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Septal nuclei enlargement in human temporal lobe epilepsy without mesial temporal sclerosis

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ABSTRACT

Objective: To measure the volume of basal forebrain septal nuclei in patients with temporal lobe epilepsy (TLE) as compared to patients with extratemporal epilepsy and controls. In animal models of TLE, septal lesions facilitate epileptogenesis, while septal stimulation is antiepileptic.

Method: Subjects were recruited from 2 sites and consisted of patients with pharmacoresistant focal epilepsy (20 with TLE and mesial temporal sclerosis [MTS], 24 with TLE without MTS, 23 with extratemporal epilepsy) and 114 controls. Septal volume was measured using high-resolution MRI in association with newly developed probabilistic septal nuclei maps. Septal volume was compared between subject groups while controlling for relevant factors.

Results: Patients with TLE without MTS had significantly larger septal nuclei than patients with extratemporal epilepsy and controls. This was not true for patients with MTS. These results are interpreted with reference to prior studies demonstrating expansion of the septo-hippocampal cholinergic system in animal models of TLE and human TLE surgical specimens.

Conclusion: Septal nuclei are enlarged in patients with TLE without MTS. Further investigation of septal nuclei and antiepileptic septo-hippocampal neurocircuitry could be relevant to development of new therapeutic interventions such as septal stimulation for refractory TLE. *Neurology*® 2013;80:487-491

GLOSSARY

ETE = extratemporal epilepsy; **FCD** = focal cortical dysplasia; **FOV** = field of view; **icEEG** = intracranial EEG; **MNI** = Montreal Neurological Institute; **MTS** = mesial temporal sclerosis; **NGF** = nerve growth factor; **NYU** = New York University; **TE** = echo time; **TI** = inversion time; **TICV** = total intracranial volume; **TLE** = temporal lobe epilepsy; **TLE-NL** = patients with temporal lobe epilepsy without mesial temporal sclerosis; **TLVV** = total lateral ventricle volume; **TR** = repetition time; **UCSD** = University of California, San Diego.

Human septal nuclei, located in the basal forebrain, consist of the medial septum and diagonal band of Broca. Septal nuclei provide the main cholinergic input to the hippocampus via the fimbria/fornix¹ and are critical for hippocampal theta oscillations that mediate learning and memory.^{2,3} In animal models of temporal lobe epilepsy (TLE), medial septal lesions facilitate epileptogenesis, and chemical or electrical septal stimulation can stop and prevent seizures.⁴⁻⁸ To our knowledge, no studies have examined septal nuclei structure in human TLE.

We used MRI in association with probabilistic maps of human septal nuclei⁹ to measure septal volume in patients with TLE either with or without mesial temporal sclerosis (MTS), patients with partial epilepsy not involving the hippocampus (extratemporal epilepsy [ETE]), and healthy controls. Based on prior human MRI studies showing atrophy of hippocampi and connected limbic regions in TLE including the fornix,^{10,11} we initially hypothesized that septal volume would be reduced in TLE. Contrary to this hypothesis, we found septal enlargement in TLE without MTS.

METHODS Subjects. All subjects provided informed consent to participate in this institutional review board-approved study. Patients with epilepsy were recruited from either the New York University (NYU) or University of California, San Diego (UCSD) Epilepsy Center. See table 1 for subject information. All patients had medically intractable seizures and were being considered for epilepsy surgery. Seizure focus lateralization/localization was made by experienced epileptologists based on clinical criteria including neuroimaging, video-EEG, and intracranial EEG (icEEG) when available. Patients with TLE were categorized as having MTS (TLE-MTS) or not based on standard criteria.¹² Patients

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Table 1 Subject characteristics^a

Group	No.	Female	Age, y (SD)	Epilepsy duration, y (SD)	Lateralization/localization
NYU TLE-NL	18	10	36.0 (10.2)	17.7 (15.3)	9 left, 8 right, 1 bilateral; icEEG performed in 10/18
UCSD TLE-NL	6	3	35.5 (9.6)	21.3 (15.4)	4 right, 2 left
NYU TLE-MTS	6	4	36.8 (8.4)	20.4 (13.4)	3 left, 3 right; icEEG performed in 1/6
UCSD TLE-MTS	14	9	37.2 (13.4)	27.2 (11.8)	4 right, 10 left
ETE (NYU only)	23	13	28.5 (11.0)	20.3 (11.4)	10 left, 8 right, 5 bilateral/uncertain; 15 frontal/central, 8 parietal/occipital; icEEG performed in 12/23
NYU controls	89	43	34.5 (12.5)	NA	NA
UCSD controls	25	13	34.1 (10.2)	NA	NA

Abbreviations: ETE = extratemporal epilepsy; icEEG = intracranial EEG; MTS = mesial temporal sclerosis; NA = not applicable; NYU = New York University; TLE = temporal lobe epilepsy; TLE-NL = patients with temporal lobe epilepsy without mesial temporal sclerosis; UCSD = University of California, San Diego.

^a Subject groups did not differ significantly by age ($F_{6,174} = 1.22, p = 0.30$), epilepsy duration ($F_{4,61} = 1.08, p = 0.37$), or sex (Pearson $\chi^2 [6, n = 181] = 2.12, p = 0.91$).

without MTS are referred to as TLE-NL, though 5/24 did have subtle mesial temporal abnormalities that did not qualify as MTS (1 with subtle parahippocampal gray-white blurring, 1 with slight hippocampal increased fluid-attenuated inversion recovery signal but no atrophy, 3 with mild atrophy but no signal change). Patients with TLE due to tumors or other non-MTS lesions were not included. Patients with ETE had normal MRI (n = 15), incidental noncortical abnormalities (n = 2), or subtle focal cortical dysplasia (FCD) characterized by signal change or gray-white blurring at the seizure focus (n = 4). Patients with grossly abnormal MRI which could interfere with image processing, serious medical/neurologic disease other than epilepsy, or serious psychiatric disease such as psychosis were not included. Controls were recruited through online advertisement and denied medical, neurologic, or psychiatric illness.

MRI scanning. High-resolution research MRI was performed at either the NYU Center for Brain Imaging on a 3 T Siemens (Munich, Germany) Allegro head-only scanner or at the UCSD Radiology Imaging Laboratory on a GE (Schenectady, NY) 1.5 T EXCITE scanner (NYU: echo time [TE] = 3.25 ms, repetition time [TR] = 2,530 ms, inversion time [TI] = 1.1 ms, field of view [FOV] = 256 mm, voxel size = 1 × 1 × 1.33 mm; UCSD: TE = 3.8 ms, TR = 10.7 ms, TI = 1,000 ms, FOV = 240 mm, voxel size = 1.25 × 1.25 × 1.2 mm).

Measurement of septal volume. Using statistical parametric mapping (SPM8, Wellcome Trust Center for Neuroimaging, London, UK), individual scans were normalized to the Montreal Neurological Institute (MNI) 152 T1-template using a 12-parameter affine transformation and partitioned into gray and white matter using a unified segmentation approach. Gray and white matter maps were registered to the segmented MNI 152 T1 template using the DARTEL toolbox, an efficient large deformation diffeomorphic framework which provides information about voxel-level local expansion and contraction necessary to deform the image to match the template.¹³ The DARTEL flow fields derived from this registration were applied to a binary mask of the septal nuclei (generated as described below). To warp the septal maps, which were in MNI template space, back to each individual subject's native space, we applied the inverse DARTEL flow field. We then calculated the volume of each subject's septal mask in mm³. We have used this method previously.¹⁴

The binary septal nuclei masks we used were based on probabilistic maps of magnocellular (presumably cholinergic) basal forebrain cell groups generated using digital images of cell-stained histologic

sections from 10 human postmortem brains that were reconstructed in 3D using the MRI scans of the fixed brain as a shape reference, then spatially normalized to the single-subject T1-weighted MNI reference brain, as described in detail elsewhere.⁹ The masks included all voxels showing ≥10% probability of being part of the medial septal nucleus or the nucleus of the diagonal band of Broca, corresponding to Mesulem's Ch1-Ch2 cell group.¹⁹

To allow correction for baseline differences in intracranial volume across subjects, total intracranial volume (TICV) was calculated using FreeSurfer 5.0 (<http://surfer.nmr.mgh.harvard.edu>).

Statistical analysis. Statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL). NYU and UCSD datasets were combined and were also analyzed separately. One-way analysis of covariance was conducted with independent variable = subject group (TLE, ETE [for NYU dataset only], and controls); covariates = age, TICV, and, when appropriate, site; and dependent variable = total septal volume. To assess an effect of MTS on septal volume, analyses were also performed with patients with TLE split into separate groups based on the presence or absence of MTS (TLE-MTS, TLE-NL). For patient groups, partial correlation analyses were performed to assess a possible effect of epilepsy duration on septal volume while controlling for age, TICV, and, when appropriate, site.

Because septal nuclei are located adjacent to and in between lateral ventricles, and ventricular enlargement (which can occur in TLE¹⁵) could potentially distort septal volume measurement, we used FreeSurfer to calculate total lateral ventricle volume (TLVV), and performed all analyses both with and without TLVV as an additional covariate.

All results were considered significant at $p < 0.05$.

RESULTS Mean septal volumes are presented in table 2. The figure shows an example of septal nuclei segmentation.

TLE vs controls. There was a highly significant effect of group, indicating that patients with TLE had larger septal nuclei than controls ($F_{1,153} = 12.9, p < 0.0005$) when controlling for age, TICV, and site. These results were similar when TLVV was included as an additional covariate ($p = 0.002$), and when NYU and UCSD datasets were analyzed separately ($p = 0.017$ and $p = 0.037$, respectively).

Table 2 Mean septal volumes

Group	No.	Septal volume, mm ³	SD
NYU TLE-NL	18	1,762.78	253.64
UCSD TLE-NL	6	1,786.67	329.86
NYU TLE-MTS	6	1,681.00	165.67
UCSD TLE-MTS	14	1,614.00	164.85
ETE (NYU only)	23	1,660.30	176.54
NYU control	89	1,734.89	218.32
UCSD control	25	1,734.24	197.01

Abbreviations: ETE = extratemporal epilepsy; MTS = mesial temporal sclerosis; NYU = New York University; TLE = temporal lobe epilepsy; TLE-NL = patients with temporal lobe epilepsy without mesial temporal sclerosis; UCSD = University of California, San Diego.

TLE-NL vs TLE-MTS vs controls. When the TLE group was divided into those with and without MTS, septal volume still differed significantly by group ($F_{2,152} = 7.432, p = 0.001$), and pairwise comparisons indicated that only TLE-NL patients had significantly larger septal volumes than controls ($p < 0.0005$). TLE-MTS patients did not differ from TLE-NL patients ($p = 0.172$) or from controls ($p = 0.120$). Results when TLVV was included as an additional covariate were similar ($p < 0.0005$), except a trend for greater septal volume in TLE-NL as compared to TLE-MTS patients became apparent ($p = 0.079$). Note that for this comparison, NYU and UCSD datasets were not analyzed separately because there were only 6 NYU TLE-MTS patients and only 6 UCSD TLE-NL patients.

TLE-NL vs TLE-MTS vs ETE vs controls. In the NYU dataset, which included patients with ETE, septal volume differed significantly by group ($F_{3,130} = 3.808, p = 0.012$), and pairwise comparisons indicated that TLE-NL patients had significantly larger septal volumes than controls ($p = 0.002$) and patients with ETE ($p = 0.004$). There was a weak trend for TLE-NL patients to have larger septal volume than TLE-MTS patients

($p = 0.093$). TLE-MTS patients did not differ from controls ($p = 0.910$) or from patients with ETE ($p = 0.778$). Results were similar when TLVV was included as an additional covariate in analysis ($p < 0.0005$).

Correlation with epilepsy duration. There was no correlation between septal volume and epilepsy duration when controlling for age, TICV, and site in patients with TLE overall ($r = 0.088, p = 0.584$) or in TLE-MTS or TLE-NL subgroups ($r = 0.142, p = 0.587; r = 0.111, p = 0.632$, respectively). These results did not change when TLVV was included as an additional covariate, or when NYU and UCSD datasets were analyzed separately.

There was a weak trend for greater septal volume with epilepsy duration in patients with ETE ($r = 0.38, p = 0.095$), and this trend became stronger when TLVV was included as an additional covariate ($r = 0.45, p = 0.056$).

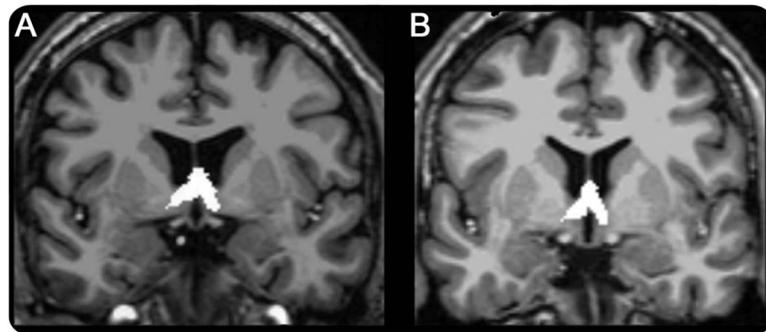
DISCUSSION Results demonstrate that patients with TLE have larger septal nuclei than controls. Septal enlargement in TLE is limited to patients without MTS; septal volume in patients with TLE with MTS does not differ from that in controls. The specificity of our results—that septal nuclei are enlarged only in TLE and not in extratemporal epilepsy—is in accord with the known anatomic specificity of septal nuclei connections with hippocampi.^{1,2}

Our results contrast with multiple prior MRI studies (none of which assessed septal nuclei) showing atrophy of hippocampi and interconnected limbic structures in TLE both with and without MTS, considered to reflect neuronal loss in the seizure focus and regions of propagated seizure activity.^{10,11} Hippocampal seizures propagate to septal nuclei,^{4,16} so how can we explain our finding of septal enlargement rather than atrophy in patients with TLE without MTS?

A potential explanation comes from animal studies demonstrating that septal cholinergic neurons are resistant to seizure-induced neuronal loss^{8,17} and may actually enlarge in TLE via a mechanism dependent upon nerve growth factor (NGF) released from hippocampus and transported to septal nuclei retrogradely along the fornix.^{18,19} NGF is an essential growth factor for septal cholinergic neurons, and its production is highly upregulated by hippocampal seizures.²⁰ While neuronal cell body enlargement does not correspond directly to regional enlargement detectable by MRI, we believe this unusual propensity of septal cholinergic neurons to survive and enlarge in an animal model of TLE provides a relevant model for understanding our MRI finding of septal enlargement in human TLE.

This translational framework also offers an explanation for septal enlargement limited to patients with TLE without MTS: severe hippocampal cell loss might preclude production of sufficient NGF in response to

Figure Coronal view of septal nuclei masks in (A) a patient with temporal lobe epilepsy and (B) a control



seizures to cause septal enlargement. In support of this idea, septal atrophy occurs following hippocampal excitotoxic ablation²¹ or septo-hippocampal disconnection.¹⁹

In the context of these prior animal studies, as well as studies of human tissue obtained at temporal lobectomy indicating increased septal cholinergic innervation of hippocampus in TLE,^{22–24} we suggest our finding of septal enlargement in human TLE without MTS represents MRI-detectable evidence of neuroplasticity/augmentation of the septal-hippocampal system in TLE.

Understanding the mechanism, consequences, and cellular basis of septal enlargement in human TLE without MTS will require additional studies. Histologic examination of septal tissue obtained at autopsy or non-invasive imaging tests such as neuroreceptor PET using cholinergic and other ligands can clarify the cellular basis of MRI-detected septal enlargement. Longitudinal studies will be important to ascertain whether septal enlargement is cause, consequence, or both of TLE. In this respect, our results showing no effect of epilepsy duration on septal volume in patients with TLE suggests that this process may occur early in TLE, and our finding of a trend toward larger septal nuclei with longer duration of extratemporal epilepsy could perhaps indicate progression of ETE to involve the hippocampus and the septo-hippocampal system over time.²⁵

Given the role of septo-hippocampal projection neurons in dampening hippocampal hyperexcitability and stopping seizures,^{4–8} a better understanding of septal nuclei in TLE could open up new antiepileptic therapeutic avenues such as septal stimulation. Septal stimulation can abort seizures in animals,⁶ and stimulation of septal outflow tract in humans is safe, and may improve memory.²⁶

Methodologic issues. The main findings of our study are based on a combined NYU-UCSD dataset. While combining data across different MRI scanners can be problematic, it has become increasingly common in the era of large, multisite neuroimaging studies,²⁷ and is generally considered appropriate so long as both patients and controls are scanned at each site, and site is included as a covariate in analysis,²⁸ as we have done. In addition, we analyzed each dataset separately, and results were concordant.

Ventricle volume as confound. Septal nuclei location in between and adjacent to lateral ventricles could distort their measurement, due to ventricular enlargement or edge effects.²⁹ By explicitly measuring lateral ventricle volume, we were able to control for this effect. It will be important for future studies, especially those focused on disorders associated with marked ventricular enlargement such as dementia, to also measure and account for ventricle volume when assessing septal volume.

We have demonstrated that septal nuclei are enlarged in patients with TLE without MTS. This initial MRI finding in humans can be understood with reference to animal and human studies demonstrating preservation or expansion of the septal-hippocampal cholinergic systems in TLE. Further investigation of this understudied antiepileptic neural circuit could be relevant to development of new therapeutic interventions for refractory TLE.

AUTHOR CONTRIBUTIONS

T. Butler: conception and design of study, data analysis, data interpretation, drafted manuscript. L. Zaborszky: conception and design of study, data analysis, data interpretation, revised manuscript. X. Wang: data analysis including critical methodologic development/implementation, revised manuscript. C.R. McDonald: data acquisition, regulatory approval at her site, data analysis, revised manuscript. K. Blackmon: data acquisition, data interpretation, revised manuscript. B.T. Quinn: study concept or design, analysis or interpretation of data, statistical analysis. J. DuBois: data acquisition, data analysis, revised manuscript. C. Carlson: data acquisition, data analysis, revised manuscript. W.B. Barr: study supervision/mentorship, data interpretation, revised manuscript. J. French: study supervision/mentorship, data interpretation, revised manuscript. R. Kuzniecky: study supervision/mentorship, data interpretation, revised manuscript. E. Halgren: study supervision/mentorship, obtained study funding, data interpretation, revised manuscript. O. Devinsky: study supervision/mentorship, data interpretation, revised manuscript. T. Thesen: conception and design of study, study supervision, obtained regulatory approval and funding, data acquisition, data analysis, data interpretation, revised manuscript.

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DISCLOSURE

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