Mapping Holmes Tremor Circuit Using the Human Brain Connectome

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Objective: Holmes tremor is a debilitating movement disorder with limited treatment options. Lesions causing Holmes tremor can occur in multiple different brain locations, leaving the neuroanatomical substrate unclear. Here, we test whether lesion locations that cause Holmes tremor map to a connected brain circuit and whether this circuit might serve as a useful therapeutic target.

Methods: Case reports of Holmes tremor caused by focal brain lesions were identified through a systematic literature search. Connectivity between each lesion location and the rest of the brain was computed using resting state functional connectivity magnetic resonance imaging data from 1,000 healthy volunteers. Commonalities across lesion locations were identified. This Holmes tremor circuit was then compared to neurosurgical treatment targets and clinical efficacy.

Results: We identified 36 lesions causing Holmes tremor, which were scattered across multiple different brain regions. However, all lesion locations were connected to a common brain circuit with nodes in the red nucleus, thalamus, globus pallidus, and cerebellum. In cases with effective neurosurgical treatment, the treatment target was connected with the lesion location, indicating that a second hit to the same circuit might be beneficial. Commonly used deep brain stimulation targets such as the ventral intermediate nucleus and subthalamic nucleus fell outside our Holmes tremor circuit, whereas the globus pallidus target was close, consistent with published clinical response rates for these targets.

Interpretation: Lesions causing Holmes tremor are part of a single connected brain circuit that may serve as an improved therapeutic target.

In 1904, Gordon Holmes described a series of patients with tremor caused by focal brain damage.[1] Later, these observations were formalized into a clinical tremor syndrome that bears his name.[2] Whether Holmes tremor represents a single clinical entity remains a matter of debate; however, symptoms in these patients tend to differ from patients with other tremor syndromes.[3] The tremor is usually slow, large in amplitude, and present at rest, with movement, and often with sustained posture.[2] Holmes tremor is frequently debilitating given its large amplitude, lack of response to medications, and heterogeneous response to deep brain stimulation (DBS).[4,5]

One obstacle to finding effective treatments for Holmes tremor is that it remains unclear whether clinically diagnosed cases share a common neuroanatomical substrate, and if so, what that neuroanatomical substrate might be. The tremor has been variably referred to as "rubral tremor," "midbrain tremor," or "thalamic tremor" based on lesion location. However, lesions outside the red nucleus, midbrain, and thalamus can also cause this syndrome.[2] One hypothesis to explain this heterogeneity is that lesions causing Holmes tremor map to one or more connected brain circuit(s).[1,2] However, which circuit has remained unclear, leading to uncertainty as to the most appropriate DBS target.[5,6] The hypothesis that lesion

TABLE 1. Case Reports of Holmes Tremor

#	First Author	Year	Body Part	Type	Time to Onset	DA Deficit	DA Response	Neurosurgical Treatment	Surgical Response
1	Akkus	2006	UL, LL	I	5 yr		Yes		
2	Alvarez	2014	UL, LL	I	4 mo			VIM thalamotomy[a]	Yes
3	Bandt	2008	UL, LL	I	7 mo			Lenticular fasciculus DBS[a]	Yes
4	Baysal	2009	UL, LL	I	2 wk		Yes		
5	Gajos	2010	UL	I	4 mo	No			
6	Hertel	2006	UL, LL	I	3 mo	No		VIM DBS	Yes
7	Kim	2009	UL	I	1 wk		No		
8	Kipfer	2013	UL	I	6 mo		No		
9	Lehericy	2001	UL	I	1 yr				
10	Martins	2016	UL	I	1 yr		Modest		
11	Miwa	1996	UL, LL	I	3 yr		No		
12	Nikkhah	2004	UL, LL	I	6 mo			VIM DBS	Yes
13	Nowak	2010	UL, LL	I	3 mo		Modest		
14	Schreuder	2010	UL	I	4 mo	Yes	No		
15	Seidel	2009	UL, LL	H	9 mo	Yes	Yes		
16	Castrop	2013	UL	H	6 mo		No	VIM DBS[a]	Yes
17	Castrop	2013	UL	H	18 mo		No	VIM DBS[a]	Yes
18	Chhetri	2014	UL	H	6 mo				
19	Ferbert	1993	UL	H	3 yr				
20	Kim	2014	UL	H	7 mo		No		
21	Lim	2007	UL	H	1 mo		No	VIM, GPi, VOA DBS[a]	Modest
22	Maki	2015	UL	H	11 mo		No	VIM thalamotomy	Modest
23	Miwa	1996	UL	H	4 yr				
24	Nakamura	1993	UL	H	4 mo				
25	Raina	2007	UL	H	1 mo		Yes		
26	Raina	2007	UL, LL	H	6 mo		Yes		
27	Remy	1995	UL, LL	H	2-11 mo	Yes	Modest		
28	Rieder	2003	UL	H	5 mo		No	Thalamotomy	Yes
29	Shepherd	1997	UL	H	8 mo		No	VIM DBS	Yes
30	Walker	2007	UL, LL	H	5 mo		No		
31	Woo	2013	UL	H	6 mo		Yes		
32	Brittain	2011	UL, LL	I	4 mo		No	VOP/ZI DBS[a]	Yes
33	Goto	2004	UL	H	20 mo		Modest	VIM DBS, pallidotomy[a]	Yes
34	Mossuto-Agatiello	1993	UL, LL	H	1 mo				
35	Suda	2012	UL	H	15 mo		Modest		
36	Velez	2002	UL, LL	H	2 mo		Yes		

Delay is the estimated time between the occurrence of the lesion and onset of Holmes tremor. Dopamine response is based on the description of the authors of the original report of the response to L-dopa or dopamine agonists. Dopamine deficit refers to decreased presynaptic dopamine function on positron emission tomographic or single photon emission computed tomographic imaging. The original papers are listed in the Supplementary Table.
[a]A figure of the neurosurgical target(s) is shown in the paper.
DA = dopamine; DBS = deep brain stimulation; GPi = globus pallidus interna; H = hemorrhage; I = ischemic stroke; LL = lower limbs; UL = upper limbs; VIM = ventral intermediate nucleus of thalamus; VOA = ventral oralis anterior; VOP = ventral oralis posterior; ZI = zona incerta.

locations causing Holmes tremor localize to one (or more) connected brain circuit(s) has never been formally tested.

Recently, it has become possible to map heterogeneous lesion locations causing the same symptom to connected brain circuits, a technique termed lesion network mapping.[7] This technique has been successfully applied to localization of hemichorea, parkinsonism, freezing of gait, and multiple different neuropsychiatric symptoms.[7] Importantly, the technique has been validated for use with 2-dimensional (2D) approximations of 3D lesions, such as those available from published figures,[8,9] and can identify therapeutic targets for techniques such as DBS.[10,11] Here, we test the hypothesis that lesions causing Holmes tremor (defined as combined rest, postural, and action tremor) map to a common brain circuit. In addition, we investigate whether lesion network mapping could help to identify therapeutic targets for Holmes tremor.

Patients and Methods

Case Reports

Cases of individuals with Holmes tremor who had occurrence of tremor following a focal brain lesion were

identified using PubMed search terms "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 tremor manifestation, including mention of presence or absence of rest, postural, and action tremor of the upper limb, whether the tremor was called "midbrain," "rubral," "Holmes," "post-traumatic," or "complex tremor"; (2) appearance of rest, postural, and action tremor attributed to a stroke (ischemic or hemorrhagic); and (3) a published figure showing the location of the focal ischemic or hemorrhagic lesion where borders of the lesion could be identified. Note that only strokes were included in the present analysis to avoid including infiltrating or diffuse lesions where the lesion extent might not be clearly identifiable from the structural brain scans. Exclusion criteria included (1) cases of tremor caused by tumor, infection, or brain lesion other than stroke; (2) poor description of tremor manifestation; (3) rest or action/postural tremor only; and (4) poor image resolution such that lesion boundaries could not be delineated. All reports were evaluated by a movement disorder specialist (L.C.S.) according to the current diagnostic criteria.[2,3]
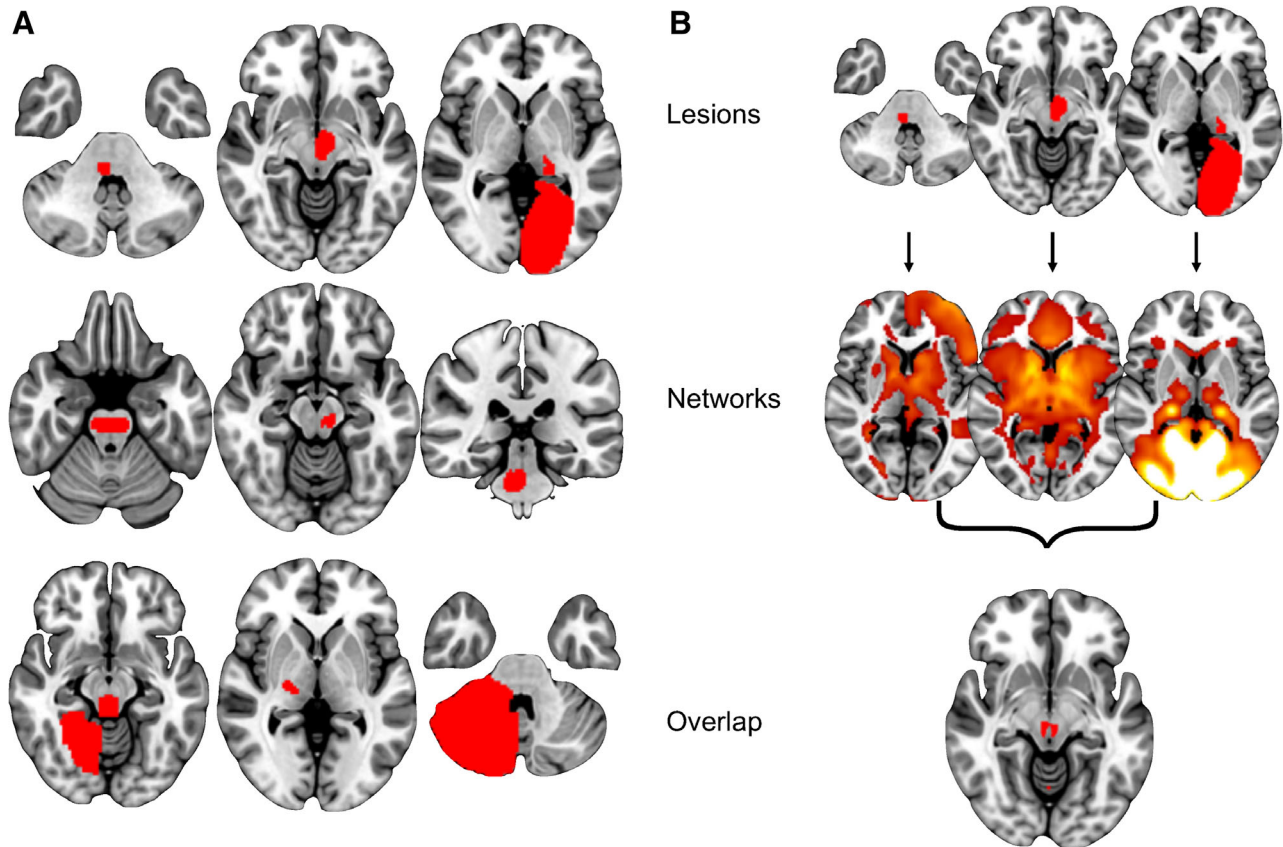
FIGURE 1: Lesion network mapping of Holmes tremor. (A) Nine representative lesions causing Holmes tremor (selected from n = 36). (B) Lesion network mapping method. Lesions from the literature are traced onto a standard brain atlas (upper row). The set of voxels functionally connected to each lesion location are identified ("lesion networks," middle row). Finally, lesion networks are overlapped to identify regions connected to all lesion locations (bottom row).
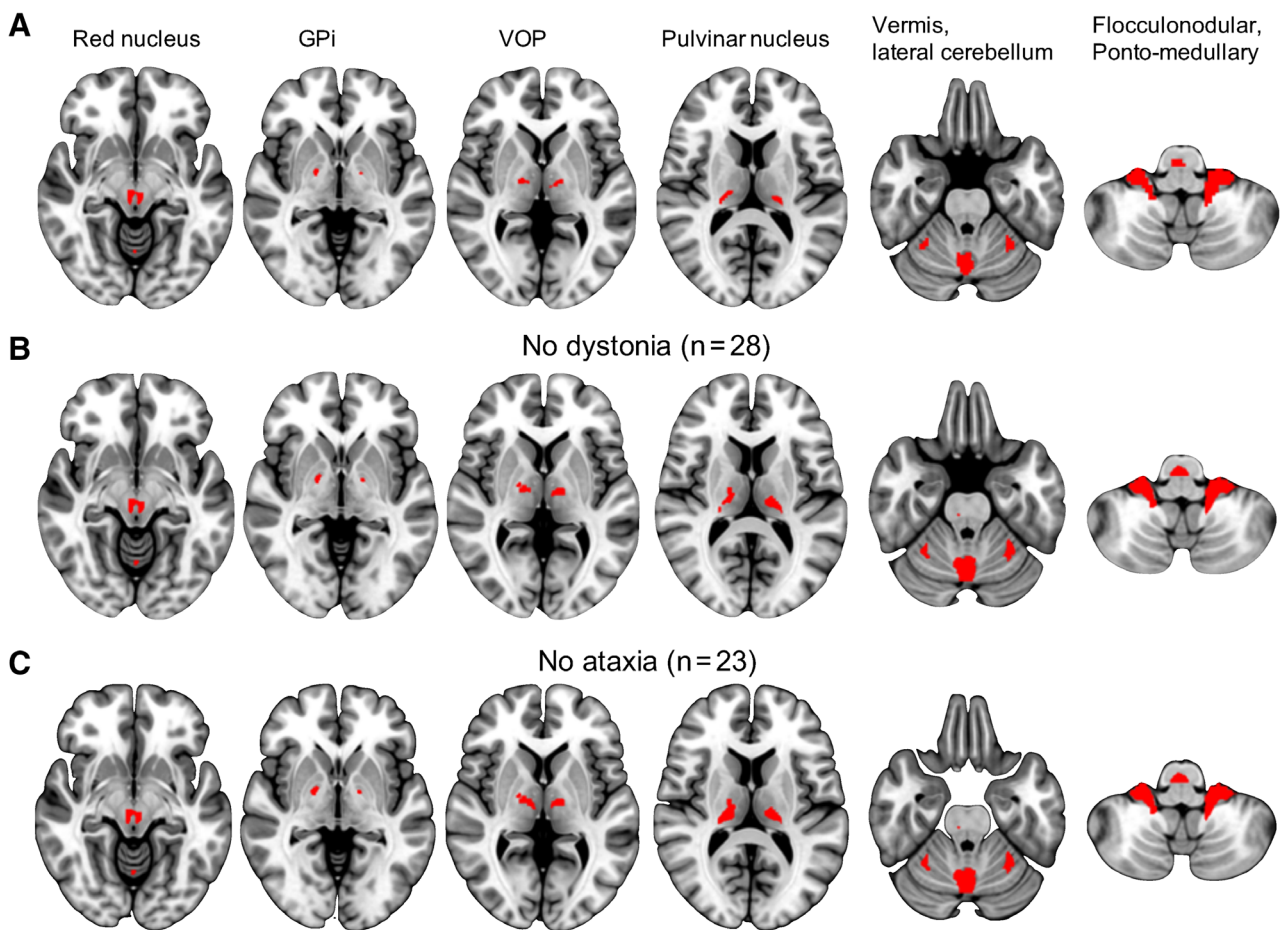
FIGURE 2: Holmes tremor circuit. (A) Brain regions connected to all 36 lesion locations causing Holmes tremor ("Holmes tremor circuit"). (B, C) Replication in patients without the most common comorbid movement disorder symptoms dystonia (B) and ataxia or dysmetria (C). GPi = globus pallidus interna; VOP = ventral oralis posterior.

TABLE 2. Lesion Network Mapping Coordinates					
Location	**Side**	**x**	**y**	**z**	**Cluster Size**
Midbrain (red nucleus)	Midline	1	−26	−13	81
GPi	R	17	−5	−3	6
	L	−16	−6	−4	1
Thalamus (VOP)	R	14	−12	3	12
	L	−12	−13	3	5
Thalamus (pulvinar nucleus)	R	21	−24	12	16
	L	−19	−24	11	14
Cerebellar vermis VI	Midline	1	−65	−22	514
CH VI (lateral cerebellum)	L	−27	−55	−24	45
	R	27	−54	−25	26
CH X (flocculonodular)	L	−19	−40	−47	185
	R	20	−40	−48	137
Pontomedullary junction	Midline	1	−29	−44	24

Center of gravity coordinates are presented for all distinct clusters. The labels of the clusters are defined visually using previously published parcellations to identify subregions of the thalamus and cerebellum.[23,24]

CH = cerebellar hemisphere; GPi = globus pallidus interna; L = left; R = right; VOP = ventro-oralis posterior nucleus.

Lesion Network Mapping

Lesion network mapping methodology has been described in detail previously,[9,12] and the code is freely available through Lead DBS software (http://www.lead-dbs.org).[13] Lesion locations were manually drawn on the Montreal Neurological Institute (MNI) anatomical template based on the published images of the lesions. This provides only a 2D approximation of the true 3D lesion, but prior work suggests this is sufficient for lesion network mapping.[8,9] Connectivity between each lesion location and all other brain voxels was computed using resting state functional connectivity magnetic resonance imaging data from 1,000 healthy volunteers.[14] The analyses were run in the MNI space with 2 × 2 × 2mm voxel size. The lesion networks were created using a threshold of t ≥ 5 (corresponding to whole brain familywise error [FWE] corrected $p < 0.05$) to binarize the connectivity maps. Finally, the lesion networks were overlaid to identify regions connected with all lesion locations. For visualization, maps were upsampled to 0.5mm voxel size and overlaid on a high-resolution MNI template using Mango software (http://ric.uthscsa.edu/mango/). This same visualization approach was used for all figures in the paper.

To examine whether our findings were influenced by the most common comorbid symptoms, the above analysis was repeated including only cases without dystonia (n = 28) and cases without ataxia or dysmetria (n = 23).

Specificity to Holmes Tremor

To test whether the identified circuit was specific for Holmes tremor, lesion network maps were compared to those of control lesions causing nonspecific neurological symptoms (n = 135)[15] or lesions causing other movement disorders previously published by our group (asterixis, hemichorea, freezing of gait, and parkinsonism; n = 102).[9,16–18] The group comparisons were performed using 2 different statistical approaches, analyzing binary (ie, included in the network or not) and
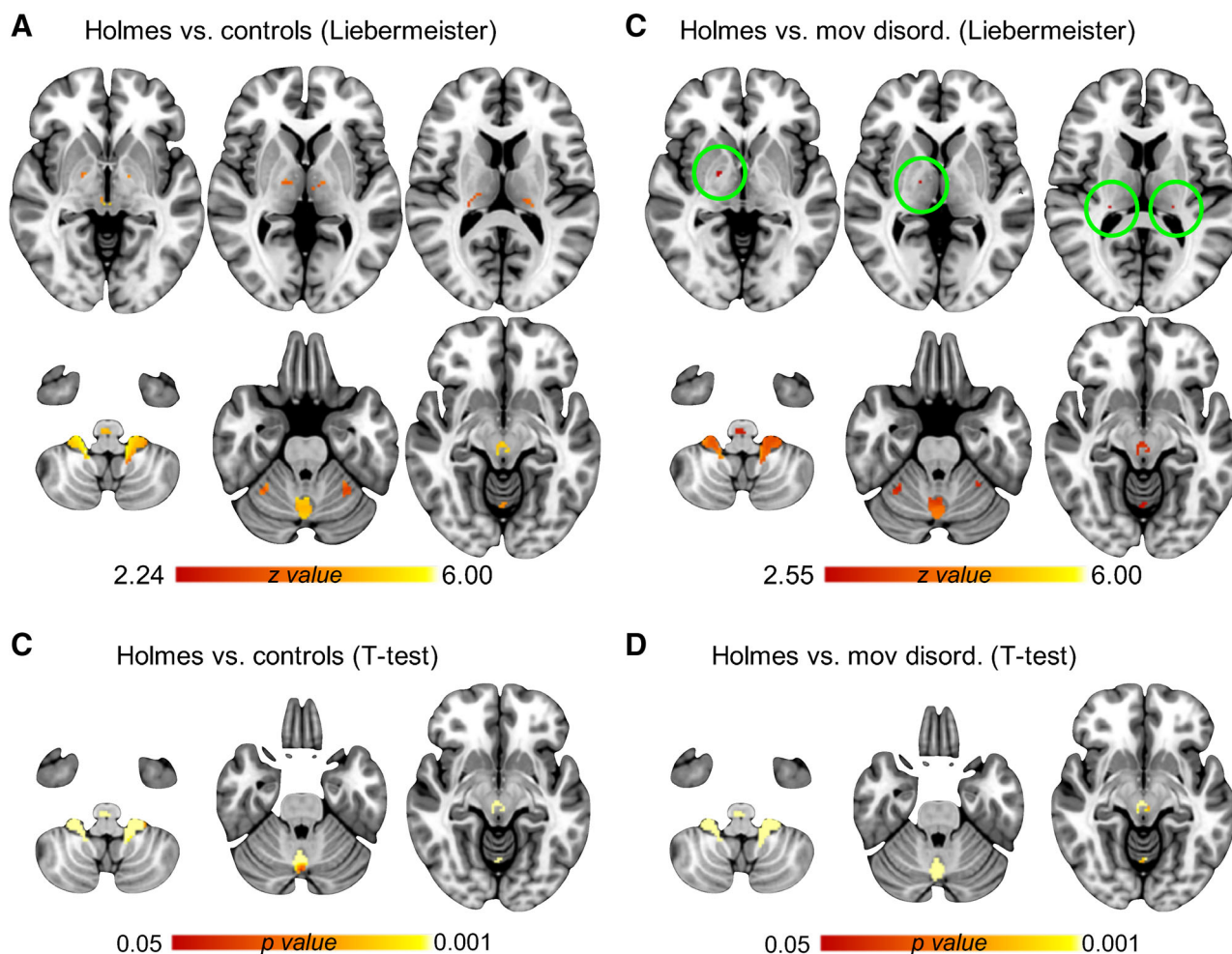

FIGURE 3: Specificity of connections to lesions causing Holmes tremor. (A, B) Lesion network maps from patients with Holmes tremor (n = 36) were statistically compared to lesion network maps from patients with nonspecific symptoms (n = 135) using binarized maps (A) and continuous connectivity maps (B). (C, D) Lesion network maps from patients with Holmes tremor (n = 36) were statistically compared to lesion network maps from patients with other movement disorders (n = 102) using binarized maps (C) and continuous connectivity maps (D). All statistical comparisons are corrected for multiple comparisons at $p < 0.05$. Green circles are used to highlight small clusters in C.

continuous (ie, strength of connection) maps, as described previously.[16–18] Analyses with binary maps were conducted using Liebermeister test implemented in voxel-based lesion-symptom mapping.[19] The analyses were conducted across the whole brain ignoring voxels affected in <10% of the lesion networks. Voxels within the identified circuit with whole brain false discovery rate corrected $p < 0.05$ were considered specific for Holmes tremor. Analyses with continuous maps were performed using general linear model implemented in FMRIB Software Library. To avoid inflated type I error rates recently associated with parametric tests,[20] the correction for multiple comparisons was performed using the permutation-based threshold-free cluster enhancement method.[21] Regions showing significant group difference (FWE-corrected $p < 0.05$) within the identified circuit were considered specific for Holmes tremor.

Network Visualization

By definition, connectivity with the nodes of the identified circuit defines a network of brain regions that encompasses our 36 lesion locations causing Holmes tremor. To visualize this network, we first identified 8 "nodes," defined as contiguous clusters of at least 5 voxels connected to all 36 lesion locations. Homologous regions in the left and right hemisphere were combined into a single node. We then used our normative connectome to compute connectivity with each node. Resulting connectivity maps were thresholded ($t \geq 5$) and binarized, and a conjunction analysis was used to identify voxels connected to all 8 nodes.

Therapeutic Targets

In our sample, 7 of 12 cases who received neurosurgical treatment (DBS or stereotactic lesions) had a published figure showing their treatment target. All of these cases responded to treatment. The surgical target location was drawn based on the published image and overlaid with the corresponding lesion network to investigate whether the target fell within this network (ie, is connected with the causal lesion).

Based on the published literature, the most commonly targeted regions for DBS in Holmes tremor include ventral intermediate nucleus of thalamus (VIM), globus pallidus interna (GPi), and subthalamic nucleus (STN).[5] Clinical response rates for these targets were taken directly from a recent systematic review,[5] where good clinical response was defined as ≥80% improvement in the clinical scale used in the study: 10/31 for VIM, 11/14 for GPi, and 1/6 for STN.[5] The probabilistic coordinates for each of the neuroanatomical treatment targets were taken from previously published work.[22] These coordinates were compared with the identified Holmes tremor circuit.

The study was approved by the local institutional review board (Beth Israel Deaconess Medical Center #2018P000128).

Results

Lesion Network Mapping

Our literature search identified 36 cases of Holmes tremor (Table 1). Lesion locations were heterogeneous and included the midbrain, cerebellum, basal ganglia, pons, medulla, cerebellum, and occipital lobe (Fig 1A; see Supplementary Table for all lesions). Connectivity between each lesion location and the rest of the brain was computed, and commonalities across the 36 lesions were identified using lesion network mapping (see Fig 1B).

All 36 lesions causing Holmes tremor were part of a common brain network, defined by connectivity to 8 specific brain regions: the red nucleus, GPi, ventral oralis posterior (VOP) and pulvinar nuclei of the thalamus, pontomedullary junction, and 3 regions in the cerebellum (cerebellar cortex and vermis in lobule VI, and cerebellar cortex in lobule X; Fig 2A, Table 2). The results did not change when excluding patients with dystonia (see Fig 2B) or ataxia/dysmetria (see Fig 2C).

When compared to lesions causing nonspecific symptoms (n = 135) or other movement disorders (n = 102), all 8 nodes showed at least some specificity to Holmes tremor (Fig 3). By definition, connectivity with these 8 regions defines a human brain network that encompasses our 36 lesion locations causing Holmes tremor (Fig 4).
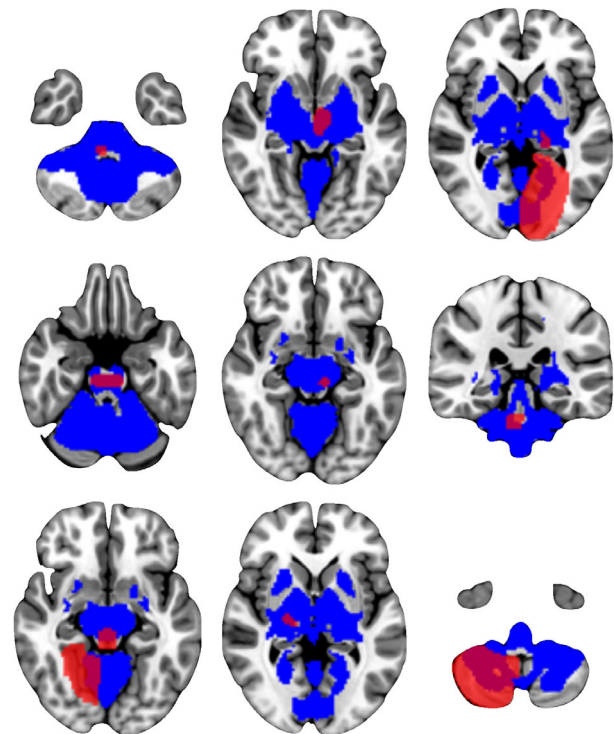

FIGURE 4: Brain network capturing the lesion locations causing Holmes tremor. Lesions (red) fall within the network defined by connectivity to all 8 Holmes tremor nodes (blue). The blue network is the conjunction of the networks from each of the 8 nodes in the Holmes tremor circuit.
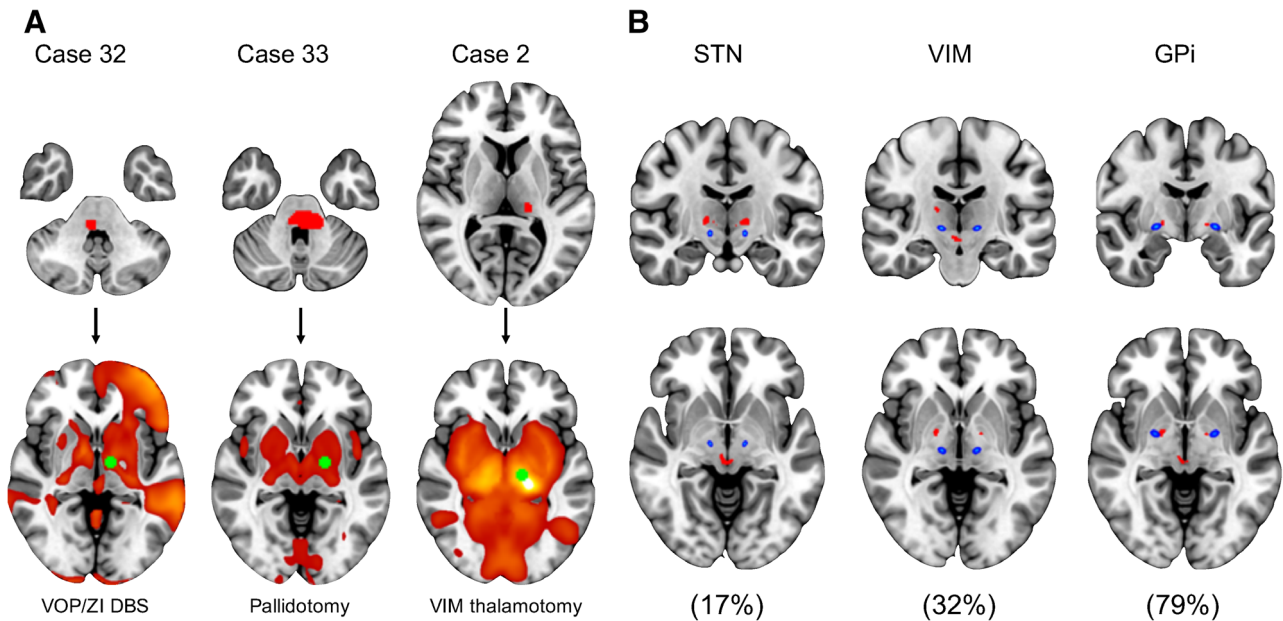
FIGURE 5: Treatment targets for Holmes tremor. (A) Three representative lesion cases with good clinical response to neurosurgical intervention (selected from n = 7). For each case, we show the lesion location (upper panel), the lesion network (lower panel), and the treatment target (green sphere). (B) Spatial relationship between commonly used deep brain stimulation (DBS) targets for Holmes tremor (blue) and our lesion-based Holmes tremor circuit (red; see also Fig 2A). Average clinical response rate (% good response) is shown according to Artusi et al.[5] Note that the globus pallidus interna (GPi) target was immediately adjacent to our Holmes tremor circuit, whereas subthalamic nucleus (STN) and ventral intermediate nucleus of thalamus (VIM) were not. VOP = ventral oralis posterior; ZI = zona incerta.

Therapeutic Targets

To test for relationships between lesion locations and neuroanatomical treatment targets, we examined 12 cases in our sample that received a focal neurosurgical intervention (see Table 1). All cases reported therapeutic benefit, and 7 cases displayed the location of the intervention. In all 7 cases, the location of the intervention that improved Holmes tremor was part of the same network as the lesion that caused Holmes tremor. In other words, the target was connected with the location of the causal brain lesion (FWE-corrected $p < 0.05$; Fig 5A). Given these results, we tested whether DBS targets commonly used to treat Holmes tremor (GPi, STN, VIM) fell within the network connected to all 36 lesion locations. None of the current targets matched our network exactly (see Fig 5B); however, the GPi target was immediately adjacent to our network, potentially consistent with its higher rate of good clinical response reported for this target.[5]

Discussion

There are several noteworthy findings in this study. First, lesions causing Holmes tremor do not localize to any single brain region, but do localize to a functionally connected brain circuit. Second, this brain circuit is defined by connectivity to 8 specific brain regions including the red nucleus, GPi, thalamus, pontomedullary junction, and cerebellum. Finally, this circuit may have therapeutic relevance as a target for neurosurgical intervention.

We provide direct support for the longstanding hypothesis that lesions causing Holmes tremor map to one or more connected brain circuit(s).[1,2,25,26] We advance these hypotheses by showing which connections are most important, identifying 8 brain regions connected to all 36 lesion locations. Connectivity to the red nucleus, thalamus, and cerebellum aligns with prior work implicating a cerebellorubrothalamic circuit in Holmes tremor.[25,26] Similarly, connectivity to the GPi and VOP aligns with prior work implicating a pallidal–thalamic pathway.[6,27] Connectivity to the pulvinar nucleus aligns with reports suggesting that posterior thalamic lesions can cause some components of Holmes tremor.[28,29] However, our results fail to support other brain regions previously thought to be important for Holmes tremor, such as VIM or the nigrostriatal tract.

VIM was not a key node in our Holmes tremor circuit, despite its established role in other tremor syndromes and being the most popular DBS target for Holmes tremor.[5] The absence of VIM is unlikely to be an artifact of our lesion network mapping technique, as prior work found that lesions improving essential tremor were connected specifically to VIM.[10] Rather, we believe our finding highlights a potentially important difference between different tremor syndromes. Specifically, both essential

tremor and Parkinson disease tremor respond extremely well to therapies targeting VIM,[30,31] but only 31% of patients with Holmes tremor show good clinical response to VIM DBS.[5] The subset of Holmes tremor patients that do respond to VIM DBS may have a lesion that is connected to VIM (in addition to our Holmes tremor circuit), a stimulation site that extends beyond VIM (perhaps intersecting VOP), or a stimulation site that is connected to our circuit, with VIM serving as an upstream node capable of modulating this circuit. A full understanding of the role of VIM in Holmes tremor requires further work, but our results suggest it may be less central to the Holmes tremor circuit than previously thought.

The nigrostriatal tract was also not a key part of our Holmes tremor circuit, despite dopaminergic medication being a first line treatment for Holmes tremor.[4] This result aligns with other data suggesting that nigrostriatal tract involvement is not necessary for development of Holmes tremor.[32] Specifically, many patients with Holmes tremor have normal dopamine neuroimaging and only half of patients respond to dopaminergic medication.[4,5,32–34]

Given that all 36 lesion locations causing Holmes tremor were connected to a common circuit, this connectivity could be considered necessary for a lesion to cause Holmes tremor. However, this should not be interpreted as sufficient to cause Holmes tremor. There may be additional (predisposing) factors that are required. In other words, all lesions causing Holmes tremor should fall within the identified circuit (see Fig 4), but not all lesions that fall within this circuit will necessarily cause Holmes tremor.

An important question is whether our Holmes tremor circuit has value as a therapeutic target. We found that surgical lesions or DBS sites that improve Holmes tremor are part of the same connected brain circuit as the lesion that caused the tremor in the first place. Although potentially counterintuitive, this finding may align with pathological oscillations recorded in Holmes tremor patients.[35] The first lesion could unbalance the circuit, setting up a pathological oscillation, and a second hit to this same circuit could break this oscillation, providing therapeutic benefit. If the therapeutic lesion must be part of the same circuit as the causative lesion, none of our current DBS targets would be expected to improve Holmes tremor in all cases. VIM and STN fell outside our circuit. The DBS target in the GPi comes close, potentially consistent with greater clinical benefit reported with this target.[5] Our results suggest a slightly more medial GPi target could be beneficial. Our results also support VOP as a therapeutic target, which, either alone or in combination with VIM DBS, has shown signs of efficacy for medication-refractory tremor related to multiple sclerosis.[36] Note that this study reported comparable efficacy between VIM and VOP DBS, whereas our results would

have predicted higher efficacy of VOP stimulation. However, the patients in this DBS study differed from our lesion cases in terms of diagnosis (progressive or relapsing–remitting multiple sclerosis vs focal stroke), number of lesions (multiple vs single), and clinical features (any type of tremor vs Holmes tremor). As such, it remains unknown whether Holmes tremor specifically would respond better to VOP DBS. Finally, our Holmes tremor circuit includes nodes that have not yet been evaluated as therapeutic targets, including multiple regions in the cerebellum. Whether neuromodulation directly targeting the circuit reported here results in improved outcomes for Holmes tremor remains a testable hypothesis in need of clinical validation.

There are several limitations. First, we used manually traced 2D lesions, which could be inaccurate and provide only an approximation of the full 3D lesion volume. However, prior work suggests that lesion networks derived from these 2D approximations are nearly identical to those derived from the full 3D lesion.[8,9] Second, there is no accepted clinical criteria for defining Holmes tremor, and what criteria do exist have changed over time.[3] In our study, all cases were required to have all 3 tremor types (rest, postural, action), consistent with the most recent consensus statement from the Movement Disorders Society,[3] but some clinical heterogeneity is inevitable. Third, our results could have been influenced by publication bias. For example, the rate of response to neurosurgical intervention is abnormally high in our included cases compared to reported rates for Holmes tremor as a whole.[5] That all our cases responded well to neurosurgical intervention also prevents us from contrasting patients with good versus poor clinical responses. Fourth, lesion network mapping uses connectome data from a large normative cohort to approximate connectivity in an individual patient at the time of the lesion, and thus ignores individual differences in brain connectivity. This appears to be a reasonable approximation given the success of lesion network mapping across many different symptoms,[7] and prior work using an age-matched or disease-matched connectome has had little impact on results.[9,37,38]

It is important to highlight that most of the above limitations, including inaccuracy of lesion tracing, clinical heterogeneity, and individual differences in brain connectivity, should all bias us against the present findings. As such, our finding that heterogeneous lesion locations causing Holmes tremor map to a common brain circuit is present despite these limitations, not because of them.

Acknowledgment

Author Contributions

All authors contributed to conception and design of the study, acquisition and analysis of data, and drafting the text and preparing the figures.

Potential Conflicts of Interest

J.J. and L.C.S. have nothing to disclose; M.D.F. has a patent on lesion network mapping pending.

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