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CASE STUDY

The cerebral tremor circuit in a patient with Holmes tremor

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Abstract

The cerebral network associated with Holmes tremor has never been determined directly. A previous study reported a brain network that is functionally connected, in healthy individuals, to different lesions that cause Holmes tremor (lesion connectome). We report a 71-year-old man with severe left-sided tremor caused by a microbleed near the right red nucleus. Using accelerometry-fMRI, we show tremor-related activity in contralateral sensorimotor cortex and cerebellar vermis. This network was distinct from, but functionally coupled to, the Holmes lesion connectome. We propose that Holmes tremor involves three distinct cerebral mechanisms: a structural lesion, an intermediate lesion connectome, and symptom-related activity.

Introduction

Holmes tremor is a syndrome of low frequency rest, postural, and intention tremor that results from an acquired brain lesion.[1] It often is highly debilitating and pharmacological treatment and deep brain stimulation have limited effects. Given its rarity, pathophysiological insights depend on case studies. Recently, 36 case studies were bundled using a technique called lesion network mapping,[2] which revealed a network that, in a group of healthy individuals, functionally connects all lesion sites known to cause Holmes tremor. This lesion connectome includes red nucleus, internal globus pallidus (GPi), thalamus (ventral oralis posterior nucleus, VOP), pontomedullary junction, and cerebellum.[3] It remains unknown how this etiology-based lesion connectome relates to a network that directly produces the symptom itself. For Holmes tremor, such a network has never been determined. However, for other tremor types such as parkinsonian tremor,[4] essential tremor[5] and dystonic tremor,[6] tremor-related activity was found in specific networks often including the cerebello-thalamo-cortical circuitry.[7] All these studies linked changes in brain activity (using functional MRI) to fluctuations in tremor (using concurrent electromyography or accelerometry). Here we report a unique case where we investigated Holmes tremor-related activity for the first time, and link it to the Holmes lesion connectome.

Methods

Case description

A 71-year-old man presented with a high-amplitude tremor of his left arm and leg. Symptoms had started 14 months after a minor stroke with dysarthria and impaired gait, from which he had completely recovered. The tremor was more severe during posturing than at rest, involved proximal muscles, and had a frequency of 4.4 Hz. There was also mild dystonic posturing of the left arm, without weakness, bradykinesia, or rigidity (see supplementary video). Susceptibility-weighted MRI revealed a microbleed near the right red nucleus (Fig. 1A, original image at: https://neurovault.org/collections/8074/). Dopamine transporter imaging (DAT-SPECT) showed an almost complete absence of tracer uptake in the right basal ganglia. Levodopa 1000 mg per day and pramipexol 4.5 mg per day gave no tremor relief. Stereotactic

lesioning of the right ventral intermediate nucleus (midpoint lesion at MNI [14.6 −16.0 0.8]) only had a transient effect. A week after surgery tremor was as severe as before. During a second surgical procedure, combined stereotactic lesions in both the right VOP and right GPi effectively reduced his tremor (midpoint lesions at MNI [15.2 −13.7 −0.3] and [23.3 −8.5 −0.5], respectively).

Functional imaging

Functional MRI scanning was done before stereotactic lesioning and without any tremor-modulating medication. The patient was scanned while resting his left arm (20 blocks, duration 14-16s) or hold the arm in a tremor-evoking posture (20 blocks of 15s). Tremor severity was quantified using a three-axial accelerometer placed on the dorsum of the left hand. Accelerometery data was detrended, demeaned, transformed to scan-to-scan tremor power at peak tremor frequency (4.4 Hz; Fig. 1B), log-transformed and convolved with the hemodynamic response function, using previously described procedures.[4]

MRI images were acquired on a Siemens PRISMA 3T MRI system, using a 64-channel head-neck coil. T2*-weighted images were obtained using multiband echo planar imaging (EPI), with multiband acceleration factor 6, repetition time 1s, echo time 34 ms, 2.0 mm isometric voxels, 72 slices and a field of view of 210 mm. A high-resolution anatomical image was acquired using an MP-RAGE (magnetization-prepared rapid gradient-echo) sequence (repetition time 2300 ms, echo time 3.03 ms, voxel size 1.0 mm isometric, 192 sagittal slices, field of view 256 mm). Functional images were pre-processed using previously described procedures with a net smoothing kernel of 6 mm.[8] We normalized functional images to MNI (Montreal Neurological Institute) space and, for optimal sensitivity, to a cerebellum specific template using the SUIT toolbox.[9]

First, we tested for tremor-related activity using a multiple regression analysis in SPM12. We included regressors modeling posture, posture onset, posture offset, and several nuisance regressors (averaged signal intensity of each scan and the time course of bilateral ventricles[10]). We specifically modelled fluctuations in tremor power by adding scan-by-scan tremor power as a parametric modulation to each of the scans during posture.[5] This allowed us to detect fluctuations in cerebral activity associated with fluctuations in tremor power (Fig. 1B), independent from cerebral activity related to posturing, posturing onset or offset movements. Second, we tested whether regions showing tremor-related activity were connected to the lesion connectome.[3] We focused on the sensorimotor cortex (SMC) and the cerebellar vermis because of their involvement in hand movement generation[11] and because these areas show tremor-related activity in other tremor types.[5,8,12] We extracted the BOLD time courses of the right SMC and cerebellar vermis and entered these, with the nuisance regressors, into two separate multiple regression analyses (seed-based connectivity). We then tested for functional connectivity between tremor-related activity (SMC and cerebellar vermis) and the regions of the Holmes lesion connectome.

For detection of activated or functionally connected areas we used a cluster-forming threshold of $P < 0.001$, with cluster level whole brain corrected (family wise error, FWE) $P < 0.05$ as significance threshold.[13,14] Additionally, we used the coordinates of the lesion connectome[3] as regions of interest for both tremor-related activity and connectivity analyses (midbrain, cerebellar vermis, pontomedullary junction, right GPi, VOP, pulvinar nucleus and left lateral and floccolunodular cerebellum). We searched for local maxima within a 5mm radius sphere around these coordinates that met a p<.05 peak level FWE-corrected significance threshold.

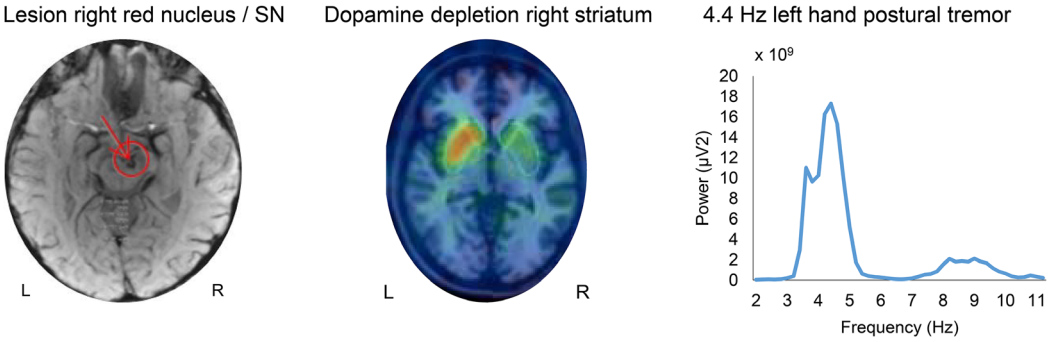
Results

All results and statistics are shown in Fig. 1. During scanning, the patient had a 4.4 Hz postural tremor of his left hand (Fig. 1A). There was significant tremor-related activity in several brain areas, including the sensorimotor cortex and cerebellar vermis (Fig. 1B, Table 1, unthresholded statistical images at https://neurovault.org/collections/8074/). Notably, region of interest analyses revealed no tremor-related activity in any of the areas in the lesion connectome that was previously derived with lesion network mapping.[3] Connectivity analyses showed that both the sensorimotor and cerebellar vermis clusters were functionally connected to five out of eight regions of interest from the lesion connectome (Fig. 1C). Scan-to-scan head displacement during scanning was 0.47 ± 0.34 mm (mean $\pm$ std). Except for one outlier (5.36 mm at scan 493), displacement was <2.1 mm. There was no correlation between scan-to-scan displacement and tremor power ($r = -0.06$, $P = 0.13$).

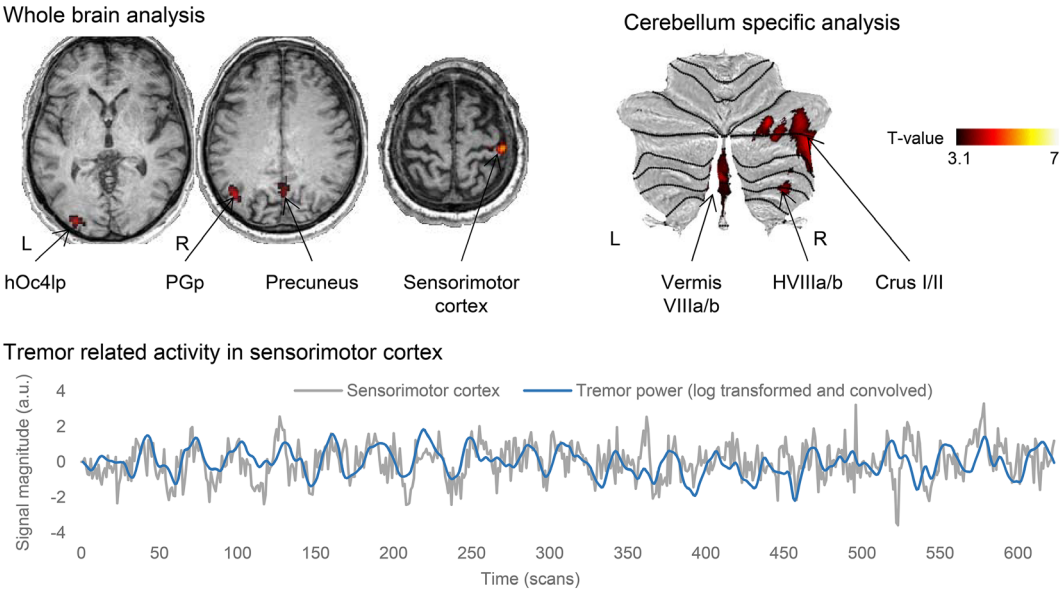
Discussion

In this patient, who developed Holmes tremor after a microbleed near the red nucleus, we demonstrate tremor amplitude-related brain activity in the contralateral sensorimotor cortex and cerebellar vermis. These brain regions showed only little anatomical overlap with the lesion connectome previously shown to be involved in Holmes tremor, based on 36 case reports.[3] However, we show that both the sensorimotor cortex and the cerebellar vermis

A. Case description



B. Tremor-related activity



C. Connectivity analysis of clusters showing tremor-related activity

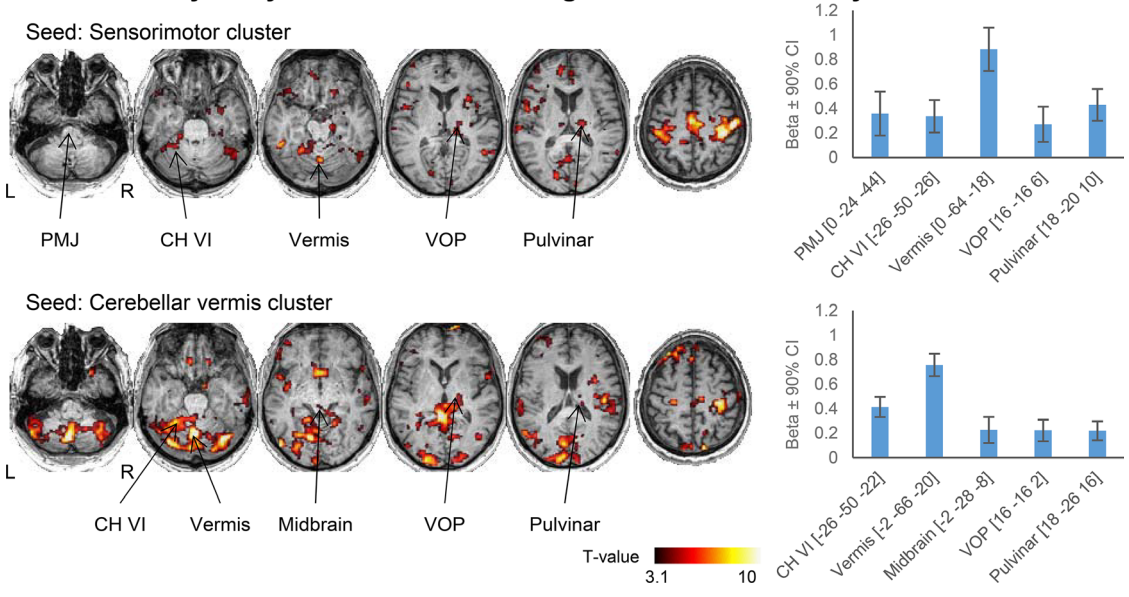


Figure 1. Holmes tremor case with tremor-related activity and connectivity profile. (A) Case description of the patient with Holmes tremor. The left panel shows the lesion location in the right midbrain, the middle panel shows severe dopamine depletion of the right striatum and the right panel shows the average power spectrum over the entire scan-session with a peak at 4.4 Hz. (B) Tremor-related activity. The top left panel shows the results of the whole brain analysis and the top right panel of the cerebellum specific analysis. Only clusters with significant tremor-related activity are displayed. The bottom panel illustrates the overlap between fluctuations in tremor power and the BOLD signal in the SMC. Note that the region of interest analysis revealed no tremor-related activity in any of the areas in the lesion connectome. (C) Results of the connectivity analyses. The top panel shows the connectivity profile with the SMC cluster as seed, the bottom panel with the cerebellar vermis cluster as seed. Only clusters with significant functional connectivity to the seed regions are displayed. The right panels show the results of the region of interest analysis. Beta and 90% confidence interval of local maxima with significant functional connectivity to the seed are shown (top panel SMC as seed, bottom panel cerebellar vermis as seed). L, left, R, Right, SN, substantia nigra, hOc4lp, posterior lateral occipital cytoarchitectonic area, PGp, caudal angular gyrus, PMJ, pontomedullary junction, CH, cerebellar hemisphere, VOP, ventralis oralis posterior thalamic nucleus.

were functionally connected to several nodes of this lesion connectome. This suggests that there might be a functional link between the tremor-related network described here and the previously described lesion connectome.[3] The patient underwent stereotactic lesioning of the right ventral intermediate nucleus (VIM), which did not reduce tremor persistently, and stereotactic lesioning of the right VOP and GPi, which significantly reduced his tremor. This observation suggests a role of the Holmes lesion connectome[3] in the pathophysiology of Holmes tremor, since the GPi and VOP are both in or close to the Holmes lesion connectome, while the VIM is not. Furthermore, both the right sensorimotor cortex and the cerebellar vermis showing tremor-related activity were significantly connected to the VOP (Fig. 1C). Stereotactic surgery of the VIM, which is highly effective in many tremor syndromes,[15] may therefore not be the first choice treatment for Holmes tremor. Taken together, we speculate that the microbleed near the right red nucleus altered GPi and VOP functioning by removing dopaminergic projections to these regions (Fig. 1A), which – together with other regions of the Holmes lesion connectome – triggered tremor amplitude-related activity in the sensorimotor cortex and cerebellar vermis through altered internetwork coupling. The observation that dopaminergic medication did not improve tremor, despite a severe presynaptic dopamine deficit, might be explained by involvement of the cerebellum. In Parkinson's tremor, dopamine-resistant patients have more tremor-related activity in the cerebellum compared to dopamine-responsive patients.[8] Likewise, involvement of the dopamine-independent cerebellum might have prevented beneficial

Table 1. Tremor-related activity

Region	*P*-value *(cluster FWE corrected)*	Cluster size *(voxels)*	T-value *(peak voxel)*	Stereotactic coordinates *(MNI)*		
				x	*y*	*z*
Whole brain analysis						
Sensorimotor cortex	<0.001	243	6.92	48	−24	58
			3.85	42	−20	54
			3.82	34	−26	66
PGp	0.003	129	4.42	−42	−68	34
Precuneus	0.023	91	4.16	2	−62	34
			3.28	4	−54	32
hOc4lp	0.002	145	4.14	−30	−92	0
			3.40	−36	−84	6
Cerebellum specific analysis						
Vermis VIIIa/b	0.016	559	4.06	−1	−66	−39
			3.38	−1	−58	−35
Crus I	0.048	404	4.42	28	−78	−29
			3.20	20	−85	−34
	0.042	421	4.04	38	−79	−38
	0.015	570	4.10	45	−61	−38
			3.23	44	−67	−31
Crus II*	<0.001	1273	4.42	42	−52	−44
			4.32	34	−54	−40
			3.94	25	−52	−47

PGp, caudal angular gyrus, hOc4lp, posterior lateral occipital cytoarchitectonic area.
*A small part of this cluster extended to HVIIIa/b, as displayed in Figure 1.

effects of dopaminergic medication in this Holmes tremor case.

A major limitation of our findings is that they are based on a single patient. This disadvantage should be weighed against the fact that Holmes tremor is extremely rare, which is the reason that fMRI studies in these patients are missing. Furthermore, we cannot distinguish afferent and efferent tremor-related activity, due to the correlational nature of fMRI. However, the interplay between afferents and efferents may be a key pathophysiological component of tremor. In Parkinson's disease for example, somatosensory afferents are thought to stabilize the tremor rhythm within the cerebello-thalamo-cortical circuit, likely through the ascending fibres to the cerebellum.[8] We therefore argue that identifying the cerebral network involved in tremor as a whole is valuable.

The concept of a lesion connectome has been applied across a wide range of neuro-psychiatric disorders,[16] including delusions in Alzheimer's disease.[17] Neuroimaging studies on delusions in Alzheimer's disease yielded heterogeneous symptom-related networks. These networks did not overlap with the lesion connectome, which includes brain areas that are functionally connected to all lesions causing delusions. However, Darby and colleagues showed that all individual symptom-related networks were functionally coupled to a common network. This common network did match the lesion connectome of delusions. In a similar vein, we hypothesize that Holmes tremor may involve three different pathophysiological elements: a structural lesion, an intermediate lesion connectome, and a tremor amplitude-related network. This hypothesis needs to be confirmed by prospective studies. Taken together, we propose that symptom-mapping and lesion network mapping are complementary approaches that can identify functionally connected networks involved in neurological symptoms.

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Author Contributions

FN and RH designed the study and performed data acquisition, data analysis and drafting of the manuscript and figures. RdB, PP, and PvdM contributed to drafting of the manuscript and figures.

Conflicts of Interest

The authors have no conflicts of interest to report.

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Supporting Information

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

Supplementary video S1. Patient with Holmes tremor. Video of a clinical examination of the Holmes tremor patient described in this case report. This video was taken before any stereotactic lesioning.

