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 \(\gamma\)-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 ability to adequately treat patients with this type of epilepsy. Whereas early models largely focused on discrete epilptogenic sources,18 many forms of epilepsy, particularly temporal lobe epilepsy (TLE), are becoming increasingly recognized as network diseases with widespread function-
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.\(^{9,13,46}\) 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 discharges\(^{17}\) 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.\(^{10,30}\) Suggested improvements in direct ANT targeting have been proposed;\(^{10,40}\) however, insufficiencies in direct structural targeting in DBS have been previously illustrated.\(^{10,37}\) 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 ≥ 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,\(^{39}\) 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 2009.23,25 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).24

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 ±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 (≥ 50% reduction in seizure frequency) and 3 patients who were nonresponders (< 50% reduction in seizure frequency). Of our 6 patients, 5 had 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.

### 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) Pre-DBS | Seizures (no./mo) Post-DBS | FU (mos) |
|----------|-----|-----------|------------------|--------------------------|---------------------------|---------|
| 1        | M   | 47        | None             | 13                       | 15                        | 27      |
| 2        | F   | 32        | Hippocampus      | 3                        | 4                         | 30      |
| 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.
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. 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).

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).
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. The basis of such variation is complex and probably multifactorial. One potential confounder is related 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. 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. It is also known that thalamic functional anatomy varies substantially compared to rigid atlas-based coordinates. 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                   |                 |                               |                 |                 |
| Diff = difference; max = maximum. |
| Cluster COG (MNI coordinate)    | Anatomical Reference            | Cluster Size (mm³) | Cluster Max t-Score Diff     | Cluster COG (MNI coordinate) | Anatomical Reference | Cluster Size (mm³) | 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 |

**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.
the ideal target remains elusive. 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.

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. Additionally, hippocampal connectivity has also been implicated as a potential mediator of ANT effect. 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, absence seizures, and reflex epilepsy, 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. However, not all DMN nodes show such decreased connectivity; in particular, the hippocampus has been shown to exhibit increased connectivity in epilepsy.

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. 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.\textsuperscript{3,27,28} 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.\textsuperscript{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 artificial 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.\textsuperscript{12} Current evidence suggests that resting-state anticorrelations are related to neuronal inhibition, probably mediated through increased \(\gamma\)-aminobutyric acid (GABA) concentration.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{43} The etiology is uncertain but has been proposed as visual overactivation in epileptic patients.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

References

1. Akram H, Dayal V, Mahlknecht P, Georgiev D, Hyam I, Foltynie T, et al: Connectivity derived thalamic segmentation in deep brain stimulation for tremor. Neuroimage Clin 18:130–142, 2018
2. Avants BB, Epstein CL, Grossman M, Gee JC: Symmetric diffeomorphomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Med Image Anal 12:26–41, 2008
3. Benuzzi F, Ballotta D, Mirandola L, Ruggieri A, Vaudano AE, Zucchelli M, et al: An EEG-fMRI study on the termination of generalized spike-and-wave discharges in absence epilepsy. PLoS One 10:e0130943, 2015
4. Bettus G, Bartolomei F, Confort-Gouny S, Guedj E, Chauvel P, Cozzone PJ, et al: Role of resting state functional connectivity MRI in presurgical investigation of mesial temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 81:1147–1154, 2010
5. Bettus G, Guedj E, Joyeux F, Confort-Gouny S, Soulier E, Laguitton V, et al: Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. Hum Brain Mapp 30:1580–1591, 2009
6. Bharath RD, Sinha S, Panda R, Raghavendra K, George L, Chaitanya G, et al: Seizure frequency can alter brain connectivity: evidence from resting-state fMRI. AJNR Am J Neuroradiol 36:1890–1898, 2015
7. Blumenfeld H, McNally KA, Vanderhill SD, Paige AL, Chung R, Davis K, et al: Positive and negative network correlations in temporal lobe epilepsy. Cereb Cortex 14:892–902, 2004
8. Bonilha L, Jensen JH, Baker N, Breedlove J, Nesland T, Lin JJ, et al: The brain connectome as a personalized biomarker of seizure outcomes after temporal lobectomy. Neurology 84:1846–1853, 2015
9. Buckner RL, Andrews-Hanna JR, Schacter DL: The brain’s default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124:1–38, 2008
10. Buentjens L, Kopitzki K, Schmitt FC, Voges J, Tempelmann C, Kaufmann J, et al: Direct targeting of the thalamic anteroventral nucleus for deep brain stimulation by T1-weighted magnetic resonance imaging at 3 T. *Stereotact Funct Neurosurg* 92:25–30, 2014

11. Cataldi M, Avoli M, de Villers-Sidani E: Resting state networks in temporal lobe epilepsy. *Epilepsia* 54:2048–2059, 2013

12. Chai XJ, Castañón AN, Ongür D, Whitfield-Gabrieli S: Anatomical connections in resting-state networks. *Proc Natl Acad Sci U S A* 103:13848–13853, 2006

13. Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, et al: Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A* 101:8418–8423, 2004

14. Danielson NB, Guo JN, Blumenfeld H: The default mode network and altered consciousness in epilepsy. *Behav Neurol* 24:55–65, 2011

15. Engel J Jr, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, et al: Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA* 307:922–930, 2012

16. Ewert S, Plettig P, Li N, Chakravarty MM, Collins DL, Herrington TM, et al: Toward defining deep brain stimulation targets in MNI space: a subcortical atlas based on multimodal MRI, histology and structural connectivity. *Neuroimage* 170:271–282, 2018

17. Fahoum F, Zelmann R, Tyvaert L, Dubeau F, Gotman J: Epileptic discharges affect the default mode network—FMRI and intracerebral EEG evidence. *PLoS One* 8:e68038, 2013

18. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al: Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 51:899–908, 2010

19. Fonov V, Evans AC, Botteron K, Almri CL, McKinstry RC, Collins DL: Unbiased average age-appropriate atlases for pediatric studies. *Neuroimage* 54:313–327, 2011

20. Gibson WS, Ross EK, Han SR, Van Gompel JJ, Min HK, Lee KH: Anterior thalamic deep brain stimulation: functional activation patterns in a large animal model. *Brain Stimul* 9:770–773, 2016

21. Hamandi K, Powell HWR, Laufs H, Symms MR, Barker GJ, Kähärä V, et al: Defining the anterior nucleus of the thalamus using probabilistic diffusion tractography for deep brain stimulation targeting in Parkinson’s disease. *AJNR Am J Neuroradiol* [epub ahead of print], 2018

22. Hodaie M, Wennberg RA, Dostrovsky JO, Lozano AM: Chronic anterior thalamic stimulation for intractable epilepsy. *Epilepsia* 43:603–608, 2002

23. Horn A, Kühn AA: Lead-DBS: a toolbox for deep brain stimulation electrode localizations and visualizations. *Neuroimage* 107:127–135, 2015

24. Horn A, Reich M, Vorwer J, Li N, Wenzel G, Fang Q, et al: Connectivity predicts deep brain stimulation outcome in Parkinson disease. *Ann Neurol* 82:67–78, 2017

25. Kim HY, Hur YJ, Kim HD, Park KM, Kim SE, Hwang TG: Modification of electrophysiological activity pattern after anterior thalamic deep brain stimulation for intractable epilepsy: report of 3 cases. *J Neurosurg* 126:2028–2035, 2017

26. Kim SH, Lim SC, Yang DW, Cho JH, Son BC, Kim J, et al: Thalamo-cortical network underlying deep brain stimulation of centromedian thalamic nuclei in intractable epilepsy: a multimodal imaging analysis. *Neuropsychiatr Dis Treat* 13:2607–2619, 2017

27. Kobayashi E, Bagshaw AP, Bénar CG, Aghakhani Y, Andermann F, Dubeau F, et al: Temporal and extratemporal BOLD responses to temporal lobe interictal spikes. *Epilepsia* 47:343–354, 2006

28. Koshino H, Minamoto T, Yaoi K, Osaka M, Osaka N: Co-activation of the default mode network regions and working memory network regions during task preparation. *Sci Rep* 4:5954, 2014

29. Lauß H, Hamandi K, Salek-Haddadi A, Kleinschmidt AK, Duncan JS, Lemieux L: Temporal lobe interictal epileptic discharges affect cerebral activity in “default mode” brain regions. *Hum Brain Mapp* 28:1023–1032, 2007

30. Lehtimäki K, Coenen VA, Gonçalves Ferreira A, Boon P, Elger C, Taylor RS, et al: The surgical approach to the anterior nucleus of thalamus in patients with refractory epilepsy: experience from the International Multicenter Registry (MORE). *Neurosurgery* [epub ahead of print], 2018

31. Li MCH, Cook MJ: Deep brain stimulation for drug-resistant epilepsy. *Epilepsia* 59:273–290, 2018

32. Liang Z, King J, Zhang N: Anticorrelated resting-state functional connectivity in awake rat brain. *Neuroimage* 59:1190–1199, 2012

33. Liao W, Zhang Z, Martini D, Xu Q, Ji GJ, Zhang H, et al: Dynamical intrinsic functional architecture of the brain during absence seizures. *Brain Struct Funct* 219:2001–2015, 2014

34. Liao W, Zhang Z, Pan Z, Martini D, Ding J, Duan X, et al: Altered functional connectivity and small-world in mesial temporal lobe epilepsy. *PLoS One* 8:e5825, 2010

35. Liu HG, Yang AC, Meng DW, Chen N, Zhang JG: Stimulation of the anterior nucleus of the thalamus induces changes in amino acids in the hippocampi of epileptic rats. *Brain Res* 1477:37–44, 2012

36. Middlebrooks EH, Holanda VM, Tuna IS, Desphande HD, Bredel M, Almeida L, et al: A method for pre-operative single-subject thalamic segmentation based on probabilistic tractography for essential tremor deep brain stimulation. *Neuroradiology* 60:303–309, 2018

37. Middlebrooks EH, Tuna IS, Grewal SS, Almeida L, Heckman M, Lesser E, et al: Segmentation of the globus pallidus internus using probabilistic diffusion tractography for deep brain stimulation targeting in Parkinson’s disease. *AJNR Am J Neuroradiol* [epub ahead of print], 2018

38. Middlebrooks EH, Ver Hoef L, Szafiłski JP: Neuroimaging in epilepsy. *Curr Neurol Neurosci Rep* 17:32, 2017

39. Morgan VL, Rogers BP, Sonmeztekin HH, Gore JC, Abou-Khalil B: Cross hippocampal influence in mesial temporal lobe epilepsy measured with high temporal resolution functional magnetic resonance imaging. *Epilepsia* 52:1741–1749, 2011

40. Möttönen T, Katsikos J, Haapasaalo T, Tähtinen T, Kiekkas T, Kääriäi V, et al: Defining the anterior nucleus of the thalamus (ANT) as a deep brain stimulation target in refractory epilepsy: delineation using 3 T MRI and intraoperative microelectrode recording. *Neuroimage Clin* 7:823–829, 2015

41. Northoff G, Walter M, Schulte RF, Beck J, Dydak U, Henning A, et al: GABA concentrations in the human anterior cingulate cortex predict negative BOLD responses in fMRI. *Nat Neurosci* 10:1515–1517, 2007

42. Osorio I, Overman J, Giffakas J, Wilkinson SB: High frequency thalamic stimulation for inoperable mesial temporal epilepsy. *Epilepsia* 48:1561–1571, 2007

43. Rajpoot K, Riaza A, Majeed W, Rajpoot N: Functional connectivity alterations in epilepsy from resting-state functional MRI. *PLoS One* 10:e0134944, 2015

44. Salanova V, Witt T, Worth R, Henry TR, Gross RE, Nazzaro JM, et al: Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology* 84:1025–1025, 2015

45. Schönke T, Kupsch A, Kühn AA, Schneider GH, Hoffmann KT: Automated optimization of subcortical cerebral MR imaging-atlas coregistration for improved postoperative electrode localization in deep brain stimulation. *AJNR Am J Neuroradiol* 30:1914–1921, 2009

46. Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi
SN, Snyder AZ, et al: The default mode network and self-referential processes in depression. *Proc Natl Acad Sci U S A* 106:1942–1947, 2009

47. Shi L, Yang AC, Li JI, Meng DW, Jiang B, Zhang JG: Favorable modulation in neurotransmitters: effects of chronic anterior thalamic nuclei stimulation observed in epileptic monkeys. *Exp Neurol* 265:94–101, 2015

48. Tatum WO IV: Mesial temporal lobe epilepsy. *J Clin Neurophysiol* 29:356–365, 2012

49. Van Gompel JJ, Klassen BT, Worrell GA, Lee KH, Shin C, Zhao CZ, et al: Anterior nuclear deep brain stimulation guided by concordant hippocampal recording. *Neurosurg Focus* 38(6):E9, 2015

50. Wu C, D’Haese PF, Pallavaram S, Dawant BM, Konrad P, Sharan AD: Variations in thalamic anatomy affect targeting in deep brain stimulation for epilepsy. *Stereotact Funct Neurosurg* 94:387–396, 2016

51. Zhang Z, Lu G, Zhong Y, Tan Q, Liao W, Wang Z, et al: Altered spontaneous neuronal activity of the default-mode network in mesial temporal lobe epilepsy. *Brain Res* 1323:152–160, 2010

52. Zumsteg D, Lozano AM, Wieser HG, Wennberg RA: Cortical activation with deep brain stimulation of the anterior thalamus for epilepsy. *Clin Neurophysiol* 117:192–207, 2006

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Author Contributions

Conception and design: all authors. Acquisition of data: Middlebrooks, Grewal, Stead, Lundstrom, Worrell. Analysis and interpretation of data: all authors. Drafting the article: Middlebrooks, Grewal, Stead. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Middlebrooks. Statistical analysis: Middlebrooks.

Supplemental Information

Online-Only Content

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