Supplemental Material

Methods Continued

Surgical Targeting

DBS and MRgFUS share similar targeting coordinates. MRgFUS lesioning is targeted 14-15mm lateral from the midline (or 11mm lateral from the third ventricle wall), anterior from the posterior commissure (PC) by 1/3 to 1/4 the inter-distance between the anterior commissure (AC) and the PC, and 2mm superior to the AC-PC line.[1] DBS targeting is the same apart from being slightly inferior, at the level of the AC-PC line.[2] Furthermore, microelectrode recordings are used to refine the targeting intraoperatively by identifying the VIM-VC border. The implanted lead is then placed 2mm anterior to the recording tract.

Image Acquisition

The image acquisition parameters have been previously described by our group.[3] In brief, high spatial resolution pre- and postoperative structural imaging were collected. Preoperative (immediately prior to procedure) and postoperative (1 or 2 days post-procedure) imaging consisted of 1.5 or 3-Tesla T1 3-dimensional spoiled gradient echo (3D-SPGR, General Electric [Boston, MA] Signa Excite/HDxt scanner).

Lead Localization and Lesion Segmentation

The method used for lead localization has been previously described by our group.[3] It was performed based on the acquired high spatial resolution structural imaging and utilized Lead-DBS v2.0 software (https://www.lead-dbs.org/).[4] Pre- and postoperative images were linearly registered using SPM12 (https://www-fil-ion-ucl-ac-uk/spm/software/spm12/)[5] and nonlinearly normalized to a Montreal Neurological Institute (MNI) template brain (ICBM 2009b NLIN asymmetric) using ANTs SyN and subcortical refinement.[6] To localize DBS electrodes the semiautomated trajectory reconstruction function in Lead-DBS was used and manually refined as necessary. Activation volumes (VTAs) were estimated using the DBS stimulation settings at follow-up as per previously published methods.[7,8] DBS stimulation parameters used from activation volume modelling were as follows (mean ± standard deviation): voltage (V) 2.5 ± 0.6, frequency (Hz) 100.2 ± 52.7, pulse width (μs) 116.7 ± 53.0. Contact configuration was monopolar 60.6%, double monopolar 3.0%, bipolar 33.3%, interleaved 3.0%.

The MRgFUS lesion segmentation and image processing methods were performed as previously described.[9] Briefly, immediate post-operative T1-weighted MRI images were used for manual segmentation. These were rigidly aligned (6df) to the preoperative T1-weighted image using FSL (FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/) and the MincTools software kit (BIC-MNI, Montreal, Canada, https://bic-mni.github.io/) used to manually delineate the lesion in axial planes as described by Wintermark et al.[10] Using the Advanced normalization tools (ANTs, http://stnava.github.io/ANTs/) the preoperative MRIs were linearly and nonlinearly transformed to MNI space.[11] The derived transforms were then applied to the lesion mask.

Statistical analysis

Probabilistic Voxel-wise efficacy maps

Probabilistic voxel-wise efficacy maps providing insight into spatial patterns of response to treatment were generated as previously described.[12] Briefly, each transformed VTA or lesion was weighted by clinical improvement (percent improvement from baseline) and voxel-wise mean improvement computed by averaging the weighted values. Using unweighted frequency maps (n-map), denoting the number of VTAs or lesions overlapping at a given voxel, the raw average maps were thresholded at 10% to exclude outlier voxels. The final average maps were masked by the n-maps and then thresholded using a Wilcoxon signed-rank test ($P<0.05$, at each voxel). In a similar fashion, to identify voxels that, within each group, were associated with above/below average outcomes, the clinical improvement scores were z transformed for both groups of patients, and average voxel efficacy maps were calculated as described above.

Structural connectivity analysis

Structural connectivity analysis was performed as previously described.[3,12] Briefly, this analysis makes use of a 12 million-streamline, whole-brain tractogram created from multishell diffusion-weighted MRI (dMRI) data[13] of 985 subjects created utilizing generalized q-sampling imaging and Lead-Connectome.[14] In the first step, all streamlines touched by each lesion or VTA were identified. Next, unweighted frequency maps were generated to identify shared streamlines implicated in each treatment across the entire group of patients, denoting the number of VTAs or lesions touching a given streamline. Group tractograms of shared streamlines were thresholded at 75%.

References

1. Lipsman N, Schwartz ML, Huang Y, et al. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. *Lancet Neurol*. 2013;12(5):462-468. doi:10.1016/S1474-4422(13)70048-6
2. Papavassiliou E, Rau G, Heath S, et al. Thalamic Deep Brain Stimulation for Essential Tremor: Relation of Lead Location to Outcome. *Neurosurgery*. 2004;54(5):1120-1130. doi:10.1227/01.NEU.0000119329.66931.9E
3. Elias GJB, Boutet A, Joel SE, et al. Probabilistic Mapping of Deep Brain Stimulation: Insights from 15 Years of Therapy. *Ann Neurol*. Published online November 30, 2020. doi:10.1002/ana.25975
4. Horn A, Kühn AA. Lead-DBS: A toolbox for deep brain stimulation electrode localizations and visualizations. *Neuroimage*. 2015;107:127-135. doi:10.1016/J.NEUROIMAGE.2014.12.002
5. Penny W, Friston K, Ashburner J, Kiebel S, Nichols T. Statistical Parametric Mapping: The Analysis of Functional Brain Images. *Statistical Parametric Mapping: The Analysis of Functional Brain Images*. Published online 2007. doi:10.1016/B978-0-12-372560-8.X5000-1

6. Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage*. 2011;54(3):2033-2044. doi:10.1016/J.NEUROIMAGE.2010.09.025
7. Åström M, Diczfalusy E, Martens H, Wårdell K. Relationship between neural activation and electric field distribution during deep brain stimulation. *IEEE Trans Biomed Eng*. 2015;62(2):664-672. doi:10.1109/TBME.2014.2363494
8. McIntyre CC, Mori S, Sherman DL, Thakor N v., Vitek JL. Electric field and stimulating influence generated by deep brain stimulation of the subthalamic nucleus. *Clinical Neurophysiology*. 2004;115(3):589-595. doi:10.1016/J.CLINPH.2003.10.033
9. Boutet A, Ranjan M, Zhong J, et al. Focused ultrasound thalamotomy location determines clinical benefits in patients with essential tremor. *Brain*. 2018;141(12):3405-3414. doi:10.1093/BRAIN/AWY278
10. Wintermark M, Druzgal J, Huss DS, et al. Imaging findings in MR imaging-guided focused ultrasound treatment for patients with essential tremor. *AJNR Am J Neuroradiol*. 2014;35(5):891-896. doi:10.3174/AJNR.A3808
11. Fonov V, Evans A, McKinstry R, Almli C, Collins D. Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *Neuroimage*. 2009;Supplement 1(47):S102. doi:10.1016/S1053-8119(09)70884-5
12. Germann J, Elias GJB, Neudorfer C, et al. Potential optimization of focused ultrasound capsulotomy for obsessive compulsive disorder. *Brain*. 2021;144(11):3529-3540. doi:10.1093/BRAIN/AWAB232
13. Glasser MF, Sotiropoulos SN, Wilson JA, et al. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage*. 2013;80:105-124. doi:10.1016/J.NEUROIMAGE.2013.04.127
14. Horn A, Blankenburg F. Toward a standardized structural–functional group connectome in MNI space. *Neuroimage*. 2016;124:310-322. doi:10.1016/J.NEUROIMAGE.2015.08.048