (psychophysiologic interaction), and graph-theoretical metrics of centrality. Results: Individuals with TLE-FBTCS had less task-related activation of bilateral thalamus, with left-sided emphasis, and left hippocampus than those without FBTCS. In TLE-FBTCS, we also found greater task-related thalamo-temporal and thalamo-motor connectivity, and higher thalamic degree and betweenness centrality. Receiver operating characteristic curves, based on a combined thalamic functional marker, accurately discriminated individuals with and without FBTCS. Conclusions: In TLE-FBTCS, impaired task-related thalamic recruitment coexists with enhanced thalamo-temporal connectivity and whole-brain thalamic network embedding. Altered thalamic functional profiles are proposed as imaging biomarkers of active secondary generalization.

Numerous animal studies have documented thalamic involvement in supporting and maintaining focal and generalized seizures. Only recently, however, have human imaging studies indirectly confirmed these findings. For example, temporal lobe epilepsy (TLE) studies have investigated thalamic involvement using various imaging measures including structural magnetic resonance imaging (MRI) to show thalamic atrophy. Structural (diffusion tensor imaging) and functional (resting state) MRI connectivity studies showed aberrant connectivity, and ictal single-photon emission computerized tomography studies showed thalamic involvement in the generation and maintenance of secondarily generalized, that is, focal to bilateral tonic-clonic seizures (FBTCS).[2,3] Direct human investigations of thalamic involvement in seizure generation and maintenance have been initiated recently. While few of the direct thalamic investigations have been published to date, the latest examined the ictal signature of the thalamus in TLE using stereo-electroencephalography (EEG) electrodes directly implanted into the thalamus.[4] These authors found that thalamic epileptogenicity correlated with extension of the epileptic networks and that it affected postsurgical outcomes. Surprisingly, however, there have been no large task-functional magnetic resonance imaging (fMRI) studies focusing on the issue of thalamic participation in seizure generation and maintenance and on the thalamic contributions to the cognitive dysfunction present in patients with TLE or other epilepsies. This is a clear shortcoming of the existing literature since task-fMRI studies are frequently performed during patient evaluation allowing for copious amounts of quality functional neuroimaging data to be collected relatively quickly. The study under consideration fills this gap.[1] These authors used a covert verb fluency fMRI task in a large cohort (>100) of patients with TLE to show that impaired thalamic recruitment coexists with increased context-dependent thalamo-temporal connectivity and thalamic network embedding. Based on their findings, they proposed altered task-related thalamic functional profiles as an

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imaging biomarker for secondary generalization of seizures. However, the study methods and data/result presentation are complicated and require some attention before we dive deeper into the discussion of the results.

The authors present data of a large but overall heterogeneous group of TLE patients—MRI-negative patients, patients with hippocampal sclerosis, dysembryoplastic neuroepithelial tumors, and cavernomas. While not necessarily a major problem, combining all these groups prior to showing that their task-related fMRI activations are not different (and that thalamic activations are not different) creates a potential confounder that is not addressed in the study. Further, they utilize their "go-to" fMRI task—verb fluency—to assess language lateralization including thalamic involvement in the task. However, since there is no performance tracking with this covert task, there is no way of knowing how well the participants performed the task and how performance on the task influenced the observed fMRI activations. To offset this, they tested letter fluency as part of their neuropsychological battery—there were some group differences including significant differences between left TLE with and without generalized seizures.

In the primary analysis, they compared fMRI activation patterns in patients with FBTCS within the last year to patients with no FBTCS (ie, only with focal seizures [FS]) in the last year to find that the activation patterns were different between the groups with higher fMRI activation and more leftward activation in patients with FS including differences in thalami. Of interest is the fact that some of the peak activations fell into the anterior thalamic nuclei that, as we all know, are the target of deep brain stimulation. In the post hoc analyses, they showed that FS patients' thalamic activations were similar to healthy controls performing the same task but active FBTCS participants had overall lower thalamic activations when compared to either of those two groups. Important is that having FBTCS in the last year was the most significant determinant of thalamic activation. The study would be very easy to understand and interpret had they stopped their analyses here. However, the authors performed several useful but very complicated analyses that undoubtedly make the interpretation of the results difficult. These additional, in-part confirmatory in-part follow-up analyses are psychophysiologic interaction, graph theory, and receiver operating characteristic (RUC) curve analyses. The understanding and interpretation of these analyses is neither intuitive nor simple. While disentangling these analyses is not part of this commentary, for the purpose of better understanding their approach, we can briefly state that psychophysiologic interaction is a between regions connectivity analysis for fMRI data that is context-dependent. Graph theory analysis, as explained previously in great detail,[5] allows mathematical analysis and description of complex systems using terms such as "hubs," "centrality," and "betweenness." Finally, the term ROC—probably most recognized by neurologists—is a binary classifier that allows diagnostic discrimination between groups. These analyses show that, in patients with active FBTCS, there is greater context-dependent thalamo-temporal and thalamo-motor connectivity, higher thalamic degree and betweenness centrality, and that ROC curves discriminate well between individuals with and without active FBTCS. These findings also indicate that having active FBTCS changes the brain more than having FS alone and that the presence and the degree of the changes may be used as a biomarker for disease severity.

As complicated as these analyses are, the authors provide meticulous description of the procedures performed and of the results in the main body of the manuscript with additional details included in the supplement. However, more important are implications of this study. Since fMRI has been a mainstay of presurgical language and verbal memory evaluation for years,[6] most epilepsy centers obtain fMRI as part of their presurgical patient staging protocol. However, we cannot expect that psychophysiologic interaction, graph theory, and ROC curve analyses of the task-related fMRI data will be performed in the course of such evaluation. Rather, what the study shows is that the task fMRI data can be used not only to perform a rather simplistic analysis of language lateralization but also to identify the negative effects of pathophysiology (here seizures) on brain networks. Whether independently or in combination with other measures (eg, functional connectivity or thalamic stereoelectroencephalography), future research could teach us if/how such results could be applied to evaluating disease severity, staging in presurgical evaluation, predicting outcomes, or deciding the treatment approaches (eg, resection vs implantable devices).

Perhaps more importantly, these findings teach us something about the disease itself. They provide information about the pathophysiology of temporal lobe seizures, about the negative effects of seizures not only on local but also on remote executive brain regions (ie, confirm the proposed a long-time ago "nociferous cortex hypothesis"[7]), and outline the negative effects of FBTCS on brain connectivity and pathways of information transfer. While previously such negative effects have been documented in resting-state studies, this effort extends those findings to cognitive tasks and task-based connectivity. This study shows that the task data can be used not only to localize and lateralize brain functions but also to measure the effects of the disease on brain networks and its severity.

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