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Lesion network mapping for symptom localization: recent developments and future directions

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Abstract

Purpose of review—Focal lesions causing specific neurological or psychiatric symptoms can occur in multiple different brain locations, complicating symptom localization. Here, we review lesion network mapping, a technique used to aid localization by mapping lesion-induced symptoms to brain circuits rather than individual brain regions. We highlight recent examples of how this technique is being used to investigate clinical entities and identify therapeutic targets.

Recent findings—To date, lesion network mapping has successfully been applied to more than 40 different symptoms or symptom complexes. In each case, lesion locations were combined with an atlas of human brain connections (the human connectome) to map heterogeneous lesion locations causing the same symptom to a common brain circuit. This approach has lent insight into symptoms that have been difficult to localize using other techniques, such as hallucinations, tics, blindsight, and pathological laughter and crying. Further, lesion network mapping has recently been applied to lesions that improve symptoms, such as tremor and addiction, which may translate into new therapeutic targets.

Summary

Lesion network mapping can be used to map lesion-induced symptoms to brain circuits rather than single brain regions. Recent findings have provided insight into long-standing clinical mysteries and identified testable treatment targets for circuit- and symptom-based neuromodulation.

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CONFLICTS OF INTEREST

JJ has received lecturer honoraria from Lundbeck. DTC has no conflicts of interest. MDF owns patents on using brain connectivity to guide brain stimulation, and has received investigator-initiated research funding from Neuronetics Inc, which is unrelated to the present work.

Keywords

lesion; localization; network; symptom; neuroimaging; lesion network mapping; diaschisis; connectivity

INTRODUCTION

Studying patients with focal brain lesions can provide unique insight into symptom localization because one can infer a causal link between the lesion location and the resulting symptoms (1). As such, lesion-based studies have provided the foundation for symptom localization in neurology for more than a century (2, 3). Lesion-based studies have advanced from individual cases to controlled data-driven whole brain analyses with sophisticated computational neuroimaging tools (4, 5). However, lesions causing similar symptoms often occur in heterogeneous brain locations with little overlap, leaving localization unclear (3, 6). One of the reasons for the lack of overlap is that lesions can also have a functional effect on remote but connected brain regions through disconnection or diaschisis, complicating efforts at lesion-based symptom localization (2, 7). Lesion network mapping (LNM) is one technique that has been introduced to help address this problem, with the goal of mapping brain lesions to brain circuits rather than individual brain regions (8). The underlying assumption is that symptoms map to a network with multiple foci in the brain and that lesion anywhere in this network will result in emergence of the symptom. Since its introduction in 2015, LNM has grown in popularity (Fig. 1), and been utilized by a growing number of research groups. Previous reviews have focused on advances in lesion-mapping methods (9), mapping symptoms to brain circuits rather than individual regions (1), and causal mapping of human brain function (10). The current review will focus on recent applications of LNM, including a comprehensive list of symptoms and studies published to date, examples of how this technique is being used to understand clinical entities, and examples of how this technique is being used to identify therapeutic targets.

LESION MAPPING TECHNIQUES

To understand the motivation and applications of LNM, it is helpful to place it in the context of other lesion mapping methods. Traditional lesion mapping techniques investigating the association between lesion locations and symptoms focus on anatomical locations alone, with the assumption that lesions causing the same symptom will intersect the same brain region or structure. This approach is often effective, such as lesions causing hemiparesis intersecting the corticospinal tract (11) or lesions causing visual field deficits intersecting retinotopic areas in primary visual cortex (12). Voxel-based lesion–symptom mapping (VLSM), uses modern statistical tools for traditional lesion-based symptom localization (4). In VLSM, lesion presence or absence at each brain voxel is defined for each patient, then lesioned voxels statistically associated with a symptom or behavioral score are identified (4).

However, lesions associated with more complex symptoms, such as visual or auditory hallucinations, motor/vocal tics, blindsight, or pathological laughter and crying (13), often fail to localize to any single anatomical structure. In such cases, LNM can extend upon traditional methods by mapping lesions to circuits, rather than just anatomical locations.

This is done by using an external dataset of resting-state functional magnetic resonance imaging (rs-fMRI) scans derived from a large sample of healthy volunteers (termed 'connectome') (14). rs-fMRI shows which brain regions have temporally coupled brain activity and are therefore considered part of the same functional network. In this way, the connectome represents the intrinsic connections of the brain, and LNM uses this to produce lesion network maps identifying the network of brain regions functionally connected to each lesion location (1). When compared to lesion network maps from lesions not causing this symptom one can identify connections specific to the symptom (Fig. 2). Of note, one must use a connectome from other, usually healthy subjects to perform this analysis, not functional connectivity data from the patient with the lesion, as the tissue in the lesion location is lost and therefore no longer functionally connected to any brain regions.

A complementary approach to localize lesions to brain circuits can also be taken using structural, instead of functional, neuroimaging. Here, a connectome derived from diffusion-weighted imaging can be used to identify tracts disrupted by the lesion and track the structural connectivity of fibers passing through each lesion location (5). This method yields complementary information to functional mapping that may explain additional variance in symptom localization (15). Although the relative advantages and disadvantages associated with the different connectivity-based tools are still under investigation, structural connectivity may be superior for mapping simple deficits such as hemiparesis, while functional connectivity may have advantages for mapping more complex symptoms (16). This may be related to the fact that the functional connectome can map polysynaptic connections while structural connections illustrate monosynaptic connections (17). The present review focuses on using LNM and the functional connectome to map complex symptoms, however these approaches are likely complementary (16).

UNRAVELLING CLINICAL ENTITIES

A part of routine clinical work in neurology is determining whether the patient's symptoms are related to an abnormality identified on brain imaging. Often this process is straightforward, such as hemiparesis in a patient with a lesion in the internal capsule. However, this can be difficult when the lesion is not in the traditional or expected location relative to the patient's symptoms. For example, patients with hemichorea can have lesions outside the subthalamic nucleus (18), patients with in hemiparkinsonism can have lesions outside the nigrostriatal tract (19), patients with amnesia can have lesion outside the hippocampus (20), and patients with post-stroke depression can have lesions outside the left dorsolateral prefrontal cortex in (21). In all these conditions, although the causal lesions were in heterogeneous locations, they fell within a common circuit specific to the symptom. Over the years, LNM has been used to identify brain circuits causally linked with a wide range of different neurological and psychiatric symptoms and behaviors, including symptoms with no traditional localization or in which the localization was largely unknown (Table 1).

One such example is in the recent use of LNM to shed light on the neuroanatomical basis of hallucinations (3). Kim, Hsu (3) used LNM to demonstrate a single 'hallucination network' across sensory modalities. All lesions causing hallucinations were functionally connected

to the superior temporal sulcus and the cerebellum (cerebellar vermis, inferior cerebellum – bilateral lobule X). There also were connections specific to the sensory modality of hallucinations: lesion locations causing visual hallucinations were connected to the lateral geniculate nucleus in the thalamus, while lesion locations causing auditory hallucinations were connected to the dentate nucleus in the cerebellum (3). These findings indicate that lesions causing hallucinations fall within a single common brain network, but the modality of the hallucinations is determined by additional connections within this network.

Similarly, LNM has recently been applied to other long-standing neurological mysteries, including motor/vocal tics, blindsight, and pathological laughter and crying (PLC), characterized by inappropriate outbursts of laughter and/or weeping (6, 13, 22). In each of these conditions, prior neuroimaging studies have provided heterogeneous results and causal lesions are scattered to many different regions across the brain, leaving the neural substrate unknown. Using LNM, lesions causing tics mapped to a common circuit with the anterior putamen as the most sensitive and specific hub of the circuit (6), lesions causing blindsight were associated with connectivity to the medial pulvinar nucleus of the thalamus (22), and lesions causing PLC were characterized by connectivity to a complex network with positive connectivity to subcortical and medial cortical regions involved in emotional processing, and negative connectivity to sensorimotor cortical regions (13). The identified circuits provide insight into the neural mechanisms of these symptoms and help to evaluate the link between patients' symptoms and brain lesion(s).

While LNM studies have demonstrated success in mapping symptoms to common brain circuits, an important consideration is the fact that most brain disorders are primary/idiopathic, and not caused by lesions. Therefore, if LNM is to be relevant to symptoms in these populations, it must be demonstrated that primary and lesion-induced symptoms involve dysfunction of the same brain networks. While LNM directly only applies to symptoms caused by lesions, recent work in cervical dystonia (23), tics (6), and mania (24) have shown that networks identified through brain lesions are also abnormal in idiopathic patients with the same disorder. In cervical dystonia, Corp, Joutsa (23) showed that the cerebellar and somatosensory regions identified by LNM showed abnormal rs-fMRI connectivity in an independent dataset of idiopathic cervical dystonia patients. Similarly, Lee, Nielsen (24) demonstrated that mania caused by both brain lesions and bipolar disorder involve dysfunction of networks involving the orbitofrontal cortex, dorsolateral prefrontal cortex, and temporal lobes.

LINKING LNM FINDINGS TO TREATMENT TARGETS

An appealing possibility for LNM is the translation of identified networks into targets for therapeutic brain stimulation, such as deep brain stimulation (DBS) or transcranial magnetic stimulation (TMS). These techniques are widely used for specific brain disorders, such as movement disorders and depression (11, 25). However, the localization of the treatment targets has been challenging and there are no data-driven systematic methods for identification of new targets (26).

Several studies have now demonstrated that LNM findings align with effective targets for neuromodulation. For example, lesions causing parkinsonism are connected to the claustrum, and DBS electrode location connectivity to this region correlated with clinical improvement in patients with Parkinson's disease treated with subthalamic nucleus DBS (19). Lesions causing cervical dystonia are connected to the cerebellum and sensory cortex, converging with connectivity with the optimal globus pallidus DBS electrode location connectivity in patients with idiopathic generalized or cervical dystonia (23). Similarly, Ganos, Al-Fatly (6) recently showed that connectivity between DBS sites and a network connected to lesions causing tics significantly predicted clinical improvement in patients. In depression, therapeutic brain stimulation (both invasive and noninvasive) and brain lesions converged on common circuits (27). Overall, these observations suggest therapeutic relevance for LNM-based findings, and that targeting the causal networks with brain stimulation might be a reasonable approach.

The aforementioned studies have used LNM to identify potential treatment targets by investigating common connectivity to lesions *causing* a symptom, however, LNM has also been used to localize networks associated with rare lesions that *relieve* symptoms (28, 29). Lesions causing essential tremor relief were commonly connected to a network centered upon the thalamus, which matched precisely with the currently used highly efficacious DBS target for tremor (Figure 3A). Lesions improving tremor also showed strong connectivity to the cerebellum, which is known to play a major role in the pathophysiology of tremor and has shown promise as a treatment target using noninvasive brain stimulation (30, 31).

In addition, a recent study applied this approach to lesions improving addiction, and localized a brain circuit thought to mediate smoking addiction remission (Figure 3B) (29). Specifically, lesions resulting in smoking addiction remission showed positive connectivity to the insula and paracingulate cortex, and negative connectivity to the medial prefrontal cortex. This circuit seemed to generalize to other substances of abuse. These findings may have important clinical implications given that the identification of effective treatment targets for addiction disorders has been exceptionally challenging, resulting in numerous neuromodulation trials with no consensus regarding the optimal targets (32). Independent of the LNM study by Joutsa, Moussawi (29), two recently published large trials (one to facilitate smoking cessation, one to reduce craving in alcoholism) reported positive results with specific coils designs (33, 34). Although these studies did not intend to target the regions identified using LNM, the peaks of these coil electric fields overlapped remarkably well with the cortical network peak of the addiction remission network, demonstrating the potential therapeutic relevance of mapping brain circuits from beneficial brain lesions. Future work is expected to expand this approach using LNM on lesions relieving symptoms to other disorders, and will demonstrate whether these findings can be translated into new treatments.

ISSUES TO BE RESOLVED

Although LNM using functional connectivity has shown promise in localizing brain circuits causally linked with symptoms, the neurobiological consequences of disrupted functional connections are not fully understood. A brain lesion causes loss of function at the lesion

location but the effects in connected regions are dependent on the nature of the connection from the lesion location. For example, a loss of excitatory connections could lead to decrease in activity in the connected region and loss of inhibitory connections could lead to increased activity (23). However, whether positive and negative functional connectivity can be interpreted as simple decreased and increased activity remains unknown. In addition, how to best combine connectivity findings using complementary techniques, including functional and structural connectivity, is under investigation (15, 17, 35). As such, LNM has lent insight into some long-standing mysteries of localization, but it would be inaccurate to suggest that LNM has fully explained or "solved" these mysteries.

Similarly, while a growing body of literature suggests that LNM can help identify therapeutic targets (6, 19, 23, 27), these studies have relied solely on retrospective patient data. It is important to take the next step and conduct prospective trials to investigate the efficacy of directly targeting LNM identified networks. The most direct test would be to conduct a trial positioning DBS electrodes or noninvasive brain stimulation within a hub of a network identified by LNM. However, a more efficient alternative approach would be reprogramming existing active contacts in DBS patients (36). This way, one could test the efficacy of numerous DBS contact locations, with the hypothesis being that greater symptom improvement will be seen for contacts with connectivity profile best matching the LNM circuits. For non-invasive brain stimulation, direct stimulation of an LNM network can be tested if LNM identifies a hub within a cortical location (23), but in order to target subcortical circuits, one would need to apply stimulation to cortical sites that are most connected to subcortical LNM hubs (37).

CONCLUSIONS

Lesion network mapping using has become popular in recent years and has shown promise in identifying the brain circuits causally linked with a wide range of neurological and psychiatric symptoms. Circuit-based localization may help to shed light into long-standing clinical mysteries, and also pave the way for the development of new therapies. However, caution for the clinical relevance of LNM is warranted until the value of this approach can be verified by prospective studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- Lesion network mapping can localize symptoms to brain circuits rather than individual brain regions.
- Recent studies using this circuit-based approach have lent insight into long-standing clinical mysteries, such as hallucinations and blindsight.
- Lesion network mapping may help to identify treatment targets for neuromodulation.

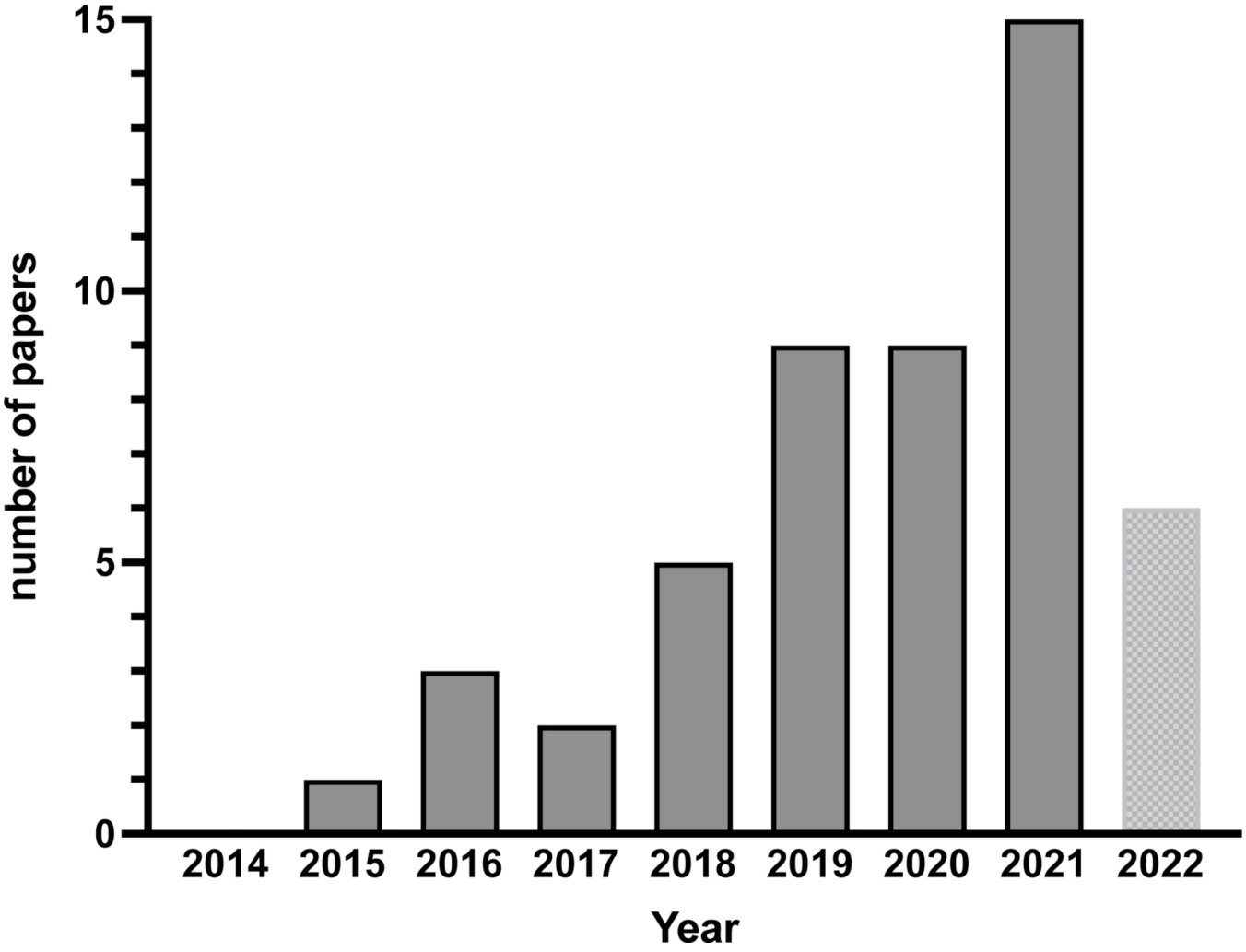

Figure 1. Lesion network mapping studies by year.

A total of 50 studies were identified by a systematic search (see Supplementary File 1 for search details).

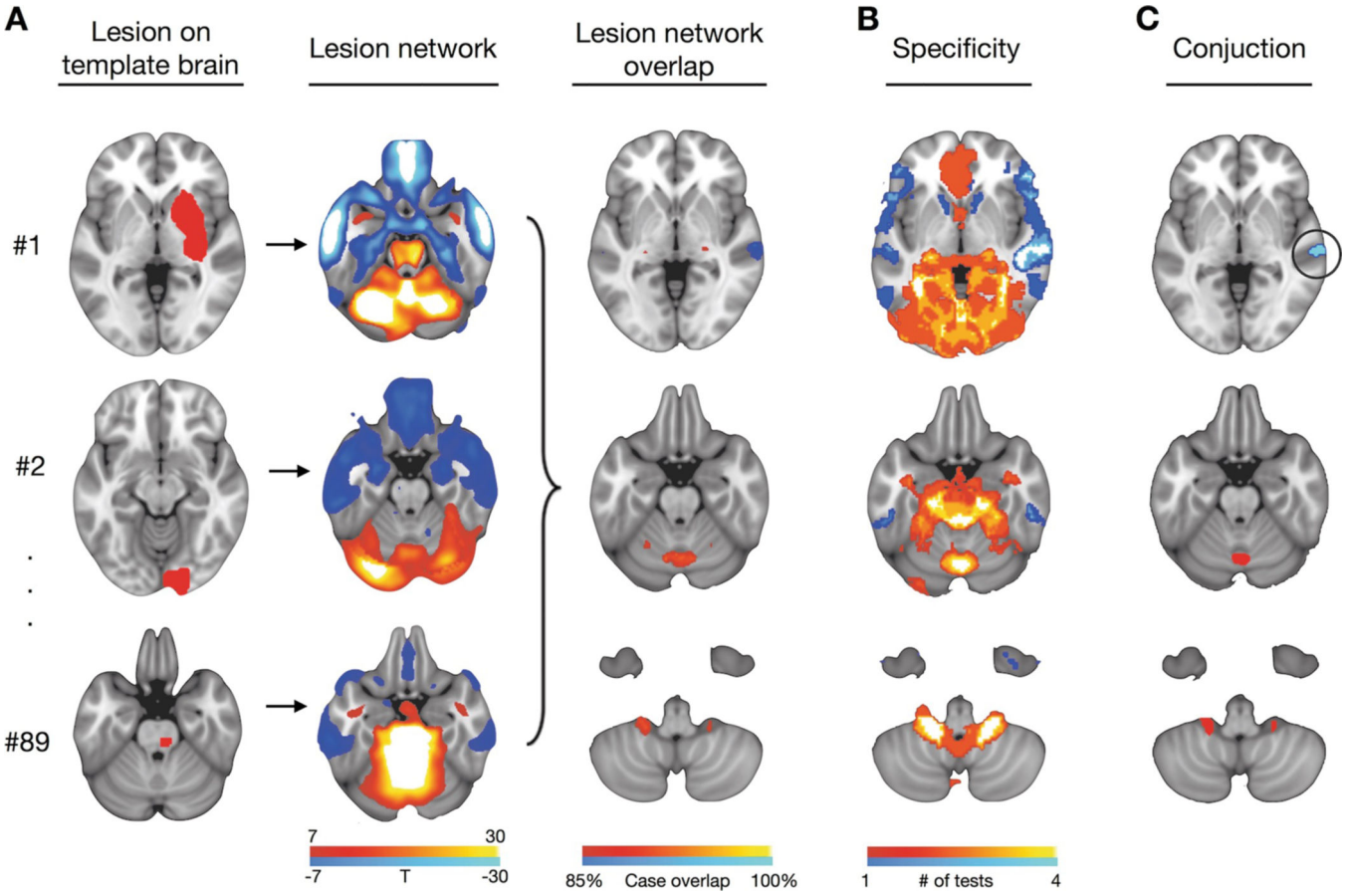

Figure 2. Lesion network mapping of hallucinations.

(A). Each of the 89 locations of lesions causing hallucinations were transferred to a common brain template (left). Functional connectivity between each lesion location and the rest of the brain was computed using resting-state functional magnetic resonance imaging data from 1000 healthy control subjects (second column). Individual lesion network maps were thresholded, binarized, and overlapped to identify common connections across the lesion locations (third column). (B). Specificity tests were used to identify connections specific to lesions causing hallucinations versus control lesions. (C). A conjunction analysis identified regions whose connectivity was both sensitive and specific for lesions causing hallucinations. Figure reproduced with permission from reference (3).

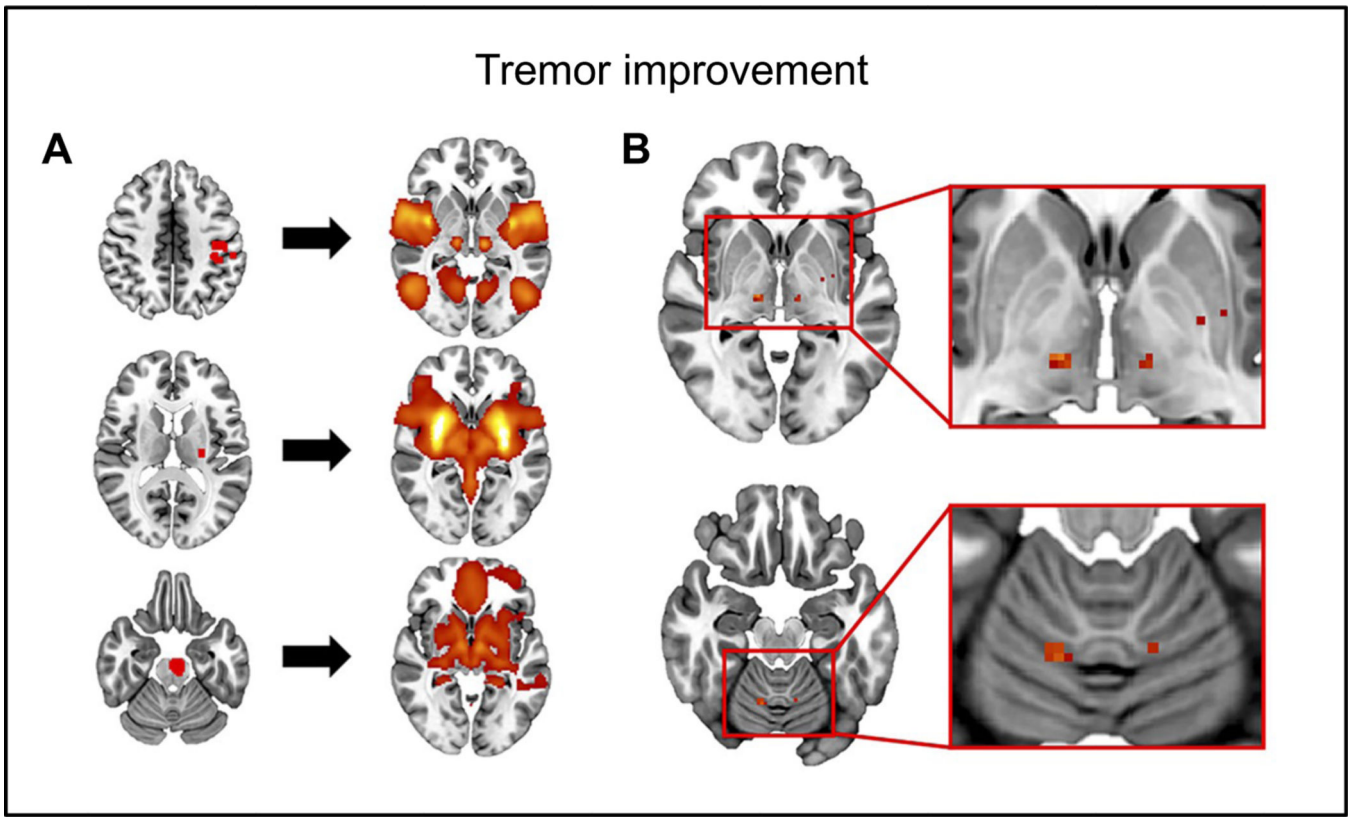

Figure 3. Lesion network mapping of treatment targets.

Brain regions resulting in improvement of essential tremor (A) were functionally connected to the ventral intermediate nucleus of thalamus, and cerebellum (B). A and B modified with permission (28). Lesion connectivity profile associated with smoking addiction remission (C). C modified with permission (29).

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Table 1.

Symptoms and functions localized by lesion network mapping to date

Motor and speech disorders		**Non-motor symptoms**		**Behavioral changes**	
Akinetic mutism	Darby, 2018	Amnesia	Ferguson, 2019	Criminality	Darby, 2018
Alien limb	Darby, 2018	Anosognosia for hemiplegia	Klingbeil, 2020	Mind wandering	Philippi, 2021
Aphasia	Wawrzyniak, 2022	Autoscopic phenomena	Blondiaux, 2021	Pedophilia	Scarpazza, 2021
	Boes, 2015	Blindsight	Kletenik, 2022	Sprituality and religosity	Ferguson, 2021
Central Hypoventilation Syndrome	Prabhakar, 2020	Bodily awareness disorders	Herbet, 2019		
Cervical dystonia	Corp, 2019	Bodily self-consciousness failure	Wawrzyniak, 2018		
Falling risk	Crockett 2022	Cerebellar cognitive affective syndrome	Albazron, 2019		
Foreign accent syndrome	Higashiyama, 2021	Cognitive impairment	Reber, 2021		
Freezing of gait	Fasano, 2017		Crockett 2021		
Infantile spasms	Cohen, 2021	Coma	Fischer, 2016		
Hemichorea	Laganiere, 2016	Decision making impairment	Sutterer, 2016		
				Improvement of symptoms	
Holmes' tremor	Joutsa, 2019	Delusional mi sidenti fi cati on	Darby, 2017		
Parkinsonism	Joutsa, 2018	Depression	Padmanabhan, 2019	Addiction remission	Joutsa, in press
Post-stroke motor outcomes	Lee, 2020	Epilepsy	Bdaiwi, 2021	Essential tremor improvement	Joutsa, 2018
Post-stroke sensorimotor outcomes	Jimenez-Marin, 2021		Mansouri, 2020		
Step length assymetry	Kyeong, 2021	Executive function impairment	Hwang, 2020		
Post-stroke functional outcomes*	Bowren 2022	Hal luci nations	Boes, 2015		
	Cohen, 2021		Kim, 2021		
	Pini, 2021	Loss of consciousness	Snider, 2020		
	Salvalaggio, 2020	Mania	Cotovio, 2020		
Tics	Ganos, 2022		Lee, 2019		
		Pain	Boes, 2015		
			Elias, 2020		
		Pathological laughter and crying	Klingbeil, 2021		
		Prosopagnosia	Cohen, 2019		
		Spatial delusions	Alves, 2021		

Only first author and year of publication are shown; full bibliographic references are located in Supplementary File 2.

*Studies also assessed non-motor outcomes. Note: Categorization of symptoms is ambiguous and should be considered suggestive.