Differences in functional connectivity profiles as a predictor of response to anterior thalamic nucleus deep brain stimulation for epilepsy: a hypothesis for the mechanism of action and a potential biomarker for outcomes

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OBJECTIVE Deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) is a promising therapy for refractory epilepsy. Unfortunately, the variability in outcomes from ANT DBS is not fully understood. In this pilot study, the authors assess potential differences in functional connectivity related to the volume of tissue activated (VTA) in ANT DBS responders and nonresponders as a means for better understanding the mechanism of action and potentially improving DBS targeting.

METHODS This retrospective analysis consisted of 6 patients who underwent ANT DBS for refractory epilepsy. Patients were classified as responders ($n = 3$) if their seizure frequency decreased by at least 50%. The DBS electrodes were localized postoperatively and VTAs were computationally generated based on DBS programming settings. VTAs were used as seed points for resting-state functional MRI connectivity analysis performed using a control dataset. Differences in cortical connectivity to the VTA were assessed between the responder and nonresponder groups.

RESULTS The ANT DBS responders showed greater positive connectivity with the default mode network compared to nonresponders, including the posterior cingulate cortex, medial prefrontal cortex, inferior parietal lobule, and precuneus. Interestingly, there was also a consistent anticorrelation with the hippocampus seen in responders that was not present in nonresponders.

CONCLUSIONS Based on their pilot study, the authors observed that successful ANT DBS in patients with epilepsy produces increased connectivity in the default mode network, which the authors hypothesize increases the threshold for seizure propagation. Additionally, an inhibitory effect on the hippocampus mediated through increased hippocampal γ -aminobutyric acid (GABA) concentration may contribute to seizure suppression. Future studies are planned to confirm these findings.

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KEYWORDS DBS; deep brain stimulation; epilepsy; anterior thalamic nucleus; fMRI; functional MRI; default mode network; hippocampus

EPILEPSY is a common, worldwide cause of disability and death.¹⁵ Unfortunately, approximately 20%–40% of patients with epilepsy have drug-refractory disease.¹⁵ Mechanisms underlying drug-resistant epilepsy are poorly understood, which has confounded the abil-

ity to adequately treat patients with this type of epilepsy. Whereas early models largely focused on discrete epileptogenic sources,⁴⁸ many forms of epilepsy, particularly temporal lobe epilepsy (TLE), are becoming increasingly recognized as network diseases with widespread function-

ABBREVIATIONS ACC = anterior cingulate cortex; ANT = anterior nucleus of the thalamus; Cm-PF = centromedian-parafascicular; COG = center of gravity; DBS = deep brain stimulation; DLPFC = dorsolateral prefrontal cortex; DMN = default mode network; fMRI = functional MRI; GABA = γ -aminobutyric acid; MNI = Montreal Neurological Institute; MPRAGE = magnetization-prepared rapid acquisition gradient echo; PCC = posterior cingulate cortex; ROI = region of interest; SANTE = Stimulation of the Anterior Nuclei of Thalamus for Epilepsy; TLE = temporal lobe epilepsy; VTA = volume of tissue activated.

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al and structural changes.^{11,38} Furthermore, some patients probably have multifocal onset, making localization and resective strategies difficult.

Although many brain networks have been shown to vary in epileptic patients compared to controls,¹¹ perhaps none have been as extensively studied as the default mode network (DMN). The DMN is a widely distributed brain network that is preferentially active during rest and deactivated during the task engagement.⁹ Core components of the DMN include the posterior cingulate cortex (PCC), precuneus, inferior parietal lobule, superior parietal lobe, medial prefrontal cortex, retrosplenial cortex, hippocampus, parahippocampal cortex, and cerebellum.^{9,13,46} Prior work has suggested a deactivation of the DMN during interictal epileptiform discharges¹⁷ and during seizures,¹⁴ when DMN suppression may be related to loss of awareness. Additional resting-state networks implicated in seizures have been studied and may also play a role in the cognitive effects of epilepsy, such as the attention network and the reward/emotion network.¹¹

The shift in the understanding of epilepsy may shed light on the variability in treatment outcomes; however, it also highlights the challenges associated with effective surgical treatment. One emerging potential treatment for refractory epilepsy is deep brain stimulation (DBS). Common targets have historically included the centromedian-parafascicular (Cm-PF) complex, hippocampus, and anterior nucleus of the thalamus (ANT).^{18,31,44} Results of the Stimulation of the Anterior Nuclei of Thalamus for Epilepsy (SANTE) trial show the long-term efficacy and safety of ANT stimulation in the treatment of focal epilepsy, but significant variability in outcomes exists.^{18,44} One potential cause for outcome variation is inadequate DBS targeting: for instance, approximately 10% of electrodes were not within the ANT in the SANTE trial and the Medtronic Registry for Epilepsy (MORE) study.^{30,50} Suggested improvements in direct ANT targeting have been proposed;^{10,40} however, insufficiencies in direct structural targeting in DBS have been previously illustrated.^{36,37} In this pilot study, we aimed to assess potential differences in resting-state functional connectivity profiles from volumes of tissue activated (VTAs) after ANT DBS in responders and nonresponders. Given that epileptiform activity has been associated with reduced activity in resting-state networks, we hypothesize that the VTA of the ANT in responders will show increased connectivity with resting-state networks compared with nonresponders.

Methods

The retrospective analysis of patients having received thalamic DBS for epilepsy was deemed exempt from full review by the Mayo Clinic Institutional Review Board. From a database of 8 patients who had undergone ANT DBS, 2 were excluded due to lack of follow-up—6 total patients were included for further analysis. Patients were arbitrarily grouped into 2 categories based on seizure reduction after DBS: the “responder” group had a $\geq 50\%$ reduction in seizure frequency, whereas the “nonresponder” group had a $< 50\%$ reduction.

Chart Review

Relative demographic and clinical information was evaluated, including history, age, sex, seizure frequency, electrophysiological data, DBS programming information, and seizure reduction after DBS. Information regarding prior surgical treatments for epilepsy, including additional DBS leads, was also recorded.

Imaging Acquisition

The imaging used for this study consisted of preoperative magnetization-prepared rapid acquisition gradient echo (MPRAGE), T2-weighted sequence, and a postoperative high-resolution noncontrast CT. The preoperative MPRAGE imaging was acquired in the axial plane at 3 T after the administration of intravenous gadolinium-based contrast. Image resolution was 0.5×0.5 mm in-plane with a 1.2-mm slice thickness. Additional parameters included a TE of 5.2 msec, TR of 1186 msec, TI of 1000 msec, and flip angle of 8° . The T2-weighted imaging consisted of a turbo spin echo sequence obtained in the axial plane with an in-plane resolution of 0.9×0.9 mm and slice thickness of 3 mm, with a TE of 102 msec and a TR of 4633 msec. Postoperative noncontrast CT scanning of the head was performed for electrode localization. The CT parameters were an in-plane resolution of 0.6×0.6 mm and slice thickness of 1 mm.

Surgical Procedure

The details of our implantation procedure have been reported previously.⁴⁹ In brief, with patients under anesthesia, a Leksell (Elekta) frame was placed, and stereotactic MR images were obtained. Using a Schaltenbrand and Wahren atlas overlay and anatomical guidance, we targeted the anterior nucleus by initially using coordinates from Hodaie et al., and modifying as necessary.²² Medtronic 3389 electrodes were then implanted in the anterior nucleus and intraoperative fluoroscopy was used to ensure their accurate placement. Five of the 6 patients had additional bilateral leads placed in the hippocampus ($n = 4$) and centromedian nucleus ($n = 1$). Electrode locations were confirmed with a CT scan and the patient was taken back to the operating theater. The leads were then tunneled and connected to lead extensions, which were then connected to a battery placed in the standard subclavicular pocket.^{22,49}

Imaging Processing

A 2-stage linear registration (rigid followed by affine) was performed to coregister the postoperative CT and preoperative MRI acquisitions by using Advanced Normalization Tools (<http://stnava.github.io/ANTs/>).² All coregistered images were then spatially normalized into Montreal Neurological Institute (MNI) ICBM_2009b_NLIN_ASYM space,¹⁹ based on a combination of the preoperative MPRAGE and T2-weighted acquisitions, by using the SyN registration approach in Advanced Normalization Tools. Nonlinear deformation into template space was achieved in 5 stages: After 2 linear (rigid followed by affine) steps, a nonlinear (whole brain) SyN registration stage was followed by 2 nonlinear SyN registrations

that consecutively focused on the area of interest as defined by subcortical masks in Schönecker et al. in 2009.⁴⁵ Corrections for brainshift on the postoperative CT were performed by applying a refined affine transform calculated between pre- and postoperative acquisitions that were restricted to a subcortical area of interest by using the brainshift-correction module of Lead-DBS software (<http://www.lead-dbs.org>).²³ Two-dimensional projection images of the most distal cathode contact (K1/K9) were generated and registered to the DBS Intrinsic Template Atlas (DISTAL).¹⁶

Image Analysis

Using each patient's recorded DBS stimulator settings, a VTA was generated using a finite element method solution with tissue-specific conductivity modeling as implemented in Lead-DBS software.^{23,24} All ANT electrodes were programmed with cathodal stimulation of the middle two contacts and with anodal stimulation of the proximal and distal contacts (a guarded cathode electrode configuration). Voltages for each patient were as follows: patient in case 1 = 5.2 V bilaterally; patient in case 2 = 2 V left and 2.5 V right; patient in case 3 = 5 V bilaterally; patient in case 4 = 6 V bilaterally; patient in case 5 = 6 V bilaterally; and patient in case 6 = 5 V bilaterally.

Each generated VTA was used as a seed point for resting-state functional MRI (fMRI) analysis performed using an averaged group resting-state fMRI database from 15 control patients, as described in Horn et al.²⁴ A t-score map was generated for each patient. The t-score maps were averaged for the 3 responders and the 3 nonresponders and were thresholded to a t-score > 2. To assess differences between the 2 groups, the averaged t-score map from the nonresponder group was subtracted from that of the responder group to assess areas of greater correlation and anticorrelation, and then thresholded to $p < 0.05$. Cluster analysis of the resultant difference maps was also performed in FMRIB Software Library version 5.0 (<http://fsl.fmrib.ox.ac.uk/fsl>) to assess cluster size, maximum t-score per cluster, and center of gravity (COG) location by using a weighted-average location based on t-score value. Coordinates were calculated in MNI reference space. Clusters were thresholded to a maximum t-score equating to a p value < 0.05 and cluster size > 30 voxels.

Due to the difficulty of assessing the hippocampus on surface-based models, additional analysis was conducted to assess differences in individual t-scores. A region of interest (ROI) was generated consisting of a 5-mm radius sphere at the hippocampal MNI coordinate of $\pm 30/-26/-11$. The mean t-score and SD of all nonzero voxels was obtained for each ROI in all individual patient t-maps.

Results

Patient Information

Patient demographic data and outcomes are listed in Table 1. The clinical follow-up period averaged 29.7 months (range 18–39 months). We identified 3 patients who responded to therapy ($\geq 50\%$ reduction in seizure frequency) and 3 patients who were nonresponders ($< 50\%$ reduction in seizure frequency). Of our 6 patients, 5 had

TABLE 1. Demographic data and outcomes in 6 patients who underwent ANT DBS for refractory epilepsy

Case No.	Sex	Age (yrs)	Additional Leads	Seizures (no./mo)		FU (mos)
				Pre-DBS	Post-DBS	
1	M	47	None	36	34	18
2	F	32	Hippocampus	13	15	27
3	M	39	Hippocampus	4	4	30
4	F	33	Hippocampus	>200	90	28
5	F	32	Hippocampus	2	0.3	39
6	F	30	Centromedian	90	2	36

FU = follow-up.

leads in an additional target (4 hippocampal and 1 Cm-PF complex). Of these 5 patients, 4 had stimulation of both targets (3 patients with ANT + hippocampal stimulation and 1 patient with ANT + Cm-PF complex). Of those 4 patients, 2 were in the responder group and 2 were in the nonresponder group.

Imaging Results

Imaging results highlight potential differences in functional connectivity that result from relatively small differences in the location of the VTA. Normalized electrode locations for all subjects are shown in Fig. 1. In general, the distal cathode contacts of electrodes in the responder group were more posterior and dorsal in location within the thalamus compared with those of nonresponders. The patient in case 4 had a VTA location more ventral on the left compared with other responders; however, the VTA was centered near the junction of the mammillothalamic tract and the ANT. Functional connectivity profiles generated from the VTA for each patient are shown in Supplementary Fig. 1.

Distinctly different connectivity profiles were present in the averaged group maps for the responders (Fig. 2 left) and nonresponders (Fig. 2 right). When comparing responders to nonresponders, group mean differences (Fig. 3) showed higher positive correlation in responders, with several areas in the DMN having t-score differences > 3, including the bilateral PCC, medial prefrontal cortex, and inferior parietal lobule (Table 2). In contradistinction, the nonresponders showed poor positive correlation with nodes in the DMN. The cluster with the greatest t-score difference between responders and nonresponders was the PCC (maximum t-score difference of 7.6 on the right and 8.6 on the left).

Additional areas with a maximum t-score difference > 3 between responders and nonresponders included the bilateral anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), amygdala, and inferior frontal regions, as well as the right inferior temporal gyrus. Similar distribution of clusters was present in both hemispheres, with the exception of a cluster in the right insula, left hypothalamus, and left orbitofrontal regions.

Interestingly, there was also a greater anticorrelation with the hippocampus seen in responders (Fig. 4). Additional significant clusters of anticorrelation that were greater in responders than in nonresponders were noted,

FIG. 1. Normalized spatial location of the distal cathode contact (K1/K9) for responders (*green asterisks*) and nonresponders (*red asterisks*) for the left thalamus (**A and B**) and the right thalamus (**C and D**). All electrodes are Medtronic 3389. Contact locations are registered to the DBS Intrinsic Template Atlas (DISTAL), showing the relationship to the anterior thalamic nucleus (*arrows*).

including the left lingual gyrus (cluster MNI COG $-14/-68/-8$; maximum t-score difference 4.0), right lingual gyrus (COG $16/-72/0$; maximum t-score difference 3.6), and left fusiform gyrus (COG $-44/-72/-16$; maximum t-score difference 3.1). Last, anticorrelation with the ventral striatum was also present (cluster MNI COG $-2/12/-4$; maximum t-score difference 3.1).

Discussion

To our knowledge, our study is the first to illustrate potential differences in epilepsy outcomes after ANT DBS based on resting-state connectivity profiles defined by the VTA location. Specifically, we found that patients responsive to therapy had VTAs located in ANT regions more

FIG. 2. Group average t-score maps for responders (*left*) and nonresponders (*right*) showing areas of positive correlation (*red-yellow on map*) and anticorrelation (*blue-green on map*).

FIG. 3. Connectivity maps representing areas of connectivity that are higher in responders than in nonresponders (responders > nonresponders) for the left and right hemispheres. Areas with higher “positive” correlation in responders compared to nonresponders are shown in *red-orange* and areas of higher “negative” correlation, or anticorrelation, are shown in *blue-green*. Maps are generated from differences in mean group maps and thresholded to p value < 0.05, corrected for degrees of freedom.

positively correlated with the DMN when compared to nonresponders. Our findings highlight the importance of precise ANT targeting and suggest that a potential mechanism of ANT DBS is modulation of the DMN. If confirmed in larger studies, this information may allow more accurate preoperative targeting to maximize outcomes in ANT DBS for epilepsy.

ANT DBS is a promising technique for treatment of refractory epilepsy; however, outcomes thus far have been variable.^{18,44} The basis of such variation is complex and probably multifactorial. One potential confounder is relat-

ed to seizure type and origin. For example, patients with extratemporal or multifocal seizure onset zones have been shown to have a less efficacious response to ANT DBS compared with patients in whom onset is in the temporal lobes.^{18,42} Another potential contributor to variable outcomes is variability in electrode localization. To date, the ideal coordinates for ANT DBS placement have not been well defined.⁵⁰ It is also known that thalamic functional anatomy varies substantially compared to rigid atlas-based coordinates.³⁶ Since the SANTE trial, others have proposed potential methods of direct targeting; however,

TABLE 2. Cluster statistics for group average t-score differences (responders > nonresponders)

Rt Hemisphere				Lt Hemisphere			
Cluster COG (MNI coordinate)	Anatomical Reference	Cluster Size (mm ³)	Cluster Max t-Score Diff	Cluster COG (MNI coordinate)	Anatomical Reference	Cluster Size (mm ³)	Cluster Max t-Score Diff
50/-34/28	Inferior parietal lobule	1629	4.0	-62/-36/36	Inferior parietal lobule	1670	5.3
4/-26/34	Posterior cingulate	1339	7.6	-4/-22/32	Posterior cingulate	1583	8.6
58/18/12	Inferior frontal	1086	4.2	-34/48/29	Dorsolateral prefrontal	1149	4.3
2/28/20	Anterior cingulate	612	3.8	-2/30/30	Anterior cingulate	965	3.7
4/30/44	Medial prefrontal	581	3.7	-60/2/10	Inferior frontal	899	3.8
30/50/16	Dorsolateral prefrontal	411	3.4	-4/34/38	Medial prefrontal	505	3.6
10/-68/40	Precuneus	292	2.2	-32/0/-12	Amygdala	177	3.2
62/-28/-24	Inferior temporal	147	3.5	-32/48/-16	Orbitofrontal	149	2.8
20/-2/-32	Amygdala	141	3.2	-34/16/-36	Temporal pole	129	2.4
42/-12/-38	Temporal pole	119	2.5	0/-70/42	Precuneus	109	2.0
44/-10/0	Insula	35	2.8	4/-10/-16	Hypothalamus	72	2.5
				-64/-42/-18	Inferior temporal	52	2.2

Diff = difference; max = maximum.

FIG. 4. Coronal images through the hippocampus ($y = -26$; MNI template space) show the mean degree of anticorrelation in nonresponders (A) and responders (B). The mean difference (responders > nonresponders) is also shown (C). The ROI analysis (lower panel) at the hippocampal MNI coordinate of $\pm 30/-26/-11$ is shown for each patient (mean t-score and SD of all nonzero voxels with the ROI). L = left; R = right.

the ideal target remains elusive.^{10,40} Given the movement toward functionally defined targets in other forms of DBS as an independent biomarker, such a functional target may also prove beneficial to ANT DBS.^{1,24,37}

The development of functional preoperative targets requires an improved understanding of the mechanism of ANT DBS in treating epilepsy. Previously, the ACC has been implicated as a central core network hub in both ANT and thalamic centromedian nucleus DBS.^{25,26,52} Additionally, hippocampal connectivity has also been implicated as a potential mediator of ANT effect.²⁰ Interestingly, Gibson et al. showed BOLD activation related to ANT stimulation in a swine model involving ACC, hippocampus, amygdala, insula, and prefrontal cortex, among others. However, these prior studies did not assess potential differences in connectivity between ANT DBS responders and nonresponders. Our study further supports prior findings illustrating a more robust connectivity profile largely corresponding to the ACC and DMN in responders compared to nonresponders.

The DMN has been extensively studied in patients with epilepsy, with numerous studies highlighting DMN abnormalities in various forms of the disease, including TLE,^{34,51} absence seizures,³³ and reflex epilepsy,⁶ among others. Baseline decreased DMN connectivity is a common feature of epilepsy, and the degree of decreased connectivity

has been shown to correlate with seizure frequency.^{6,33,34,51} However, not all DMN nodes show such decreased connectivity; in particular, the hippocampus has been shown to exhibit increased connectivity in epilepsy.^{4-6,39} In fact, Bettus et al. reported that an increase in connectivity of the hippocampus and amygdala contralateral to the side of the seizure onset zone had the highest specificity for epileptogenic zone localization.⁵ Additional prognostic value of these findings has been shown by Bharath et al., who found hippocampal increased connectivity only in patients with frequent seizures and not in the infrequent seizure group or controls, suggesting that this connectivity profile may be an indicator of drug-resistant seizures.⁶ This is also supported by evidence that patients with greater disturbance in the DMN, including the hippocampus, were less likely to respond to anterior temporal lobectomy.⁸

In addition to baseline disturbances in DMN connectivity, studies have also evaluated dynamic changes in the DMN during a seizure event. An intriguing finding is that seizure onset coincides with deactivation of components of the DMN, whereas seizure termination corresponds to increased activation in the DMN.^{3,7,27,29} Given the proposed role of the DMN in consciousness, these findings would seemingly fit clinical observations. Importantly, these findings suggest a role of the DMN in propagation and cessation of seizure activity.

In our study, we found that patients responding to ANT DBS had VTAs in thalamic regions with connectivity to the DMN. The profile of responders differed from that of nonresponders whose VTAs had less correlation with the DMN. In particular, we found a positive correlation with the PCC, medial prefrontal cortex, inferior parietal lobule, and precuneus. Based on previous evidence that decreased DMN connectivity preceded seizure onset, we propose that modulation of the DMN potentially underlies the therapeutic effect of ANT DBS by raising the threshold for DMN suppression and propagation of seizures.^{3,7,27,29} Last, greater connectivity between the VTA and the ACC and DLPFC was found; these are traditionally considered part of the working memory network. The role of the working memory network in seizures is not well studied, but these findings may still be related to DMN connectivity given the described frequent coactivation of the DMN and working memory network during task preparation.²⁸

Our results also show an anticorrelation between thalamic VTAs and the hippocampus of responders that was not present in nonresponders. The etiology of resting-state blood oxygen level–dependent anticorrelations is not entirely clear. Initially, these anticorrelations were thought to be artifactual and related to the application of global signal regression in data preprocessing; however, subsequent work has shown that anticorrelations are indeed likely to be of biological origin.¹² Current evidence suggests that resting-state anticorrelations are related to neuronal inhibition, probably mediated through increased γ -aminobutyric acid (GABA) concentration.^{32,41} The presence of hippocampal anticorrelation in our responders is an intriguing finding given the evidence of baseline increased connectivity in the hippocampus in patients with frequent seizures.^{4–6,39} Our results suggest that VTAs in the ANT DBS responder group may create a suppression of baseline hippocampal hyperconnectivity. This is further supported by animal studies showing sustained increases in GABA levels in the hippocampus after ANT stimulation.^{35,47}

Additional areas of anticorrelation were found within the occipital lobes that were greater in responders compared with nonresponders. It has been previously shown that patients with epilepsy have increased intralobe connectivity within the occipital lobe.⁴³ The etiology is uncertain but has been proposed as visual overactivation in epileptic patients.⁴³ Along these lines, the observation of increased connectivity between the temporal lobe and occipital lobe during seizure propagation suggests that the occipital lobe may play a role in several forms of epilepsy.²¹ To date, this effect is not fully understood; therefore, the anticorrelation found in our study is of uncertain importance.

Several limitations of our study are noteworthy. First, the small sample size limits the ability to assess the robustness of the findings, and reflects the pilot nature of this study. Second, the use of atlas-based functional data may not fully account for variability in single-subject functional anatomy. Third, some patients also had additional DBS leads, such as Cm-PF complex or hippocampal leads, which could confound the results because of lesion effects. In addition to the potential lesional effect of having a lead in another target, 4 patients had simultaneous stimulation

of the ANT and another target, and our activation data do not account for stimulation at multiple sites. Our preliminary study serves to introduce a concept and posit a potential mechanism of ANT stimulation, but it must be validated in a controlled and prospective manner. Last, it is also known that variation in stimulation parameters and lead type affect activation patterns.²⁰ As such, further understanding is needed to generalize these findings to other devices and programming, given that all patients in our group had the same lead implants and stimulation profiles. Nevertheless, the results of our pilot study may help shed light on the potential mechanism of ANT DBS and help guide preoperative targeting in the future.

Conclusions

Based on our pilot study, we hypothesize that successful ANT DBS in epilepsy produces increased connectivity in the DMN and increases the threshold for seizure propagation. Additionally, an inhibitory effect on the hippocampus may contribute to seizure suppression. Determining which of these effects is the dominant driver of seizure suppression, or whether they are complementary effects, will require further study. Identification of this connectivity profile related to the thalamic VTA may aid in better definition of functional preoperative targets for ANT DBS. These findings will have to be confirmed in future studies.

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Supplemental Information

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