Neurotherapeutics 21 (2024) e00375

Contents lists available at ScienceDirect

Neurotherapeutics

journal homepage: www.sciencedirect.com/journal/neurotherapeutics

Original Article

Evaluating functional connectivity differences between DBS ON/OFF states in essential tremor

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ARTICLE INFO

Keywords:
Deep brain stimulation
Dentato-rubro-thalamic tract
Essential tremor
Resting-state functional MRI
Functional connectivity

ABSTRACT

Deep brain stimulation (DBS) targeting the ventral intermediate (Vim) nucleus of the thalamus is an effective treatment for essential tremor (ET). We studied 15 ET patients undergoing DBS to a major input/output tract of the Vim, the dentato-rubro-thalamic tract (DRTt), using resting state functional MRI (rsfMRI) to evaluate connectivity differences between DBS ON and OFF and elucidate significant regions most influential in impacting tremor control and/or concomitant gait ataxia. Anatomical/functional 1.5T MRIs were acquired and replicated for each DBS state. Tremor severity and gait ataxia severity were scored with DBS ON at optimal stimulation parameters and immediately upon DBS OFF. Whole brain analysis was performed using dual regression analysis followed by randomized permutation testing for multiple correction comparison. Regions of interest (ROI) analysis was also performed. All 15 patients had tremor improvement between DBS ON/OFF ($p < 0.001$). Whole brain analysis revealed significant connectivity changes between states in the left pre-central gyrus and left supplemental motor area. Group analysis of ROIs revealed that, with threshold $p < 0.05$, in DBS ON vs. OFF both tremor duration and tremor improvement were significantly correlated to changes in connectivity. A sub-group analysis of patients with greater ataxia had significantly decreased functional connectivity between multiple ROIs in the cortex and cerebellum when DBS was ON compared to OFF. Stimulation of the DRTt and concordant improvement of tremor resulted in connectivity changes seen in multiple regions outside the motor network; when combined with both structural and electrophysiologic connectivity, this may help to serve as a biomarker to improve DBS targeting and possibly predict outcome.

Introduction

Essential tremor (ET) is considered the most common movement disorder in adults [1–3]. It is proposed that the ventrointermediate nucleus (Vim) of the thalamus plays a key pacemaker role in this disease [4–6], where ultimately an abnormal rhythmic output travels from the cerebellar dentate nucleus to the contralateral red nucleus, Vim, and motor cortex via the dentato-rubro-thalamic tract (DRTt). Deep brain stimulation (DBS) to the Vim thalamus is considered a mainstay treatment for drug-refractory ET [7–9] because of its high efficacy, possibly improved by direct targeting fibers of the DRTt as is our current practice [8,10,11]. Visualization of such fibers through tractography has elucidated certain structures that are implicated in the pathophysiology of tremor, but it continues to be poorly understood.

Functionally, the DRTt consists of fibers that emanate from the cerebellar output nuclei (dentate, emboliform, globose) and ascend in the superior cerebellar peduncle, where most decussate, surround and enter the contralateral red nucleus, projecting onward to the Vim or ventralis oralis posterior nucleus (Vop) of the thalamus before terminating in the primary motor cortex [10,12,13]. Tractography defining this pathway has been the subject of multiple analyses in healthy controls as well as in tremor patients [8,10,11,14].

fMRI is a noninvasive technique that enables us to explore brain networks and better understand normal and abnormal physiology [4,5,

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https://doi.org/10.1016/j.neurot.2024.e00375
Received 29 October 2023; Received in revised form 5 May 2024; Accepted 13 May 2024

15,16]. Resting-state fMRI (rsfMRI) evaluates interactions between segregated brain areas in the absence of an explicit task, where activity is observed through changes in spontaneous fluctuations of blood-oxygen-level-dependent (BOLD) signal [17].

rsfMRI imaging findings pre/post-Vim thalamotomy have illustrated alterations in the brain's resting state networks that tend to normalize post-procedure [18,19] as well as showing that increased functional connectivity of visual association areas with Vim is predictive of tremor arrest in ET patients [20,21]. rsfMRI has been performed post-DBS in Parkinson's disease to show functional connectivity changes in the motor network [22,23], however, rsfMRI has not been evaluated in ET post-DBS and specifically, to study connectivity beyond the cortico-thalamo-cerebellar motor circuit.

In this study, we used rsfMRI to describe functional connectivity changes between implicated regions of interest in ET patients after DBS surgery in two different states: with DBS ON and with DBS OFF. This study is a proof of concept that rsfMRI can be performed successfully to evaluate functional connectivity changes outside the cortico-thalamo-cerebellar motor circuit in the ET population between DBS OFF and DBS ON. Such a study has yet to be published.

We hypothesized that as tremor clinically changed with DBS state, network connectivity would change as well, with normalization of increased connectivity seen with DBS OFF and exhibition of tremor compared to DBS ON (tremor cessation). Specifically, we performed a whole-brain analysis of connectivity and then evaluated specific regions of interest (ROIs) that lie along an 'extended' tremor network, defined by recent studies to include visual association areas [20,24] and validated by our own findings. We also investigated the feasibility of determining BOLD differences between the DBS target region (Vim thalamus) and these specific ROIs between DBS states. By collecting rsfMRI scans with DBS ON at parameters for optimal tremor control, and then again with DBS OFF, our goal was to evaluate functional connectivity differences between the two states in the hopes of elucidating which regions might be most involved in tremor regulation. Also, as ET patients can demonstrate gait ataxia, related to their degenerative pathology or secondary to DBS [25], we wanted to see what FC changes exist in the most ataxic patients relative to those without ataxia in order to possibly elucidate differences between ataxic/non-ataxic patients and relationship to DBS control of tremor.

Methods

Essential tremor patients who had previously undergone DBS of the DRTt as it enters the Vim thalamus were asked to participate in this study. Eligible patients were those implanted by the same surgeon (AJF) with Medtronic (Minneapolis, MN, USA) Activa PC DBS devices, targeting the DRTt as has been commonly performed for years. All patients had electrodes placed within the DRTt fibers, which were illustrated using deterministic tractography during targeting [10,11] and verified using post-operative CT merged onto the planning MRI. The estimated volume of tissue activated [26] from each patients' therapeutic contacts at the parameters used to control tremor incorporated fibers of the DRTt. At the time of the MRI examinations all patients had stable parameters for at least 3 months, with excellent tremor control. Impedance checking was performed immediately before imaging to ensure that circuit connectivity was valid. All patients had their DBS devices in bipolar configurations.

Motor examinations were performed in the MRI suite while stimulation was turned ON and then within 10 min after DBS was turned OFF. MRI sequences were performed sequentially on the same day, with DBS ON sequences immediately preceding DBS OFF sequences. Tremor severity using The Essential Tremor Rating and Assessment Scale (TETRAS) [27] and cerebellar gait ataxia using Items 1–3 of the Scale for Assessment and Rating of Ataxia (SARA) [28] were scored with DBS ON at optimal stimulation parameters and then upon DBS OFF. Tremor Improvement was defined as the difference between baseline tremor and DBS ON using TETRAS scores. Optimal stimulation parameters were defined by the parameter set which provided the best tremor relief and which remained stable for at least 3 months, at the time of the MRI study.

All patients consented to this study which was performed in accordance with UT Health Houston Institutional Review Board #HSC-MS-20-0739 policies.

MRI Sequences and Image Pre-processing

All MRI examinations were performed according to the Medtronic guidelines and with use of bipolar stimulation [29]. All imaging was performed in an Ingenia 1.5T MR system (Phillips Healthcare, USA) with an 8-channel head coil.

All patients underwent two sessions of 1.5T MRI studies, replicated for the two DBS states of ON or OFF. The total scan time was approximately 24 min for each DBS state. This MRI protocol included anatomical imaging sequence with parameters: 3D T1-weighted fast gradient echo sequence (FFE), echo time 3 ms, repetition time 6.4 ms, flip angle 10, spatial resolution of $0.5 \times 0.5 \times 1$ mm^3 (6:02 min duration); two BOLD fMRI imaging sequences with parameters: BOLD EPI 2D GR sequence, echo time 3 ms, repetition time 3400 ms, spatial resolution of $3 \times 3 \times 3$ mm^3; these two fMRI sequences were acquired back to back with dynamics of 300 and 150 vol, respectively (17:50 min duration total).

Whole brain analysis

Whole brain analysis was performed using a dual regression analysis technique using the MELODIC software in the FSL 6.0 package, as described previously [30,31]. This analysis was performed on the first 300 vol only. The first regression found independent components at the group level. The second regression projected the independent components from the group level to the individual level. We used FSL Randomise with a two-group paired *t*-test to assess differences between DBS ON and OFF in each network, with 5000 permutations and cluster-mass based thresholding (with cluster forming threshold $Z = 2.3$), to achieve a corrected family-wise error rate, $p < 0.05$ [32].

ROI analysis

Anatomical 3D T1-weighted data during DBS OFF were used for parcellation of functional regions to gain 11 regions of interest (ROIs) to serve as pre-defined nodes of a network relative to essential tremor, based on previous literature findings of their involvement in tremor [19,22,29,30]. First, Freesurfer 7.1.1 [33,34] was used to divide a brain into 216 regions including gray matter parcels and nuclei, but excluding the cerebellum. 6 ROIs obtained directly from a result of Freesurfer were the left and right precentral gyri, and superior and inferior parietal lobules (SPL/IPL).

Thalamic segmentation was performed by Freesurfer by using segmentThalamicNuclei.sh [35], among those nuclei Left-ventrolateral posterior thalamus (VLP) and Right-VLP were extracted. However, upon inspection it was realized that the resultant VLP segment was larger in the rostral-caudal extent than the true Vim thalamus. To better approximate the Vim, the resultant VLP was divided in half along its rostral-caudal dimension and the caudal half was chosen to represent the bilateral Vim which was used as a ROI for connectivity analysis (see Fig. 1).

Cerebellum anatomical parcellation was performed by software implementing U-Net with locally constrained optimization [36]. The cerebellar nodule ROI was created by combining parcels of Left_I-III and Right_I-III and edited to form the final cerebellar nodule ROI for each patient while the right and left dentate nuclei (DN) ROIs were extracted and separated from the parcel of Corpus_Medullare and erode was performed to avoid partial volume effects. Registration between 3D T1 and BOLD EPI was carried out by using epi_reg in FSL utility [37]. Subsequently, these 11 ROIs were converted into masks and projected into EPI

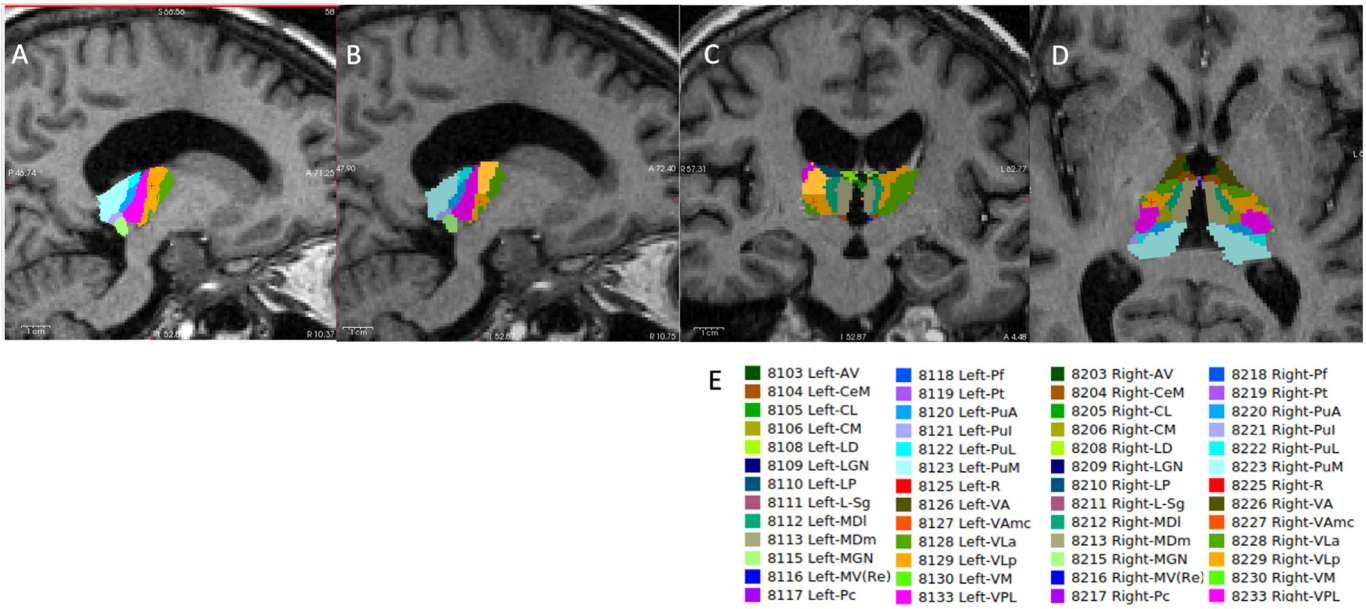

Fig. 1. Thalamic segmentation performed using segmentThalamicNuclei.sh (Freesurfer [34]) to obtain the region of VLP (orange with red cross) shown in sagittal orientation (A). The resultant VLP was divided into dorsal and ventral portions at the rostral-caudal halfway point to obtain the Vim (darker orange with red cross) shown in 3 dimensions (B, C, D). (Color codes are shown in (E) provided by Freesurfer [34].

space from anatomical space. These ROIs were thus chosen before analysis as a planned comparison between DBS states. See Fig. 2.

Image preprocessing of BOLD EPI

Two BOLD data of 300 and 150 dynamics were concatenated together to form a single functional data with 450 dynamics, and then input into iClinfMRI software [38] with default parameters: slicing timing correction, motion correction, alignment to 2 mm T1 using CBR, despiking, linear detrending, nuisance regression, bandpass filtering (0.01–0.08 Hz) and smoothing with a 4 mm full-width at half-maximum (FWHM) filter then occurred.

Each patient had two preprocessed BOLD data, one for DBS ON and another for DBS OFF. Co-registration between anatomical 3DT1 image in Freesurfer space and BOLD space was performed and subsequently 11 ROIs in Freesurfer space were transformed into the patient's BOLD space.

All patients had their electrode-extension connections placed on the left parietal location; the EPI distortion and susceptibility artifact from these implants resulted in signal loss, to which a mask was applied to exclude from analysis. The mask of the signal drop was created on the subject resting-fMRI image by using automatic VOI function of MRIcroGL 1.2.20200331. First, we manually placed the cursor near the center of the artifact, then set constraints: difference from origin of 16 and radius (mm) of 32. The sensitivity of connectivity to the precise choice of mask was not quantified. See Fig. 3. Finally, we extracted time-series of average signals of 11 ROIs for DBS ON and OFF, respectively.

Statistical analysis

The 11 ROIs defined the nodes of a brain network related to the response due to our DBS treatment. The DBS-induced change of connection strength between a pair of nodes, known as an edge in the

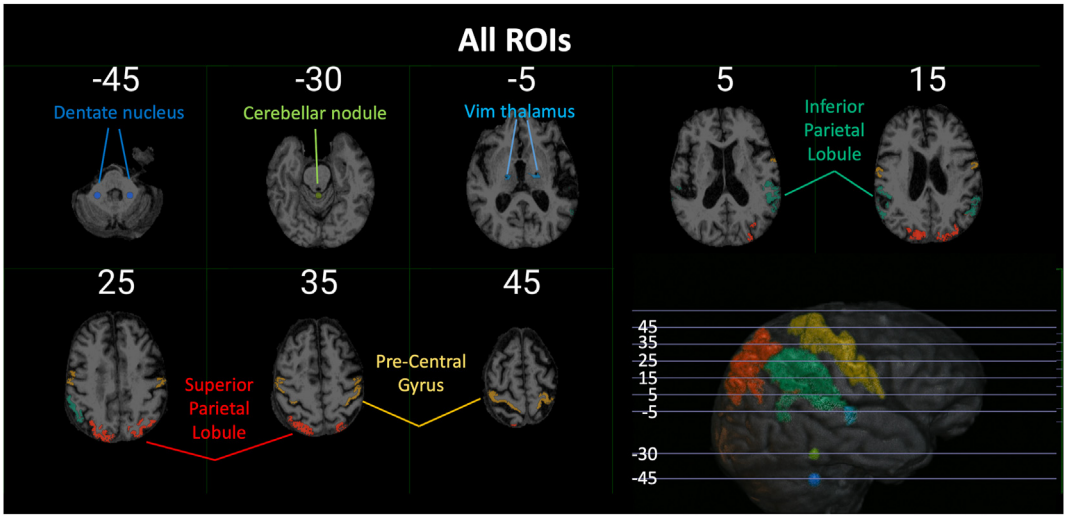

Fig. 2. All pre-specified ROIs depicted in fMRI space, axial slices at specific Z as indicated on reference lines. Inferior/Superior parietal lobules and pre-central gyrus ROI masks created after parcellation and segmentation of 3DT1 data using Freesurfer [34], and then registered with preprocessed fMRI data using FSL [35,36]. Dentate nucleus and cerebellar nodule ROIs manually drawn in fMRI space. Bilateral Vim thalamus ROI depicted using segmentation on Freesurfer [34] (see Fig. 1).

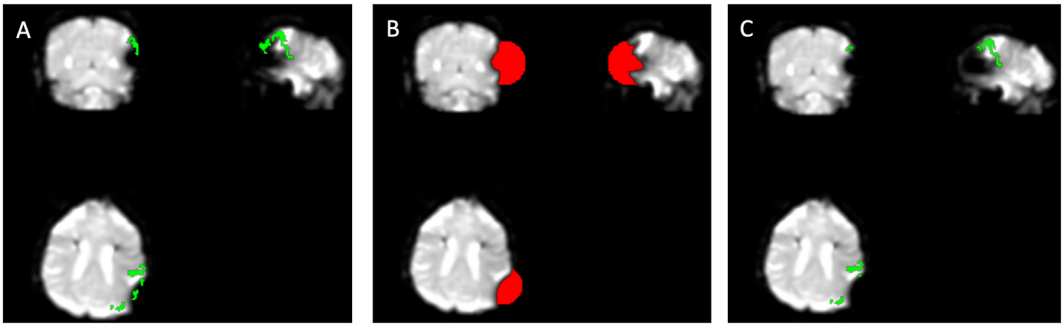

Fig. 3. EPI distortion and susceptibility artifact from the DBS extension wiring results in signal loss, all at the left parietal region. (A) Green line outlines the left inferior parietal lobule (IPL) ROI. (B) Mask for the region excluded due to artifact (solid red). (C) Green outline depicts the remaining IPL ROI after subtraction of the mask region of artifact shown in (B).

network, was measured by the z-score of correlation coefficient difference between DBS ON and OFF and corresponding *p*-value computed by using a method of R. A. Fisher [39], which represents change on an individual level.

In this study, we applied Fisher's z-transformation to correlation coefficients, which presents functional connection strength between regions, for both DBS ON and OFF, respectively [39,40]. Taking advantage of properties of a normal distribution of the transformed correlation coefficient, we derived the connection change due to DBS ON in comparison to DBS OFF using an analysis by Karl L. Wuensch, 2019 [41].

In this study, z-score = (r_transformed_ON − r_transformed_OFF)/ sqrt(var_ON + var_OFF). According to Fisher's paper, var_ON and var_OFF can be calculated based on number of volumes of our resting fMRI. Therefore, the normal distribution of the transformed correlation was used in the calculation of z-scores. For an edge in brain network, the average z-score is the mean value of z-scores over all 15 subjects, indicating the connection change when DBS is ON.

To evaluate the effect of DBS treatment at the group level, we applied thresholds on average z-scores: larger than 2 for the significant positive change and less than −2 for the significant negative change, resulting in two separated connectivity matrices.

Furthermore, by introduction of additional classification, we ranked patients by SARA score (items 1–3) and identified subgroups with SARA score >3. This resulted in 3 patients, with 12 patients remaining; we then relaxed the threshold SARA score to >2, which resulted in 6 patients (9 remaining). Applying the same previous z-score averaging and thresholding on these four new subgroups, we gained 8 new connectivity matrices and calculated the differences in z-scores between DBS ON and OFF states for each node.

In addition, Pearson correlation analysis was individually performed between z-score and tremor duration, tremor severity (baseline) and tremor improvement (between pre-op to post-op assessment) to see their effects on connectivity change on each edge.

Result and visualization

The results of average-z-score were presented in a glass brain using BrainNet Viewer Version 1.43 [42]. In a glass brain, change of brain network connectivity are visualized in a brain volume mapping to surface with nodes and edges. In each figure, nodes were drawn in different colors for different anatomical regions while edges were drawn with different thicknesses to represent the average z-score. Due to the fact that these few ROIs were pre-defined based on the literature findings [21,24,25,43], this analysis was considered a planned comparison; as such, correction for multiple comparisons was not performed [44,45].

Results

Fifteen patients were recruited for this study, four male and eleven female; all were right-handed. Minimal peri-ventricular white matter changes were seen in three patients; gliosis observed along the electrode tracts in two patients. Mean age at surgery was 68.1 (SD 7.0) years and mean disease duration was 27.7 (SD 18.3) years. Mean time after surgery for MRI acquisition was 402.5 days (SD 313.1). Mean bilateral appendicular TETRAS with DBS ON was 2.5 (SD 2.1); DBS OFF was 7.6 (SD 2.8). Difference in tremor severity with DBS ON/OFF was highly significant (TETRAS $p < 0.001$); all patients had appreciable control of tremor with DBS ON. See Table 1. At the time of the MRI exam, no patients had significant gait ataxia with DBS ON as defined by the Scale for Assessment and Rating of Ataxia (SARA, Items 1–3) ≥ 5 (see reference 25). However, at time of MRI exam 3 patients had SARA (Items 1–3) ≥ 3 and 6 patients had SARA (Items 1–3) ≥ 2.

All patients were implanted with Medtronic Activa PC DBS systems with bilateral Medtronic 3387 model electrodes inserted into the bilateral DRTt/Vim thalamus and with left-sided parietal subgaleal lead-extension wire looping. The mean (standard deviation) parameters used for tremor control at the last assessment were: left electrode [2.1 (1.1)mA, 70 (18) us, 151 (21) Hz], right electrode [2.6 (1.2) mA, 77 (22) us, 151 (21) Hz)].

Whole Brain Analysis

All of the individual EPI sequences were transformed onto the MNI template; these were then concatenated using the same TR value for the whole data set. In 3 patients, there were large discrepancies in the TR values; in one patient, there was poor quality of the non-linear registration from EPI space to MNI space. As such these 4 patients were excluded (patients 1,4,12,15 on Table 1) and so 11 patients' data was useable. 25 independent components (ICs) were identified. Following randomized permutation testing comparison correction with *p*-correct <0.05, two out of the 25 ICs were statistically significant. Please see Supplemental Table 1. One IC in the left pre-central gyrus was found to have increased connectivity with DBS ON > OFF; the second IC in the left supplementary motor area (SMA) was found to have increased connectivity with DBS OFF > ON. Please refer to Fig. 4.

ROI Analysis

Group analysis shows that, for all 15 patients, DBS ON vs. OFF does not cause much change in connectivity among the 11 ROIs. Please see Fig. 5A and B. With DBS ON vs. OFF, at a Z-Score threshold of 2 (i.e., greater connectivity in the ON vs. OFF state) there is increased connectivity between R SPL and R Pre-central gyrus (PCG), L SPL and R PCG, and between L and R DN; at a Z-score threshold of −2 (i.e., lower connectivity in the ON vs. OFF state), there is decreased connectivity between L and R IPL.

When we ranked patients by tremor severity (TETRAS), tremor duration (before DBS), or tremor improvement (pre-op vs. post-op assessment on TETRAS), only tremor duration and tremor improvement had a significant effect on functional connectivity. At threshold $p <$

Table 1
Patient characteristic and stimulation settings.

Patient	Age (y)	Sex	Tremor duration (y)	Pre-op TETRAS[a]	Post-op TETRAS (DBS ON)	Difference TETRAS	Pre-op SARA[a] (Items1-3)	Post-op SARA (Items1-3) (DBS ON)	Difference SARA (Items1-3)	Time (d) after surgery (ON/OFF)	L DBS parameters	R DBS parameters
1	60	F	4	12	5.5	6.5	0	2	−2	490	2.8 mA, 60 us, 160Hz	1.6 mA, 60 us, 160Hz
2	69	M	13	5.5	5	0.5	1	0	1	385	4.5 mA, 120 us, 185 Hz	4.5 mA, 120 us, 185 Hz
3	77	M	50	7.5	5	2.5	0	1	−1	420	2 mA, 60 us, 130Hz	2.2 mA, 60 us, 130Hz
4	73	F	5	5.5	4	1.5	0	0	0	493	4.1 mA, 60 us, 130Hz	4.1 mA, 60 us, 130Hz
5	59	F	25	6.5	4	2.5	4	0	4	336	1.4 mA, 60 us, 150Hz	2 mA, 60 us, 150Hz
6	61	F	50	5.5	4	1.5	2	2	0	140	1 mA, 60 us, 130 Hz	1.2 mA, 60 us, 130Hz
7	73	F	34	5	3	2	6	0	6	308	2.9 mA, 70 us, 140Hz	1.4 mA, 60 us, 140Hz
8	64	M	50	11.5	3	8.5	4	2	2	217	4.7 mA, 80 us, 165Hz	4.3 mA, 80 us, 165Hz
9	79	F	34	5	2	3	2	4[b]	−2	203	2.9 mA, 90 us, 145Hz	4 mA, 100 us, 145Hz
10	64	F	13	12	2	10	3	3	0	147	1.9 mA, 60 us, 185Hz	3 mA, 110 us, 185Hz
11	61	F	20	9	0	9	0	0	0	371	3.2 mA, 90 us, 165Hz	3.8 mA, 90 us, 165Hz
12	70	F	24	5	0	5	4	4	0	401	2.1 mA, 50 us, 150 Hz	2.1 mA, 56 us, 150 Hz
13	61	F	25	6	0	6	0	0	0	1461	1.9 mA, 60 us, 125Hz	1.2 mA, 60 us, 125Hz
14	73	F	61	7	0	7	0	0	0	294	3.5 mA, 70 us, 170Hz	4.6 mA, 100 us, 170Hz
15	77	M	7	12	0	12	0	1	−1	371	2.5 mA, 70 us, 135Hz	1.8 mA, 70 us, 135Hz
Mean (SD)	**68.1 (7.0)**		**27.7 (8.3)**			**5.2 (3.6)**			**0.5 (2.1)**	**402.5 (313.1)**	**2.7 (1.1) mA, 70 (18) us, 151 (21) Hz**	**2.6 (1.2) mA, 77 (22) us, 151 (21) Hz**

[a] Pre-op TETRAS and SARA scores were the same (except for 1 patient)[#] as Post-op DBS OFF during the acquisition of MRI, acquired 10 min after programming change.
[b] Patient 9 with increased SARA score (Items 1–3) post-op DBS ON of 4 remained at 4 with DBS OFF; d = day, y = year. Patients 1,4,12,15 were excluded from whole brain analysis.

0.05, for all 15 pts, significant connectivity changes between DBS ON and OFF correlated with tremor duration were found 1) between R IPL and R PCG (significant increase (ON > OFF) in connectivity with tremor duration, correlation coefficient R = 0.618 and $p = 0.014$); 2) between R Vim thalamus and L SPL (significant decrease (ON < OFF) in connectivity with tremor duration, correlation coefficient R = −0.726 and $p = 0.002$). Please see Fig. 5C. At threshold $p < 0.05$, for all 15 pts, significant connectivity changes between DBS ON and OFF correlated with tremor improvement were found between R SPL and R Vim thalamus (significant increase (ON > OFF) in connectivity with tremor improvement, correlation coefficient R = 0.576 and $p = 0.024$). Please see Fig. 5D.

When we ranked patients by severity of ataxia at their post-op assessment by SARA score (items 1–3), this resulted in three patients having a SARA score ≥3, with 12 patients remaining. When we relaxed the threshold SARA score to ≥2, this resulted in 6 patients (with 9 remaining). Applying the same previous z-score averaging and thresholding on these four new subgroups, we gained 8 new connectivity matrices.

The functional connectivity differences between the top 3 ranked and top 6 ranked ataxia patients was minimal, causing us to infer that the top 3 ranked ataxia scores drove both results. It is important to note that when we looked at these 3 patients with DBS ON and DBS OFF, there was minimal change in their ataxia between baseline and with DBS ON and then with DBS OFF (i.e., 2 patients had 0 change, and one patient was 2 points worse with DBS ON which remained the same with DBS OFF, which would imply that it was not caused by DBS and rather due to natural progression). Thus, in this set of ataxia severity patients, we looked at DBS ON/OFF differences related to significant tremor improvement.

For the 3 patients with the highest SARA (≥3) at a threshold of mean Z-score greater than 4, there were increases in connectivity with DBS ON vs. OFF seen between multiple ROIs in the cortex and in the cerebellum, but they remained for the most part segregated. Conversely, for the same patients at threshold of mean Z-score less than −4, all ROIs (except the bilateral VIM thalamus) displayed more significant connectivity decreases between each other in the cortex and with the bilateral DN with DBS ON vs. OFF. Please see Fig. 6A and B. When the remaining 12 patients with SARA <3 were analyzed for connectivity with DBS ON vs. OFF at a threshold of mean Z-score greater than 2, there were multiple increases in connectivity with DBS On vs. OFF seen. There were no significant decreases with DBS ON vs. OFF at Z-score −2 threshold. Please see Fig. 6C.

Please refer to Supplemental Tables 2,3,4,5 for individual subject data of differences in Z-scores between the ROIs shown to be most significant (Z-score threshold ≥2); ranges of Z-score differences are described in the figure legends of Figs. 5 and 6. Z-scores (both significant and non-significant) between each of the 11 ROIs for each of the 15 individual patients are provided in Supplemental Table 6.

Discussion

In this evaluation of functional connectivity differences between DBS states in a cohort of fifteen ET patients who underwent DRTt DBS, overall with DBS ON vs. OFF we saw changes in whole brain functional connectivity in the left pre-central gyrus and left SMA. When looking at our hypothesis-driven ROI based analysis, we observed an increase in FC between the PCG and SPL and a decrease in FC between the bilateral IPL. We found that tremor duration (before DBS) and tremor improvement were significantly correlated with connectivity. Most surprisingly, when we ranked patients by post-op DBS ON gait ataxia, the highest ataxia-scoring patients (ranked by SARA) had highly significant decreases in FC between the cerebellum and other ROIs with DBS ON vs. OFF, as compared to other non-ataxic patients.

These results expand upon previous literature findings of increased functional connectivity in the sensorimotor network [18,46] and cerebellar network [18,47] in ET post-lesion treatment compared to healthy

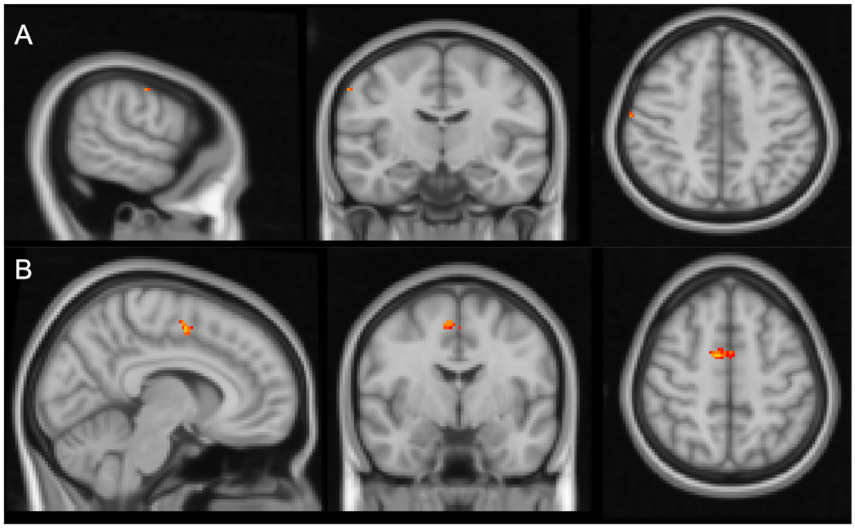

Fig. 4. Whole brain dual regression analysis yielded 2 independent components (IC) that survived correction for multiple comparison (FWE <0.05). (A) An IC in the left pre-central gyrus showed increased functional connectivity with DBS ON vs. DBS OFF state. (B) An IC in the supplemental motor area showed increased functional connectivity with DBS OFF vs. DBS ON state. Please refer to Supplemental Table 1 for individual IC *p*-values between DBS ON and OFF states.

controls [5,18,20,48,49] as it demonstrates that visual association cortical connectivity is correlated with tremor severity, which can be similarly reversible depending on DBS state.

Kato et al. [18] analyzed 15 ET patients who underwent unilateral MR-guided focused ultrasound (MRgFUS) ablation of the Vim thalamus and compared their FC states pre and post-MRgFUS as well as with healthy controls. Using dual regression whole brain analysis and also correcting for multiple comparisons, post-treatment there was an increase in FC in the somatosensory and visuospatial networks (SMN and VSN) compared to pre-op. In our cohort, we saw the exact same location of increased FC in the pre-central gyrus in the DBS ON vs. OFF state. This is quite interesting but anatomically not surprising, as it seems that this location in the motor cortex is responsive to treatment effect (i.e., significantly improved tremor), whether it is due to ablation or stimulation. Such FC change has not yet been described in the DBS literature. Along similar lines, the same group found a decrease in FC in the SMN between post-FUS and healthy controls, as well as an increase in FC in the cerebellum. In our analysis, we did not have a healthy control comparison; however, we did also find a similar decrease in FC in the SMA between DBS ON and OFF, which implies that perhaps this location also is also modulated by treatment. It is interesting that both of these significant changes were unilateral only on the left; although bilateral stimulation was employed, perhaps the more dominant side had a more significant change after stimulation and tremor improvement. Unfortunately, we did not find cerebellar changes in our whole brain analysis, which likely is a function of a lower number of patients (11 vs. planned 15) who could undergo this analysis. We hypothesize that the areas of significance would increase in size for each IC and perhaps more ICs would be significant with a larger cohort.

Our ROI analysis evaluated specific areas based on previous literature findings of involvement in tremor: key parts of the visual association (SPL, IPL ROIs), motor (PCG) and cerebellar (DN, cerebellar nodule) networks, which were identified as having significant functional connectivity changes in previous whole-brain analyses of ET [18,20,24,46,48].

A view into the greater tremor network has been gained by functional connectivity findings in ET patients, showing altered BOLD signaling on rsfMRI between not only Vim, M1, and cerebellum [49] but also supplementary motor and visual association cortices [20,21]. Increased visual feedback was previously seen to exacerbate tremor severity which was correlated with abnormal BOLD signal in the superior and inferior parietal lobules (SPL, IPL) in a fMRI study by Archer et al. [24]. In this study, increased visual feedback was correlated with abnormal changes in BOLD signal in ET patients as compared to controls in motor and sensory cortex as well as SPL and IPL, lingual gyrus, and cerebellum [24]. Increased connectivity to visuomotor pathways in ET patients has been identified previously [47,49,50]; the IPL has specifically been implicated in ET pathology [43,51], where measures of cortical thickness served to best characterize and diagnose ET patients from healthy controls [52].

These above studies together have elucidated a larger network beyond the nodes of the tremor motor pathway connected by the DRTt, which we wanted to incorporate into our evaluation of functional connectivity differences in tremor post-DBS and hence is the reason why they were chosen as ROIs. Indeed, we observed that changes in FC correlated with tremor duration between R IPL and R pre-central gyrus (increases) and between L SPL and R Vim (decreases) in DBS ON vs. OFF states, as well as FC increases between R SPL and R Vim correlated with tremor improvement.

Functional imaging studies post-DBS in ET have yet to be performed. Samamartino et al. [53] described the use of acquiring pre-op rsfMRI scan and intra-op rsfMRI post-ceramic cannula insertion in 10 ET patients undergoing asleep DBS. Although there was no electrode inserted, the ceramic cannula was at the Vim DBS target site, and there was a generalized trend of decreased functional connectivity in the motor network (thalamus, pre-motor, and motor cortices) post-cannula insertion compared to the pre-op asleep state. Group analysis revealed no statistical significance [53].

Boutet et al. [22] in their study of 102 patients demonstrated the feasibility and safety of performing functional MRI on DBS patients. The metallic susceptibility artifact due to the DBS lead and subgaleal extension wire coiling in the parietal area was observed; masks were applied to the parietal area to exclude the artifact from analysis. Artifact probability maps were created for 4 target areas but not for the Vim; however, based on inspection of the volumes of these artifacts it appears that the artifact due the electrode contacts in our series was equivalent. These authors concluded that the obscuring electrode artifact will likely limit functional MRI analysis at specific targets such as the STN, but not of the larger circuits influenced by DBS [22,54]. In our analysis, we used a different technique by choosing the inferior half of the segmented VLP thalamus as an ROI for analysis, which resulted in a useable volume, as well as enabled us to evaluate the greater network modulated by stimulation.

In a recent study of post-DBS ET patients with the development of progressive gait ataxia, ^{18}FDG positron emission tomography (PET) imaging elucidated increased cerebellar nodule metabolism with DBS ON,

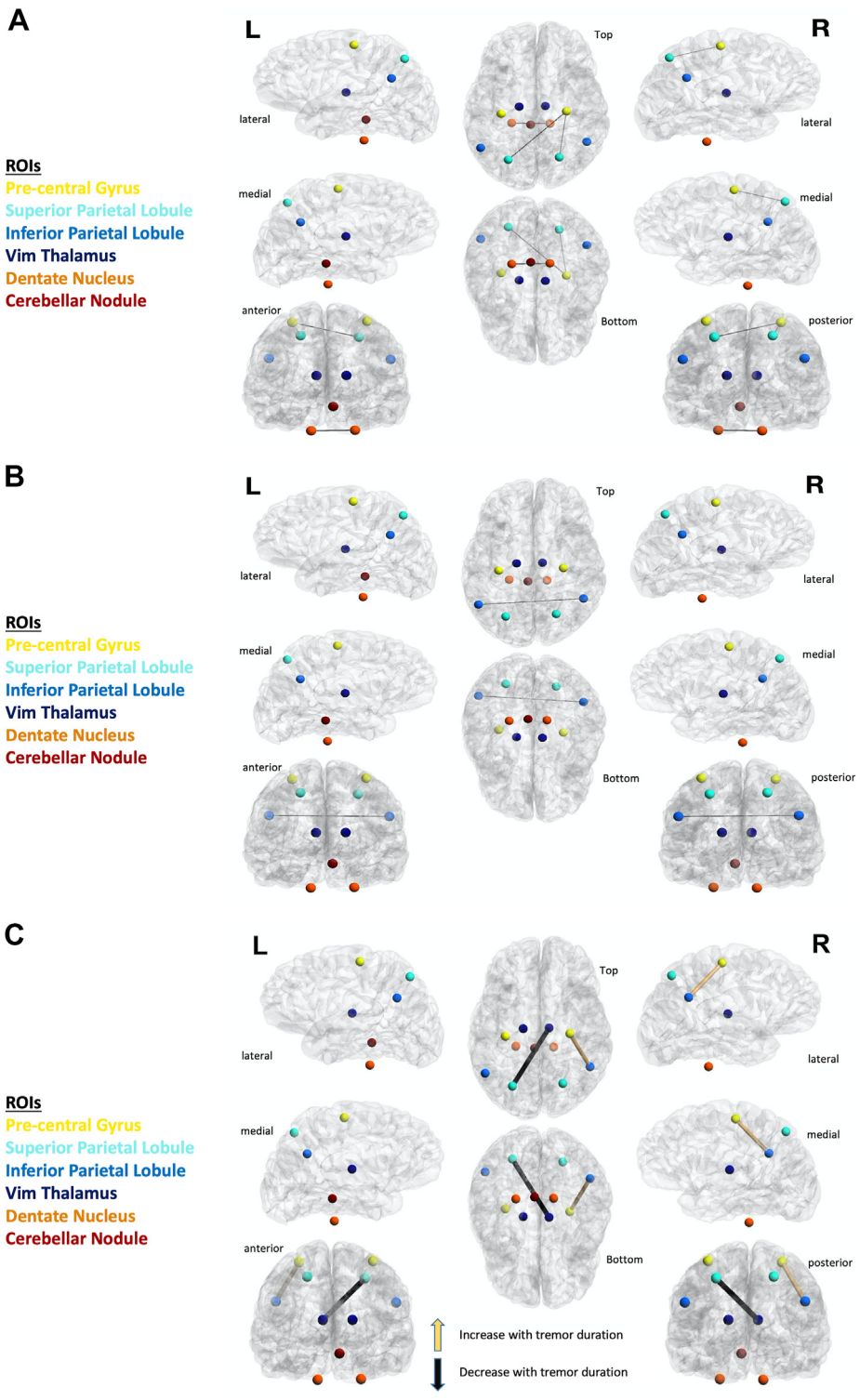

Fig. 5. Functional Connectivity Changes in DBS ON v. OFF. Group Analysis of all 15 patients. (A) At threshold of mean z-score greater than 2, lines between ROIs represent significant connectivity increases with DBS ON v. OFF. The greater the difference in z-score, the thicker the line [range: 2.02–3.91]. Please refer to Supplemental Table 2 for individual z-score differences between DBS ON and OFF states. (B) At threshold of mean z-score less than 2, lines between ROIs represent significant connectivity decreases with DBS ON v. OFF. z-score [3.22]. Please refer to Supplemental Table 3 for individual z-score differences between DBS ON and OFF states. C) Correlation of Tremor Duration with Functional Connectivity. At threshold $p < 0.05$, for all 15 patients, significant connectivity changes between DBS ON and OFF states were found. 1) Between R inferior parietal lobule (IPL) and R Pre-central gyrus, there was a significant increase in connectivity between DBS ON - OFF states (with DBS ON > OFF) that correlated with an increase in tremor duration (correlation coefficient R = 0.618 and $p = 0.014$); 2) between R Vim thalamus and L superior parietal lobule (SPL), there was a significant decrease in connectivity between DBS ON - OFF states (with DBS ON < OFF) that correlated with a decrease in tremor duration (correlation coefficient R = −0.726 and $p = 0.002$). (D) Correlation of Tremor Improvement with Functional Connectivity. At threshold $p < 0.05$, for all 15 patients, significant connectivity changes between DBS ON and OFF were found between R SPL and R Vim thalamus, where an increase in connectivity between DBS ON - OFF states (with DBS ON > OFF) correlated with an increase in tremor score difference (TETRAS pre-post-operative scores, Pearson correlation coefficient R = 0.576 and $p = 0.024$). ROIs: bilateral precentral gyrus (yellow), superior parietal lobule (teal), inferior parietal lobule (blue), dentate nucleus (orange), cerebellar nodule (maroon); bilateral Vim (dark purple). Visualization of ROIs in 8 views (as indicated) using BrainNet Viewer [41].

which resolved with DBS OFF [23], and which was not seen in the non-ataxic DBS patients. As ET disease progresses, gait ataxia can develop in certain patients; alternatively, gait ataxia can be induced as a side effect of DRTt/Vim DBS, which was observed by Reich et al. [23] to be due to inadvertent stimulation of the uncinate tract of the fastigio-bulbar pathway, important in axial coordination, which is functionally connected to the cerebellar nodule. We chose to include the cerebellar nodule as an ROI to corroborate this evaluation.

None of our patients had SARA score ≥ 5 as in Reich et al. [23] with DBS OFF. When we performed a sub-analysis of the patients with the most severe gait ataxia by SARA (items 1–3), this resulted in 3 patients having a SARA score ≥ 3, with 12 patients remaining; with threshold SARA score to ≥ 2, this resulted in 6 patients (with 9 remaining). In both groups of sub-analysis, there were significant FC decreases with DBS ON v. OFF between cerebellar and multiple other ROIs in the ataxic group vs. no FC decreases in the remaining non-ataxic patients. This is interesting

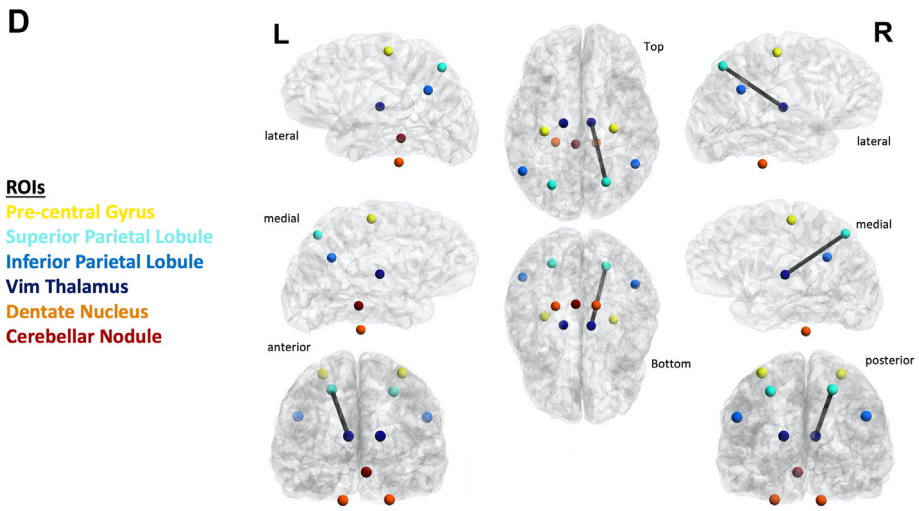

Fig. 5. (*continued*).

that in patients with even slight gait ataxia (SARA score $\geq$ 2 on items 1–3), DBS induced tremor improvement caused much different FC change than in those with SARA <2 (minimal to no ataxia).

It is not surprising that ataxia patients have different FC than non-ataxic patients, with or without DBS, as primary ataxic patients have decreased FC between cerebellar networks and other RSNs relative to healthy controls [55,56]. It is important to note that assessments of gait ataxia pre-DBS and then ON and OFF DBS did not change much for any assessment. Of the 3 most ataxic patients, one had an increase in SARA (likely due to disease progression), and 2 stayed the same between pre-op and post-op assessments; none of these patients displayed a demonstrable rebound gait ataxia when DBS was turned OFF for the MRI. Also, the DBS parameters used for optimal tremor control in these different groups were not significantly different from each other. Based on this subset of 3 patients with mild ataxia, we cannot definitively conclude that DBS did induce any effect on ataxia; we will need a larger cohort for analysis.

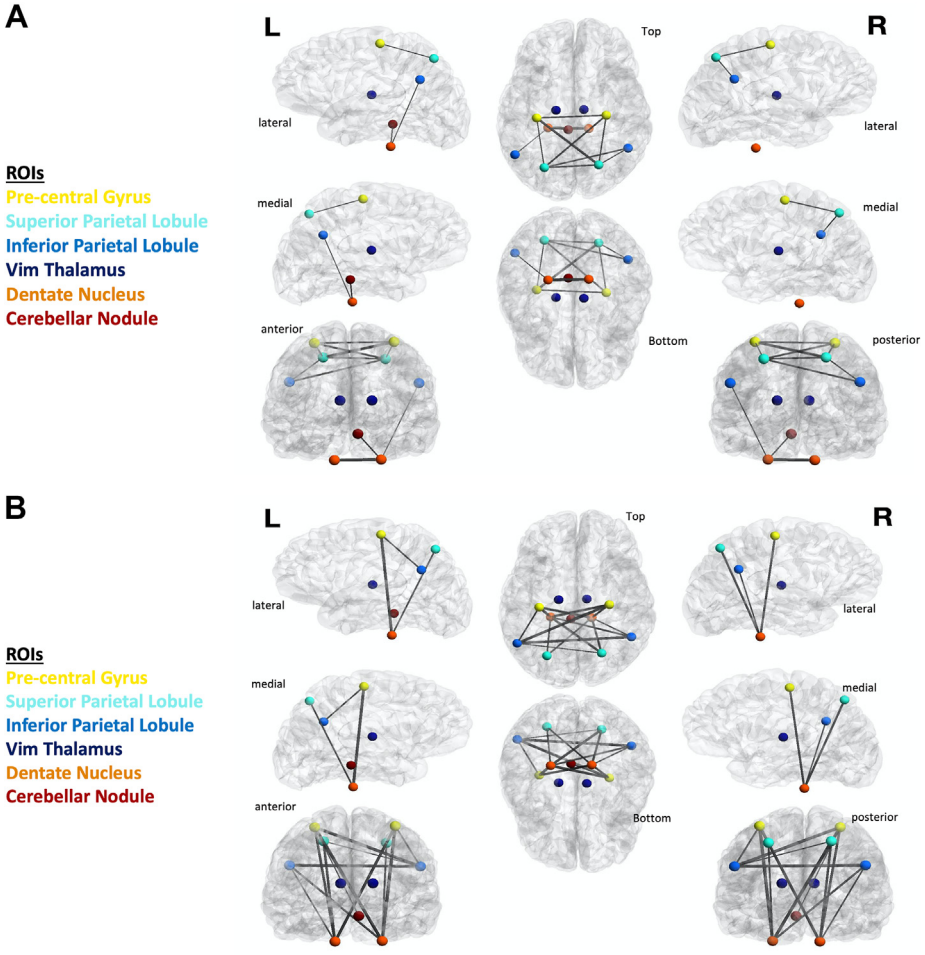

Fig. 6. Correlation of Ataxia Severity with Functional Connectivity in DBS ON vs. OFF. (A) For the 3 patients with the greatest post-op ataxia (SARA), at a threshold of mean z-score greater than 4, lines between ROIs represent significant connectivity increases with DBS ON v. OFF. The greater the difference in z-score, the thicker the line [range: 4.12–12.27]. Please refer to Supplemental Table 4 for individual z-score differences between DBS ON and OFF states. (B) For the 3 patients with the greatest post-op ataxia (SARA Items 1–3 <2), at a threshold of mean z-score less than −4, lines between ROIs represent significant connectivity decreases with DBS ON v. OFF. The greater the difference in z-score, the thicker the line [4.29–12.01]. Please refer to Supplemental Table 5 for individual z-score differences between DBS ON and OFF states. (C) For the 12 patients with the least post-op ataxia (SARA Items 1–3 <2) at a threshold of mean z-score greater than 2, lines between ROIs represent significant connectivity increases with DBS ON v. OFF. The greater the difference in z-score, the thicker the line [2.12–2.70]. There were no significant decreases with DBS ON v. OFF at z = −2 threshold. ROIs: bilateral precentral gyrus (yellow), superior parietal lobule (teal), inferior parietal lobule (blue), dentate nucleus (orange), cerebellar nodule (maroon); bilateral Vim (dark purple). Visualization of ROIs in 8 views (as indicated) using BrainNet Viewer [39].

Overall, the strengths of this paper are that we successfully depict differences in functional connectivity between DBS states in ET, which has not been discussed previously. By using a total rsfMRI scan time of nearly 18 min for each DBS state, we corroborate published findings of ET patients undergoing Vim ablation using similar whole-brain analysis techniques. We expand upon functional connectivity findings seen in the disease state and include visual association areas in our hypothesis-driven ROI analysis, now thought to play a larger role in the pathology of tremor [5,18,20,21,48].

Limitations

Several limitations to this paper include the fact that this proof-of-concept study observes changes in a small cohort of patients (n = 15); however, this is similar in size to other studies investigating FC differences pre-post MRgFUS thalamotomy in ET [18,19]. Although a smaller number (n = 11) was used in the whole brain analysis, we corroborate previous findings of functional connectivity differences in tremor pre/-post treatment [5,18–21,48]. It is very likely that in a larger cohort other ICs would survive correction for multiple comparisons, including expected changes seen in the cerebellar network. Also, we were limited by the fact that we could only use the first 300 vol acquired for dual regression analysis; when we tried to concatenate the 300 and 150 vol into one series, limitations in the FSL software prevented us from performing dual regression analysis. Likely, use of a larger number of volumes would have allowed us to detect a better signal. Regardless, our targeted hypothesis-driven ROI analysis elucidated FC changes between DBS states in selected areas of a larger tremor-related network, which was especially apparent in the more-ataxic group compared to those with minimal ataxia. We acknowledge that these patients were not of severe ataxia; a larger cohort including more such ataxic patients would enrich these findings.

Also, it is unclear if the observed changes in connectivity correlated with tremor presence are only due to DBS state or also at least partly due to the confounding occurrence of functional reorganization. Perhaps functional connectivity due to neural reorganization post-DBS changes over time, which was not controlled for in this study, as each patient's disease duration and length of time post-DBS implantation was variable. Future work with serial rsfMRI imaging with DBS ON/OFF at specified time points post-DBS, with a larger cohort of patients, will give us a more substantive picture of the key regions implicated in tremor and can control for such reorganization.

Clinical applications

As stated, future work with a larger cohort is needed to better characterize such functional changes induced by successful DRTt DBS. As the disease of ET progresses over time, DBS has the unique advantage over other unmodifiable interventions (i.e., radiosurgery, high-frequency ultrasound) to be adjusted for symptomatology changes, where the volume of tissue activated is increased/changed to maintain tremor control. Potentially, through visualizing strength of connectivity to key regions in a larger visuomotor network, rsfMRI can guide programming of patients over time to maintain tremor control and avoid side effects, such as ataxia, which could be attributed to cerebellar nodule activation [23]. Specific contacts can be prospectively selected based on the strength of connectivity to particular ROIs. Perhaps, DBS targeting the DRTt at the ACPC plane (as performed herein), at the posterior subthalamic area, or elsewhere can be prospectively compared for both tremor efficacy and development of side effects, correlated with rsfMRI connectivity patterns, to confirm or refute equivocalness. The overall goal is to improve the current state of Vim-DRTt modulation to optimize successful tremor control indefinitely. We are currently performing a more detailed analysis across several timepoints (i.e., pre-DBS, and with post-DBS ON and OFF) so that we can better ascertain exactly how DBS to the DRTt modulates the larger tremor network in exerting its clinical effect.

It has become evident that there exists a visually sensitive functional network in ET, where increased visual feedback has been correlated with abnormal BOLD signal in motor and sensory cortex as well as superior and parietal lobules, and cerebellum [24], which is normalized after treatment and correlated with tremor reduction [21].

In our study we demonstrate that such an abnormal functional connectivity in this greater visuomotor network, beyond the nodes connected by the DRTt, is directly implicated in tremor production. We have also uniquely exploited the reversible nature of DBS, whereby we evaluated functional changes in networks modulated by the electrode at the target structure, in this case the DRTt as it enters the Vim nucleus, across DBS ON and OFF states, which has not been performed previously. Ongoing parallel structural and electrophysiological connectivity [57] analyses confirm that the SPL and IPL are critical regions that are involved in tremor modulation. Further work to characterize the correlation of clinical response to stimulation evoked functional changes could improve DBS for tremor.

Financial support

Work on this study was partly funded by the NIH NINDS, grant 1R01NS113893-01A1.

Author Contributions

AJF is the senior author, the PI, conceptualized the study, conducted the experiment, data analysis, discussion, and wrote all drafts of the paper.

ZDC and SFK devised the methods, generated the results, data analysis, and assisted with interpretation of results, approved final manuscript.

RJR and CRC helped with data acquisition, interpretation of results, approved final manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Albert Fenoy reports financial support was provided by National Institute of Neurological Disorders and Stroke. Stephen Kralik reports financial support was provided by National Institute of Neurological Disorders and Stroke. Zili Chu reports financial support was provided by National Institute of Neurological Disorders and Stroke. Albert Fenoy reports a relationship with Medtronic Inc that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurot.2024.e00375.

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