Identifying Therapeutic Targets from Spontaneous Beneficial Brain Lesions

Juho Joutsa, MD, PhD ,[1,2,3,4,5*] Ludy C. Shih, MD,[2,3*] Andreas Horn, MD ,[6] Martin M. Reich, MD,[2,3,7] Ona Wu, PhD,[1] Natalia S. Rost, MD,[8] and Michael D. Fox, MD, PhD[1,2,3]

Brain damage can occasionally result in paradoxical functional benefit, which could help identify therapeutic targets for neuromodulation. However, these beneficial lesions are rare and lesions in multiple different brain locations can improve the same symptom. Using a technique called lesion network mapping, we show that heterogeneous lesion locations resulting in tremor relief are all connected to common nodes in the cerebellum and thalamus, the latter of which is a proven deep brain stimulation target for tremor. These results suggest that lesion network mapping can identify the common substrate underlying therapeutic lesions and effective therapeutic targets.

ANN NEUROL 2018;84:153–157

Brain damage such as stroke usually results in problematic symptoms and an overall decrement in function. Rarely, brain damage can lead to improvement in function, referred to as paradoxical functional facilitation.[1] Ideally, these spontaneously occurring lesions would help identify therapeutic targets for neuromodulation, allowing for relief of similar symptoms in other patients. However, translating spontaneous lesion cases into therapeutic targets has been challenging, because these lesion cases are rare and tend to occur in multiple different brain locations, leaving the therapeutic target unclear. Furthermore, symptomatic benefit may depend on the effect of the lesion on remote but connected brain regions, obscuring the target altogether.[1,2] Due to these challenges, spontaneously occurring therapeutic lesions have played little role in identifying neuromodulation targets in use today.[3]

A recently validated technique termed lesion network mapping is ideally suited to address these problems.[4] By integrating a map of brain connectivity into lesion analysis, lesions in different locations can be linked to common neuroanatomy. This approach has proven broadly applicable for clinical symptoms or syndromes caused by focal brain lesions.[5] Here, we apply this same technique to lesions providing symptomatic benefit. For proof of concept, we focus on spontaneously occurring lesions that improve upper limb function in patients with essential tremor. This focus is motivated by the relatively high prevalence of essential tremor, especially in the age group at risk for stroke, and the presence of an established therapeutic target in the ventral intermediate nucleus of the thalamus (VIM).[6,7] We test the hypothesis that this therapeutic target can be identified from case reports of spontaneously occurring beneficial lesions and a publicly available map of the human brain connectome.

Patients and Methods

Cases of Paradoxical Functional Facilitation of Essential Tremor

Cases of individuals with essential tremor who had relief of tremor following a focal brain lesion were identified using PubMed keywords and MESH (or subject heading) search terms "tremor", "essential tremor", "stroke", and "ischemic stroke". The search was performed in September 2016. A total of 1,119 articles were found. Inclusion criteria were (1) a clear description of prestroke essential tremor, including postural and action tremor of the upper limbs; (2) acute relief of tremor attributed to an ischemic event; and (3) a published figure showing the location of the focal ischemic lesion. Exclusion criteria included (1) cases of tremor relieved by hemorrhage, tumor, infection, or other structural lesion; (2) poor description of pre-existing tremor; (3) parkinsonian tremor or obvious presence of parkinsonism; (4) poor image

From the [1]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA; [2]Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, Boston, MA; [3]Harvard Medical School, Boston, MA; [4]Department of Neurology, University of Turku, Turku, Finland; [5]Division of Clinical Neurosciences, Turku University Hospital, Turku, Finland; [6]Charité–Universitätsmedizin Berlin, Berlin, Germany; [7]Deparment of Neurology, University Hospital and Julius Maximilian University, Würzburg, Germany; and [8]Stroke Research Center, Department of Neurology, Massachusetts General Hospital, Boston, MA

Address correspondence to Dr Joutsa, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, 149 13th St, Charlestown, MA 02129; E-mail: jjoutsa@bidmc.harvard.edu; jtjout@utu.fi or Dr Fox, Beth Israel Deaconess Medical Center, Neurology/KS 448, 330 Brookline Ave, Boston, MA 02215; E-mail: mfox3@bidmc.harvard.edu

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Received Apr 19, 2018, and in revised form Jun 29, 2018. Accepted for publication Jun 29, 2018

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25285.

*Equal contribution.

resolution such that lesion boundaries could not be delineated. All case reports were evaluated by a movement disorders specialist (L.C.S.) for compliance with the above criteria.

Lesion Network Mapping

Lesion network mapping was performed in 3 steps using previously validated methods[4,8]: (1) published images of each lesion were traced by hand onto a common reference brain; (2) the lesion volume (combination of all 2-dimensional [2D] slices) was used as a seed region of interest in a resting state functional connectivity magnetic resonance imaging analysis that used normative data from 1,000 subjects (http://neuroinformatics.harvard.edu/gsp/), as described earlier[8]; and (3) the resulting network associated with each lesion volume was thresholded at a t value of 7 (corresponding to voxel-level familywise error–corrected $p < 10^{-6}$ for whole brain search volume) and overlaid across lesions to identify common sites of network overlap.

Refinement of Lesion Network Topography

Ideally, we would have liked to compare lesion networks improving essential tremor to lesion networks that failed to improve essential tremor; however, identifying an adequate number of these lesion cases was not feasible. Instead, we compared our lesion networks to those derived from 486 consecutive stroke patients[9] using Bayesian Spatial Generalized Linear Mixed Model software (https://warwick.ac.uk/fac/sci/statistics/staff/academic-research/nichols/software/bsglmm/).[10] This analysis identified voxels most predictive of tremor relief, correcting for bias that could come from lesion locations in general.

Correspondence to Known Therapeutic Targets

We compared our lesion network mapping results to established therapeutic targets for essential tremor using 2 approaches. First, we computed the spatial overlap between our results and a previously derived optimal thalamic deep brain stimulation (DBS) target for essential tremor (Montreal Neurological Institute [MNI] coordinates ± 13.05, −18.38, −2.01mm).[11] Second, we compared our lesion network mapping results to a publicly available high-resolution thalamic atlas.[12,13] Lesion network targets in the left and right thalamus were averaged together for atlas overlay and visualization of DBS leads using Lead DBS software (www.lead-dbs.org).[14]

The study was approved by the institutional review board at Beth Israel Deaconess Medical Center (protocol #2018P000128) and conducted according to the principles of the Declaration of Helsinki.

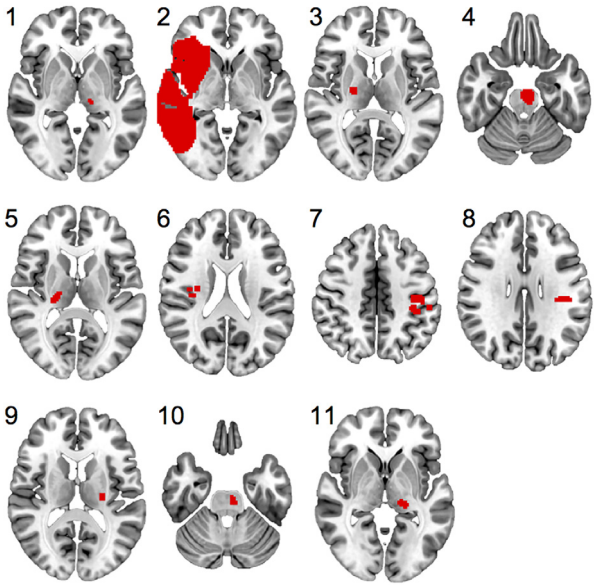

FIGURE 1: Lesion locations providing tremor relief in patients with essential tremor. [Color figure can be viewed at wileyonlinelibrary.com]

Results

Our search identified 11 cases of ischemic stroke causing relief of pre-existing essential tremor (Fig 1, Supplementary Table 1). Although lesion locations were heterogeneous, they were part of a common network, with functional connectivity to a common set of brain regions (Fig 2). All 11 lesion locations were connected to the bilateral thalamus, bilateral cerebellum, left globus pallidus, and left putamen (Supplementary Table 2). The connectivity most predictive of tremor relief was to the right thalamus (peak MNI coordinate 12, −18, −2mm), followed by the left thalamus and right dorsal cerebellum. Results were nearly identical when excluding 4 cases that involved lesions to the thalamus itself.

Lesion network mapping results aligned well with the existing therapeutic target for essential tremor, with near perfect overlap (Fig 3). Our peak coordinate for tremor relief derived from spontaneous brain lesions was identical to the peak coordinate for targeting DBS, within the constraints of our 2 × 2 × 2mm spatial resolution (12, −18, −2mm vs 13.05, −18.38, −2.01mm). When our lesion network results were overlaid on a high-resolution thalamic atlas, they overlapped the VIM nucleus (see Fig 3B).

Discussion

There are 3 main findings. First, lesions improving pre-existing essential tremor occur in multiple different brain

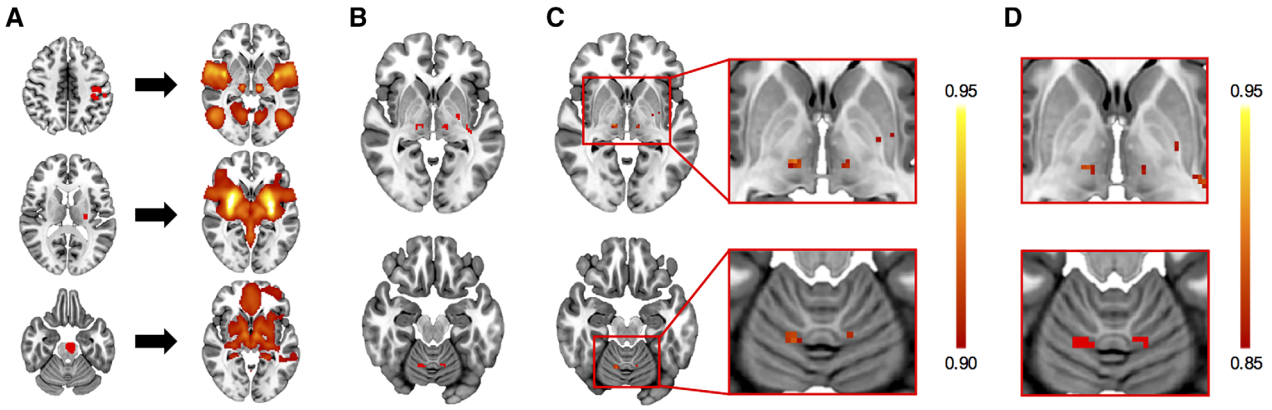

FIGURE 2: Lesion network mapping. (A) Each lesion location (3 examples shown) was converted into a lesion network using a large resting state functional connectivity database. (B) Lesion network overlap showing voxels functionally connected to all 11 lesion locations. (C) Posterior probability of voxels most associated (probability > 0.9) with tremor relief. (D) Posterior probability when cases with thalamic lesions are excluded. [Color figure can be viewed at wileyonlinelibrary.com]

locations. Second, these heterogeneous lesion locations are all part of the same functionally connected brain network. Finally, the peak of this lesion network is in the VIM, a proven therapeutic target for essential tremor. These findings suggest that lesion network mapping might be used to identify therapeutic targets from spontaneous beneficial brain lesions.

The search for locations to surgically induce therapeutic lesions has been guided in large part by trial and error and serendipity. For example, the first surgical lesions to improve tremor were not to the thalamus, but to nerve roots, the spinal cord, the cerebral peduncles, and the motor cortex.[3] These lesions improved tremor, but also caused paralysis. One of the first lesions to improve tremor without weakness was discovered when the thalamus was inadvertently damaged during an operation aimed at other brain structures. Here, we provide evidence that spontaneously occurring brain lesions providing paradoxical functional benefit might inform this process.

This is the first study to use lesion network mapping for brain lesions that provide functional benefit. Previous lesion network mapping studies have been restricted to lesions that cause specific symptoms.[5] By investigating lesions that improve pre-existing symptoms, we show that lesion network mapping can help identify therapeutic targets. As spontaneously occurring brain lesions can improve

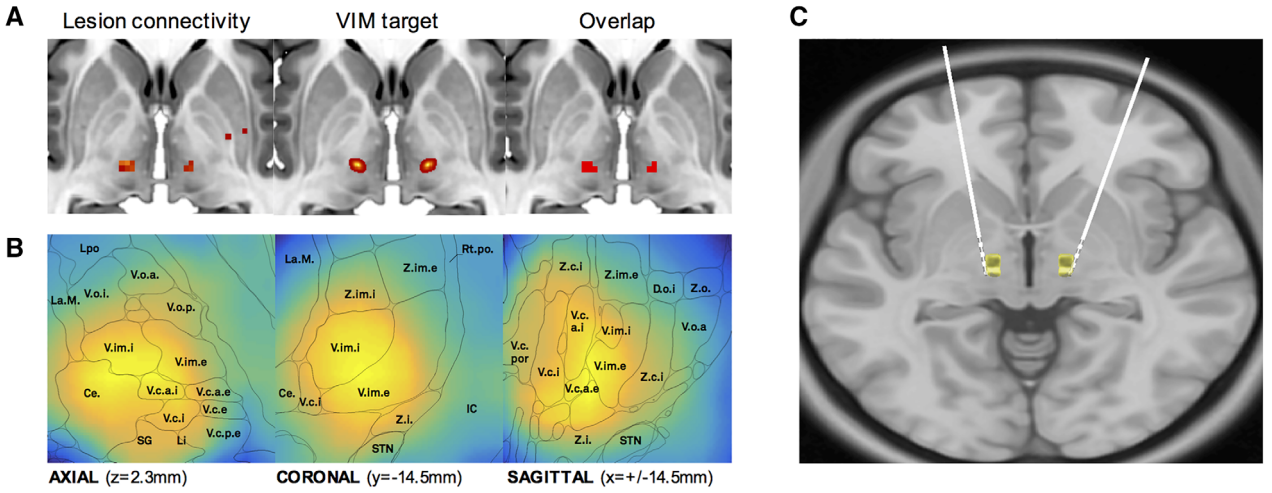

FIGURE 3: Lesion network mapping identifies the ventral intermediate nucleus (VIM) deep brain stimulation (DBS) target for essential tremor. (A) Lesion network map (left panel), probabilistic coordinates of the VIM target for DBS (middle), and their overlap (right). (B) Bilateral average of the lesion network map overlaid on a high-resolution thalamic atlas. (C) Example of the DBS electrode position in a patient with essential tremor with good therapeutic response. The electrodes are run immediately next to the lesion network overlap clusters (shown also in B) and are likely to be within the activation field with multiple lead contacts. Note that the brain is slightly tilted to enable visualization of the lead trajectories within the 3-dimensional brain volume. Abbreviations follow Hassler nomenclature as equally used in the Schaltenbrand-Wahren stereotactic atlas.[12] V.im.e = ventral intermedius externus; V.im.i = ventral intermedius internus. For other abbreviations in panel B, see Ewert et al.[13] [Color figure can be viewed at wileyonlinelibrary.com]

other symptoms including other movement disorders, depression, migraine, and addiction, this technique may prove broadly applicable.[1] Unfortunately, there are not enough published cases displaying the lesion location to readily apply this technique to these other symptoms. We hope that the current paper, demonstrating the value of such cases, will motivate increased reporting moving forward.

Although the whole brain peak of lesion network mapping of tremor relief was in VIM, a secondary peak was present bilaterally in the cerebellum. The location of this peak falls in the motor cerebellum, in close proximity to the hand region.[15] The cerebellum is thought to play a key role in essential tremor, part of a cerebellar–thalamic circuit.[16,17] Whether the cerebellar sites identified by lesion network mapping represent a secondary therapeutic target remains unknown, but could prove valuable for patients whose tremor is refractory to VIM DBS. Furthermore, noninvasive stimulation of the cerebellum has shown some promise for treatment of essential tremor[18] and different therapeutic targets across neuromodulation methods tend to converge on common brain networks.[19]

There are some limitations. We used 2D instead of 3D lesions and used a normative connectome that was not age- or disease-matched to the lesion patients. However, these factors have been previously investigated and found to have little effect on lesion network mapping results.[4,20] Second, our analysis was based on a relatively small number of lesions that improved tremor. Third, we did not have an optimal control group, namely patients with essential tremor and lesions that did not improve tremor. Instead, the topography of findings was refined using a large heterogeneous group of stroke patients, and some of these control lesions could conceivably also have provided tremor relief. However, these limitations should bias us against the present findings. Finally, our study was limited to a single syndrome, essential tremor. Whether the same approach can identify treatment targets in other conditions remains to be determined.

Acknowledgment

J.J. was supported by the Academy of Finland (295580), Finnish Medical Foundation, and Orion Research Foundation. L.C.S. was supported by private donor support to the Department of Neurology, Harvard Medical School. A.H. was supported by Deutsche Forschungsgemeinschaft (KFO247), Thiemann Foundation, Berlin Institute of Health, and Stiftung Charité. M.M.R. was supported by the Interdisciplinary Center for Clinical Research (Z-3/64) of the University Hospital Würzburg and the German section of the International Federation of Clinical Neurophysiology. O.W. was in part supported by the NIH-NINDS R01NS059775, R01NS082285, R01NS086905, P50NS051343, and NIBIB P41EB015896. N.S.R. was in part supported by the NIH-NINDS K23NS064052, R01NS082285, and R01NS086905; American Heart Association/Bugher Foundation Centers for Stroke Prevention Research (0775010N). M.D.F. was supported by the Dystonia Medical Research Foundation, Nancy Lurie Marks Foundation, Mather's Foundation, and NIH (NINDS K23NS083741, NIMH R01M H113929). This research was carried out in part at the Athinoula A. Martinos Center for Biomedical Imaging at the Massachusetts General Hospital, using resources provided by the Center for Functional Neuroimaging Technologies, P41EB015896, a P41 Biotechnology Resource Grant supported by the National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institutes of Health. This work also involved the use of instrumentation supported by the NIH Shared Instrumentation Grant Program and/or High-End Instrumentation Grant Program; specifically, grant number(s) S10RR023043 and S10RR023401.

We thank C. Ashton and Dr R. Darby for their assistance with the collection of the lesions.

Author Contributions

J.J., L.C.S., and M.D.F. contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of data. J.J., L.C.S., A.H., and M.D.F. contributed to drafting the text and preparing the figures. All authors reviewed and critiqued the manuscript.

Potential Conflicts of Interest

M.D.F. has submitted patents using connectivity imaging to identify brain stimulation targets. The other authors have nothing to disclose.

References

1. Kapur N. Paradoxical functional facilitation in brain-behaviour research. A critical review. Brain 1996;119(pt 5):1775–1790.
2. Monakow C. *Die Lokalisation im Grosshirn: und der Abbau der Funktion durch kortikale Herde*. Wiesbaden, Germany: Verlag von J.F. Bergmann, 1914.
3. Guridi J, Lozano AM. A brief history of pallidotomy. Neurosurgery 1997;41:1169–1180; discussion 1180–1183.
4. Boes AD, Prasad S, Liu H, et al. Network localization of neurological symptoms from focal brain lesions. Brain 2015;138(pt 10): 3061–3075.
5. Fox MD. Mapping symptoms to brain networks with the human connectome. N Engl J Med (in press).
6. Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. N Engl J Med 2016; 375:730–739.

7. Flora ED, Perera CL, Cameron AL, Maddern GJ. Deep brain stimulation for essential tremor: a systematic review. Mov Disord 2010;25: 1550–1559.

8. Darby R, Horn A, Cushman F, Fox M. Lesion network localization of criminal behavior. Proc Natl Acad Sci U S A 2018;115:601–606.

9. Wu O, Cloonan L, Mocking SJ, et al. Role of acute lesion topography in initial ischemic stroke severity and long-term functional outcomes. Stroke 2015;46:2438–2444.

10. Ge T, Müller-Lenke N, Bendfeldt K, et al. Analysis of multiple sclerosis lesions via spatially varying coefficients. Ann Appl Stat 2014;8: 1095–1118.

11. Horn A, Kühn AA, Merkl A, et al. Probabilistic conversion of neurosurgical DBS electrode coordinates into MNI space. Neuroimage 2017;150:395–404.

12. Schaltenbrand G, Wahren W. *Atlas for stereotaxy of the human brain*. Stuttgart, Germany: Thieme Medical Publishers, 1977.

13. Ewert S, Plettig P, Li N, et al. Toward defining deep brain stimulation targets in MNI space: a subcortical atlas based on multimodal MRI, histology and structural connectivity. Neuroimage 2018;170: 271–282.

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

15. Buckner RL, Krienen FM, Castellanos A, et al. The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol 2011;106:2322–2345.

16. Hallett M. Tremor: pathophysiology. Parkinsonism Relat Disord 2014;20(suppl 1):S118–S122.

17. Louis ED. Linking essential tremor to the cerebellum: neuropathological evidence. Cerebellum 2016;15:235–242.

18. Popa T, Russo M, Vidailhet M, et al. Cerebellar rTMS stimulation may induce prolonged clinical benefits in essential tremor, and subjacent changes in functional connectivity: an open label trial. Brain Stimul 2013;6:175–179.

19. Fox MD, Buckner RL, Liu H, et al. Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. Proc Natl Acad Sci U S A 2014;111: E4367–E4375.

20. Darby RR, Laganiere S, Pascual-Leone A, et al. Finding the imposter: brain connectivity of lesions causing delusional misidentifications. Brain 2017;140(pt 2):497–507.