Epilepsy Currents
2021, Vol. 21(4) 270–272

DOI: 10.1177/15357597211021080
journals.sagepub.com/home/epi
SAGE

Are We Inviting Another Attendee to the Temporal Lobe Epilepsy Party?

Role of the Nucleus Basalis as a Key Network Node in Temporal Lobe Epilepsy

González HFJ, Narasimhan S, Johnson GW, et al. *Neurology*. 2021;96(9):e1334-e1346. doi:10.1212/WNL.0000000000011523

Objective: To determine whether the nucleus basalis of Meynert (NBM) may be a key network structure of altered functional connectivity in temporal lobe epilepsy (TLE), we examined functional magnetic resonance imaging (fMRI) with network-based analyses. Methods: We acquired resting state fMRI in 40 adults with TLE and 40 matched healthy control participants. We calculated functional connectivity of NBM and used multiple complementary network-based analyses to explore the importance of NBM in TLE networks without biasing our results by our approach. We compared patients to controls and examined associations of network properties with disease metrics and neurocognitive testing. Results: We observed marked decreases in connectivity between NBM and the rest of the brain in patients with TLE (0.91 $\pm$ 0.88, mean $\pm$ SD) versus controls (1.96 $\pm$ 1.13, $P < .001$, *t* test). Larger decreases in connectivity between NBM and fronto-parietal-insular regions were associated with higher frequency of consciousness-impairing seizures ($r = -0.41$, $P = .008$, Pearson). A core network of altered nodes in TLE included NBM ipsilateral to the epileptogenic side and bilateral limbic structures. Furthermore, normal community affiliation of ipsilateral NBM was lost in patients, and this structure displayed the most altered clustering coefficient of any node examined (3.46 $\pm$ 1.17 in controls vs 2.23 $\pm$ 0.93 in patients). Abnormal connectivity between NBM and subcortical arousal community was associated with modest neurocognitive deficits. Finally, a logistic regression model incorporating connectivity properties of ipsilateral NBM successfully distinguished patients from control datasets with moderately high accuracy (78%). Conclusions: These results suggest that while NBM is rarely studied in epilepsy, it may be one of the most perturbed network nodes in TLE, contributing to widespread neural effects in this disabling disorder.

Commentary

Although the most common structural defect associated with medial temporal lobe epilepsy (mTLE) is hippocampal sclerosis,[1] studies with magnetoencephalography (MEG),[2] functional magnetic resonance imaging (fMRI),[3] and positron emission tomography (PET)[4] have characterized large-scale functional networks of brain activity or connectivity in this population. Studies with fMRI have been especially useful in exploring the connectivity of different brain regions far from the temporal lobe. Liao et al[5] used graph theory analysis of fMRI data collected from patients with temporal lobe epilepsy (TLE) to examine functional connectivity in a broad set of brain regions and demonstrated significantly increased connectivity within the medial temporal lobes, but decreased connectivity with frontal and parietal regions. Holmes et al[6] used voxel-wise linear regression analysis to show a network of impairment in TLE associated with thalamus, midcingulate gyrus, precuneus, and postcentral gyrus. Other studies have implicated the amygdala, the entorhinal cortices, lateral temporal neocortices, the inferior frontal lobes, the cerebellum, and the brainstem as part of the TLE network.

The work of González et al[7] introduces the nucleus basalis of Meynert (NBM) as a significant node in the altered network of mesial TLE. Their finding is provocative in that the NBM is not within the traditional limbic system of subcortical structures commonly associated with mTLE. The authors studied the resting state eyes-closed 10-minute T2*-weighted blood oxygenation level–dependent fMRI in 40 consecutive patients with mTLE and 40 age- and sex-matched controls. The article details an elegant series of experiments that carefully addresses functional connectivity from several different complementary approaches. They defined 133 regions of interest for functional connectivity analyses including 108 from the Harvard-Oxford atlas which they called whole brain. The authors used CONN toolbox 17 to visualize seed-to-voxel NBM bivariate correlation functional connectivity differences between patients with mTLE and controls. To complement seed-based NBM connectivity comparisons, they analyzed how the community structure of NBM may change in mTLE with community detection. Four hypothetical network models were postulated to determine which one best explains the central connectivity network

difference between patients and controls. For all networks generated in the 4 models, the authors calculated the main network metrics analyzed: NBM connectivity with the whole brain, NBM clustering coefficient, and node strength to module of ipsilateral NBM to limbic community. To further elucidate the reliability of NBM connectivity alterations in mTLE, the authors analyzed 3 network characteristics and used binary logistic regression models to determine whether connectivity properties of ipsilateral NBM alone could accurately identify whether each participant's dataset belonged to a patient or controls. Results showed that patients displayed connectivity decreases between NBM and broad neocortical regions compared to controls. Data also suggest closer functional connections between NBM and limbic structures than with other subcortical arousal nuclei in controls. Results indicate decreased connections involving ipsilateral but not contralateral NBM, bilateral hippocampi, and amygdala. Of the 4 hypothetical network models postulated, the ipsilateral NBM had a sensitivity and specificity of 75% and 83%, respectively, in predicting whether a participant's dataset belonged to a patient or controls. The authors conclude that their results suggest that NBM ipsilateral to epileptogenic zone represents a key structure in the altered mTLE network.

The main strength of this article is the use of a series of experiments to demonstrate that the NBM is intricately tied to the medial temporal lobe in patients with mTLE. The authors went to great lengths to eliminate potential bias: mTLE patients were selected consecutively, the controls were age- and gender-matched, and the whole brain was analyzed as opposed to only the "common" areas typically linked to TLE. The initial analysis was made using seed-to-voxel group-level comparisons between the different regions in epilepsy patients and controls. Then, community detection algorithms identified groups of brain nodes that most strongly functionally connect to each other. Network-based statistic was used to identify core networks of connected nodes with connectivity decreases in patients compared to controls. The use of unbiased network-sampling methods to compare 4 hypothetical models was an additional substudy not usually seen in fMRI connectivity papers. The overall experimental design approached the research question from several complementary angles, and the results were concordant in demonstrating the voxel containing the NBM ipsilateral to the side of seizure onset may contain one of the most disturbed brain network nodes in TLE.

Although this was an elegant series of experiments, there are a couple of methodologic concerns. The NBM is a small structure in the basal forebrain in close proximity to the medial temporal lobe. The $3.0 \times 3.0 \times 4.0\ mm^3$ voxel used this study is standard for most fMRI studies of the forebrain but incorporates a fairly large region of interest. It is crucial to ensure that the NBM voxel does not include any portion of the ipsilateral medial temporal lobe, or the nucleus accumbens, which has recently been implicated in the mTLE network.[8] Data from multi-echo acquisition sequences combined with smaller voxel sizes may be needed to validate the current results. A second concern (which was noted by the authors) is that the study did not provide a method to confirm that patients remained fully awake during the resting state fMRI acquisition. Although one can reasonably postulate that this limitation would apply equally to patients and controls, I would argue that patients with TLE are more likely to become drowsy in that testing environment as they are on medication(s) which often have sedation and somnolence as common side effects.

The possibility that the NBM is an important node in the mTLE network is a novel discovery. If validated, this finding has ramifications for potentially explaining some of the comorbidities associated with the disease. The NBM has long been known to be a major source of cholinergic input to the cortex and neuronal loss in this structure is seen in some dementing illnesses such as Alzheimer's Disease and Parkinson's Disease. Studies suggest that the modulation of cortical activity through this cholinergic system subserves cognitive functions, especially in the domains of memory and attentional processing.[9] Selective lesions to the NBM region in animal models disrupt cortical cholinergic neurotransmission and are associated with impaired performance on spatial learning and target detection tasks.[10] Dysfunction in the NBM caused by recurrent pathological electrical activity in the mTLE network may contribute to the memory and cognitive deficits in patients with TLE. Further studies are needed to determine whether the NBM can attend the mTLE party.

By Jerry J. Shih

ORCID iD

Jerry J. Shih https://orcid.org/0000-0002-0680-0362

References

1. Margerison JH, Corsellis JA. Epilepsy and the temporal lobes. A clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. *Brain*. 1966;89(3):499-530. doi:10.1093/brain/89.3.499
2. Shih JJ, Weisend MP, Lewine J, Sanders J, Dermon J, Lee RR. Areas of interictal spiking are associated with metabolic dysfunction in MRI-negative temporal lobe epilepsy. *Epilepsia*. 2004; 45(3):223-229. doi:10.1111/j.0013-9580.2004.13503.x PMID: 15009223.
3. Maccotta L, He BJ, Snyder AZ, et al. Impaired and facilitated functional networks in temporal lobe epilepsy. *Neuroimage Clin*. 2013;2:862-872. doi:10.1016/j.nicl.2013.06.011 PMID: 24073391.
4. Vanicek T, Hahn A, Traub-Weidinger T, et al. Insights into Intrinsic Brain Networks based on Graph Theory and PET in right- compared to left-sided temporal lobe epilepsy. *Sci Rep*. 2016;6. doi:10.1038/srep28513 PMID: 27349503.
5. Liao W, Zhang Z, Pan Z, et al. Altered functional connectivity and small-world in mesial temporal lobe epilepsy. *PLoS One*. 2010; 5(1). doi:10.1371/journal.pone.0008525 PMID: 20072616.
6. Holmes MJ, Yang X, Landman BA, et al. Functional networks in temporal-lobe epilepsy: a voxel-wise study of resting-state

functional connectivity and gray-matter concentration. *Brain Connect*. 2013;3(1):22-30. doi:10.1089/brain.2012.0103 PMID: 23150897.

7. González HFJ, Narasimhan S, Johnson GW, et al. Role of the nucleus basalis as a key network node in temporal lobe epilepsy. *Neurology*. 2021;96(9):e1334-e1346. doi:10.1212/WNL.0000000000011523 PMID: 33441453.
8. Yang R, Zhao X, Liu J, et al. Functional connectivity changes of nucleus Accumbens shell portion in left mesial temporal lobe epilepsy patients. *Brain Imaging Behav*. 2020;14(6):2659-2667. doi:10.1007/s11682-019-00217 -1 PMID: 32318911.
9. Hasselmo ME, Sarter M. Modes and models of forebrain cholinergic neuromodulation of cognition. *Neuropsychopharmacology*. 2011;36(1):52-73. PMID: 20668433.
10. Browne SE, Lin L, Mattsson A, Georgievska B, Isacson O. Selective antibody-induced cholinergic cell and synapse loss produce sustained hippocampal and cortical hypometabolism with correlated cognitive deficits. *Exp Neurol*. 2001;170(1):36-47. PMID: 11421582.