Pretherapeutic Functional Imaging Allows Prediction of Head Tremor Arrest After Thalamotomy for Essential Tremor: The Role of Altered Interconnectivity Between Thalamolimbic and Supplementary Motor Circuits

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OBJECTIVE: **To correlate pretherapeutic resting-state functional magnetic resonance imaging (rs-fMRI) measures with pretherapeutic head tremor presence and/or further improvement 1 year after stereotactic radiosurgical thalamotomy (SRS-T) for essential tremor (ET).**

METHODS: **We prospectively collected head tremor scores (range, 0–3) and rs-fMRI data for a cohort of 17 consecutive ET patients in pretherapeutic and 1 year after SRS-T states. We additionally acquired rs-fMRI data for a healthy control (HC) group (n = 12). Group-level independent component analysis (n = 17 for pretherapeutic rs-fMRI) was applied to decompose neuroimaging data into 20 large-scale brain networks using a standard approach. Through spatial regression, we projected 1 year after SRS-T and HC rs-fMRI time points, on the same 20 brain networks.**

RESULTS: **Pretherapeutic interconnectivity (IC) strength between the network including bilateral thalamus and limbic system with left supplementary motor area predicted head tremor improvement at 1 year after SRS-T (family-wise corrected $P < 0.001$, cluster size $K_c = 146$). For the statistically significant cluster, IC strength was strongest in HCs (mean, 4.6; median, 3.8) compared with pre- (mean, 0.1; median, 0.2) or posttherapeutic (mean, −0.2; median, 0.09) states.**

CONCLUSIONS: **Baseline measures of IC between bilateral thalamus and limbic system with left supplementary motor area may predict head tremor arrest after thalamotomy. However, procedures such as SRS-T, for this particular clinical feature, do not align patients to HCs in terms of functional brain connectivity. We postulate that supplementary motor area is modulating head tremor appearance, by abnormal connectivity with the thalamolimbic system.**

INTRODUCTION

Essential tremor (ET) is one of the common movement disorders.[1] A major clinical feature is arm tremor.[2] However, additional head tremor may occur with a frequency as high as 60.6% in selected samples, such as brain

Key words
- Essential tremor
- fMRI
- Head tremor
- Resting state
- Stereotactic radiosurgery
- Thalamotomy
- Ventrointermediate nucleus

Abbreviations and Acronyms
BOLD: Blood-oxygen-level dependent
DBS: Deep brain stimulation
ET: Essential tremor
HC: Healthy control
HIFU: High focused ultrasound
IC: Interconnectivity
MRI: Magnetic resonance imaging
rs-fMRI: Resting-state functional magnetic resonance imaging
SMA: Supplementary motor area
SRS-T: Stereotactic radiosurgical thalamotomy
Vim: Ventrointermediate nucleus

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repositories.[3] Although many studies attempted to understand the pathophysiology of tremor in general and ET in particular,[4-6] its underlying mechanisms remain largely unknown. In the same sense, head tremor intimate mechanisms of appearance remain also unrevealed. Typically, it is considered to follow hand tremor, while considering a somatotopic spread of the involved parts of the body.[7] Head tremor is related to several already supported features: older age and older age of onset of ET, female sex, and associated voice tremor.[8] Regarding directionality, 3 types are usually described: yes-yes, no-no, and round and round.[9] Very few reports have focused on the investigation of head tremor in ET.

It has been previously advocated that in the context of ET, thalamic neurons display firing patterns correlated with tremor, predominantly in the cerebellar input-receiving area (mainly from the dentate nucleus) and further in the contralateral red nucleus, thalamic ventrointermediate nucleus (Vim), and precentral gyrus.[10] The thalamic nuclei, particularly the Vim, were found to be involved in the tremor network, as a relay between the dentate nucleus and the primary motor cortex.[11] Also, the definition of the Vim as an electrophysiologic concept,[12] with successful targeting in functional neurosurgery for movement disorders,[13] has confirmed the role of this key structure within the network.

Primary treatment for ET is pharmacologic (e.g., β-blockers [mainly propranolol], primidone), but effectiveness remains insufficient. Drug-resistant ET can benefit from standard functional neurosurgery procedures. Historically, radiofrequency thermocoagulation was initially used.[14] Then deep brain stimulation (DBS) became a standard of care after the pioneering series of Benabid et al.[15] Radiosurgery, aiming at the same target (e.g., Vim), has been considered a minimally invasive, safe, and effective alternative for tremor alleviation.[16,17] More recently, high focused ultrasound (HIFU)[18] as an alternative to radiofrequency thermocoagulation has also showed promising results. HIFU generates a controlled thermocoagulation, with an immediate radiologic and clinical effect.[19] The mechanisms by which tremor stops after HIFU or stereotactic radiosurgical thalamotomy (SRS-T) remains largely undiscovered.

Resting-state functional magnetic resonance imaging (rs-fMRI) assesses interregional functional connectivity based on physiologic connection that changes on a moment-by-moment basis, rather than anatomic connectivity.[20] This is based on the fact that the brain continues to be functionally and metabolically active even at rest: that is, in the absence of any task performance or stimulation.[21] Spontaneous fluctuations in the blood-oxygen-level dependent (BOLD) signal have been documented and investigated, with the reliable feature that regions with related functions, such as the left and the right sensorimotor cortices, display coherent BOLD fluctuations, even in the absence of movement under resting conditions, which has been reported as early as in the seminal study of Biswal et al.[22] Evaluation of such connectivity offers an alternate approach for studying intrinsic network interactions of the human brain. This approach has led to important new insights in many diseases, including in ET,[23-26] because of the minimal patient compliance and the possibility to obtain rich information in a noninvasive manner.[27] Numerous methods to extract functional connectivity or interconnectivity (IC)—if within a functional network—have been suggested to measure temporal dependencies of neuronal activation between anatomically separated brain regions. Recent work in systems neuroscience has characterized several major brain networks that are identifiable in resting brain state.[28] Many clinical applications could benefit from imaging-based drive from obtaining diagnostic biomarkers of a disease, identifying disease heterogeneity or the effect of treatment in longitudinal analysis.[29]

In the present study, head tremor presence has been evaluated before thalamotomy, but its drop in points 1 year after the intervention was also assessed. Here, we conjecture that measures of network integration from pretherapeutic rs-fMRI are informative to indicate head tremor arrest 1 year after SRS-T. Our hypothesis was that parts of the so-called tremor network[10] would eventually present an altered baseline IC with other sensorial systems, including visual. Our method is not specifically designed to test or support existing physiopathologic theories; therefore, these findings might shed new light on the implication of networks and their alterations on head tremor generation and disappearance.

METHODS

Patients

We prospectively included 17 consecutive patients (right-sided tremor, drug-resistant, fulfilling criteria, subsequently discussed) treated only with left unilateral SRS-T in Marseille, France, between September 2014 and August 2015. Ethical Committee of the Marseille (CHU Timone) University Hospital (CPPRB1) approved our study. Written informed consent was obtained from all patients. All cases were referred by a movement disorders neurologist (T. W.).

Only patients meeting the following inclusion criteria were analyzed: confirmed ET diagnosis, able to give formal approval, drug resistance after adequate trials, age between 18 and 80 years, and targeted thalamic area apparent on pretherapeutic magnetic resonance imaging (MRI). Patients with mixed or Parkinsonian tremor were excluded, as were those with previous contralateral SRS-T, epilepsy, brain tumors, or stroke, susceptible to alter functional connectivity from other causes than primary disease (e.g., ET). The main indications for SRS-T other than stereotactic DBS or thalamotomy were medical comorbidities, advanced age, or patient refusal of DBS.

Patients meeting inclusion criteria were enrolled and participated in screening visits, including at baseline (n = 17) and 1 year (n = 17) after SRS-T tremor (by T.W.); they underwent neuroimaging assessment, with structural MRI and additional rs-fMRI (3-T [Siemens, Munich, Germany]; for rs-fMRI, no sedation was used and participants were asked to relax with their eyes closed, without falling asleep or engaging in cognitive or motor tasks); the same neuroimaging protocol was used for healthy controls (HCs) (n = 12).

For ET patients, the mean age was 70.1 years (range, 49–82). The mean duration of symptoms was 38 years (range, 6–70) (**Table 1**). The mean time to tremor improvement was 3.32 ± 2.7 months (range, 0.2–10 months).

Table 1. Demographic Data

Variable	Mean ± SD	Minimum	Maximum
Duration of symptoms (years)	38 ± 19.5	6	70
Age (years)	70.1 ± 9.8	49	82
Head tremor score (baseline)	0.9 ± 0.8	0	3
Head tremor score (improvement, drop in points)	−0.4 ± 1	−2	1
ADL (baseline)	29.1 ± 12	13	49
ADL (% improvement 1 year after SRS-T)	82.9 ± 27.3	0	100
TSTH (baseline)	18.6 ± 5.5	8	30
TSTH (% improvement 1 year after SRS-T)	67.3 ± 28.2	13.3	100
Time to improvement after SRS-T (months)	3.3 ± 2.7	0.5	10

ADL, activities of daily living; TSTH, tremor score on the treated hand; SRS-T, stereotactic radiosurgical thalamotomy.

For the HC group, the mean age was 69.3 years (range, 59–83 years; $P > 0.05$, 2-sample t test with the ET patient's age).

Clinical Evaluation and Outcome Measures After SRS-T

Clinical evaluation was made using validated and well-established outcome measures. Head tremor score (n = 17; range, 0–3) was evaluated using the Tremor Research Group Essential Tremor Rating Assessment (range, 0–3). The mean baseline head tremor score (n = 17; range, 0–3) was 0.8 (range, 0–3), and at 1 year after SRS-T the mean drop in points was −0.4 (−2 to 1; n = 11; for those with pretherapeutic head tremor score ≥1); the mean age was 72.9 years (range, 59–79), the mean duration of symptoms was 43.6 years (range, 6–70), and there was a clear female dominance (female/male ratio, 9:2).

Tremor severity was assessed using the questionnaire designed by Bain et al.[30] (e.g., activities of daily living),[30] the tremor score on the treated hand (e.g., right), the Fahn-Tolosa-Marin tremor rating scale,[31] and the head tremor score (Table 1).

Cognitive Assessment

The mean pretherapeutic Mattis Dementia Rating Scale[32] score was 135.9, and posttherapeutic it was 135.5 ($P > 0.05$).

SRS-T Procedure

All SRS-T procedures were performed by the same neurosurgeon (J.R.). After application of Leksell Coordinate Frame G (Elekta AB, Stockholm, Sweden), all patients underwent stereotactic MRI. Indirect targeting was performed using standard methodology by Guiot's diagram,[12] placed 2.5 mm above the anterior commisure-posterior commisure line and 11 mm lateral to the wall of the third ventricle. A single 4-mm isocenter and a maximal prescription dose of 130 Gy were used.

rs-fMRI Data Acquisition, Preprocessing, and Motion Scrubbing

Imaging was done on head-only 3-T MRI scanner (32-channel receive-only phased-array head coil [Siemens, Munich, Germany]) with T1-weighted without (pretherapeutic) and with gadolinium contrast and rs-fMRI images. The following parameters were used: for T1-weighted, repetition time/echo time = 2300/2.98 milliseconds, isotropic voxel of 1 mm^3, and 160 slices; for T2*-weighted fast echo planar imaging (BOLD contrast), repetition time/echo time = 3.3 seconds/30 milliseconds/90°, voxel size of 4 × 4 × 4 mm^3, 300 volumes acquired per subject, and 46 interleaved axial slices. The rs-fMRI experiments, acquired with no explicit task, consisted of a 10-minute run in which participants were asked to relax with their eyes opened, without falling asleep or engaging in cognitive or motor tasks. In addition, a field map was acquired to correct for the effect of field inhomogeneity.

Processing of fMRI data were performed using standard software suites (SPM12 [London, United Kingdom]; www.fil.ion.ucl.ac.uk/spm). We computed the Power framewise displacement index for each rs-fMRI time point[33] and excluded those exceeding 0.5 mm as upper limit movement. Only the remaining frames were further considered for analysis.

rs-fMRI Network Extraction

Group-level independent component analysis (n = 17 for the baseline rs-fMRI) was applied to decompose the fMRI data into networks of temporally coherent spontaneous activity using the GIFT Toolbox (Medical Image Analysis Lab, University of New Mexico, Albuquerque, New Mexico, USA).[34] The concat–independent component analysis approach is data-driven and considers the concatenated data of the pretherapeutic 17 scans.[35]

The total number of independent components was set to 20, which is the common setting in literature to identify large-scale distributed networks (Figures 1 and 2 display networks [or components as they are also named] generated by our own data).

The 20 large-scale brain networks were generated using pretherapeutic rs-fMRI data. Furthermore, through spatial regression, we projected 1 year after SRS-T and HC rs-fMRI time points, on the same identified 20 brain networks, as displayed in Figures 1 and 2.

rs-fMRI Statistical Analysis

Imaging data were analyzed in Lausanne, Switzerland, mainly by 2 persons not involved in patient selection, treatment, or posttherapeutic evaluation (C.T. and D.V.D.V.).

For rs-fMRI data, analysis of variance was implemented in SPM12 as a flexible factorial model, on each component, by using individual subject-level maps.

For all 17 cases, a first general linear model tested the correlation between baseline pretherapeutic head tremor (range, 0–3) and brain IC within the particular networks (20 large-scale networks, as previously described in Figures 1 and 2). Eleven cases with head tremor (range, 1–3) were subsequently included in a second model to test any eventual alleviation 1 year after SRS-T.

We then report corrected P values using conventional cluster-level family-wise error correction.

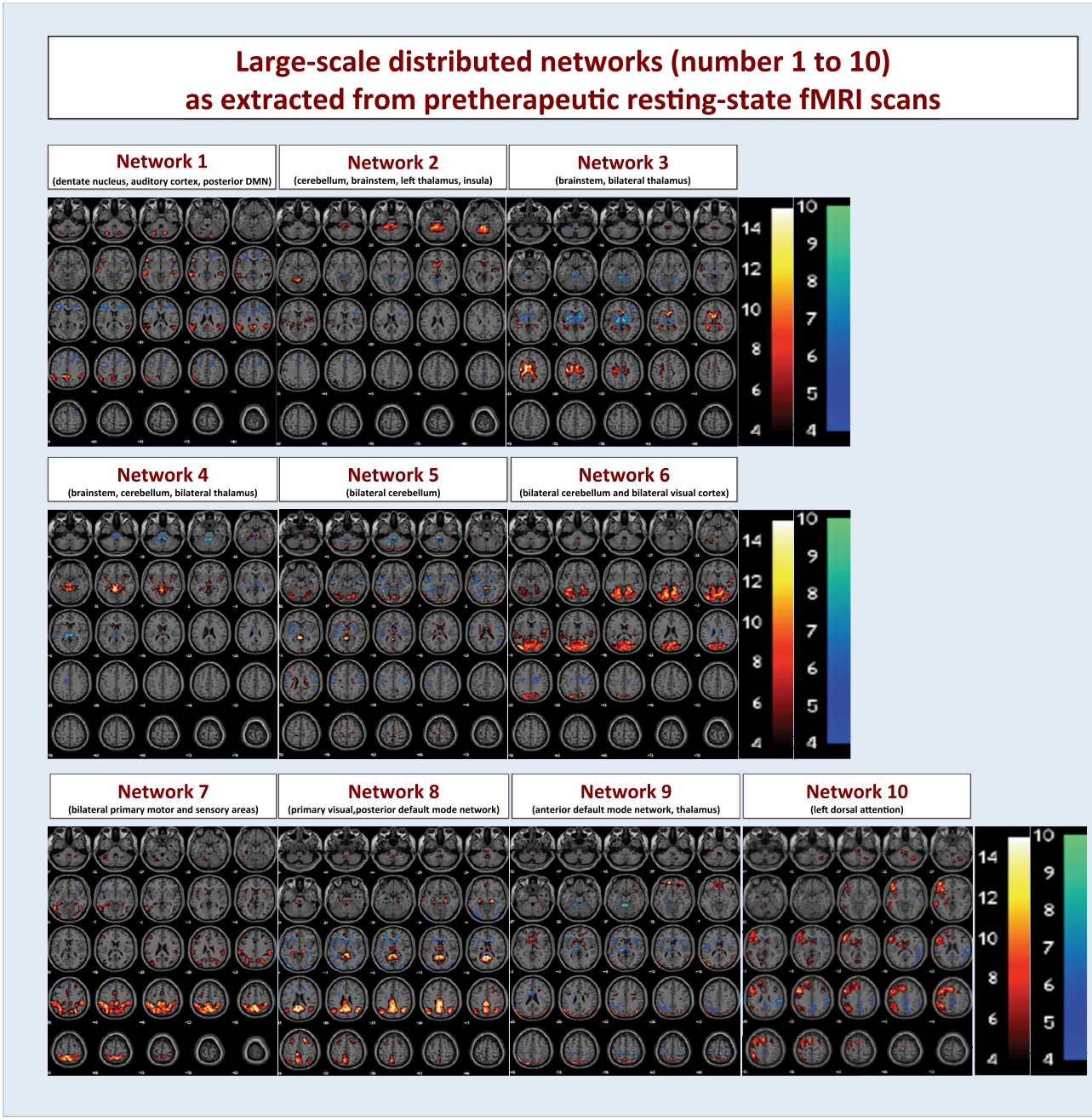

Figure 1. Identification of a set of 20 networks spanning the whole brain (using an established independent component analysis pipeline and defined including the baseline scans of all subjects). Networks 1—10 are illustrated: 1) dentate nucleus, auditory cortex, posterior default mode network (DMN); 2) cerebellum, brainstem, left thalamus, insula; 3) brainstem, bilateral thalamus; 4) brainstem, cerebellum, bilateral thalamus; 5) bilateral cerebellum; 6) bilateral cerebellum, bilateral visual cortex midcingulate; 7) bilateral primary motor, sensory areas and midcingulate; 8) primary visual, posterior DMN; 9) anterior DMN, thalamus; and 10) left dorsal attention. fMRI, functional magnetic resonance imaging. Adapted from Tuleasca et al. Pretherapeutic functional neuroimaging predicts tremor arrest after thalamotomy. *Acta Neurol Scand* 2018. https://doi.org/10.1111/ane.12891. [Epub ahead of print].

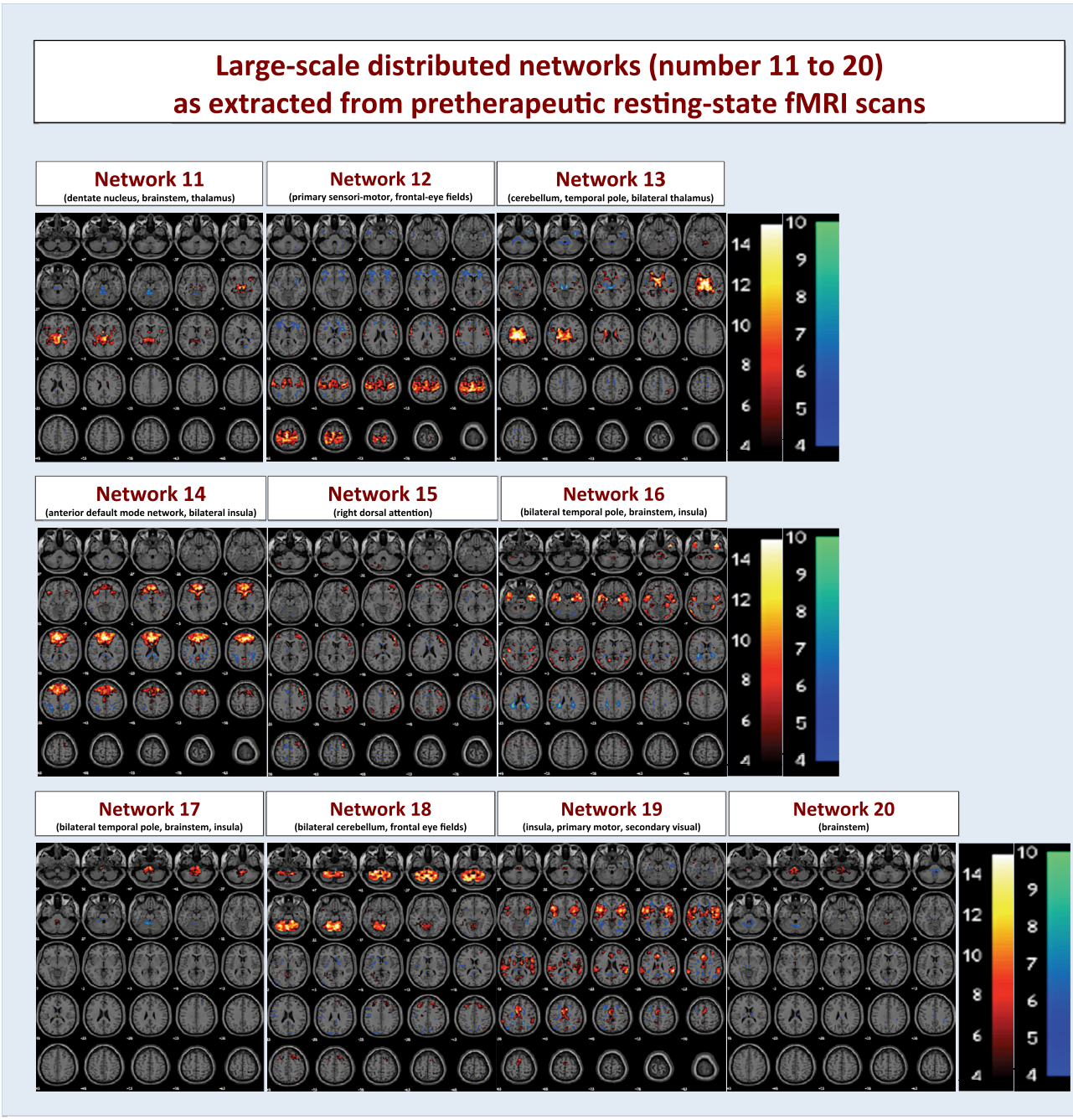

Figure 2. Identification of a set of 20 networks spanning the whole brain (using an established independent component analysis pipeline and defined including the baseline scans of all subjects). Networks 11–20 are illustrated: 11) dentate nucleus, brainstem, thalamus; 12) primary sensorimotor, frontal eye fields; 13) bilateral thalamus and parts of the system; 14) anterior default mode network, bilateral insula; 15) right dorsal attention; 16) bilateral temporal pole, brainstem, insula; 17) bilateral temporal pole, brainstem, insula; 18) bilateral cerebellum, frontal eye fields; 19) insula, primary motor, secondary visual; and 20) brainstem. fMRI, functional magnetic resonance imaging. Adapted from Tuleasca et al. Pretherapeutic functional neuroimaging predicts tremor arrest after thalamotomy. *Acta Neurol Scand* 2018. https://doi.org/10.1111/ane.12891. [Epub ahead of print].

For correlation between IC values and previously detailed tremor scores, Stata version 11 (StataCorp LLC, College Station, Texas, USA) was used.

Radiologic Characteristics: MRI Signature Volume 1 year After SRS-T

The mean thalamotomy MRI signature volume after SRS-T was 0.125 ± 0.162 mL (range, 0.002–0.600 mL). The MRI signature volume was drawn on the T1 (gadolinium-injected) MRI, 1 year after SRS-T, which is considered the definitive radiologic answer in our experience. To ensure the accuracy of this volume calculation, each patient's MRI at 1-year follow-up was imported into Leksell GammaPlan software (Elekta AB) and coregistered with the therapeutic images. Manually, using the segmentation tools, the draw was made for the individual cases. The volume module inside the station was used to extract the values.

RESULTS

Pretherapeutic Functional Neuroimaging and Baseline Head Tremor

None of the networks showed significant IC for presence of pretherapeutic head tremor (n = 17).

Pretherapeutic Functional Neuroimaging and Head Tremor Improvement 1 Year After SRS-T

In patients with head tremor (n = 11), the network that included the bilateral thalamus and limbic system (i.e., network 13) (Figure 3, 3.1.) was the only one that related in a statistically significant way (family-wise error–corrected $P < 0.0001$; cluster size $K_c = 146$) to head tremor arrest 1 year after SRS-T.

In particular, the IC was altered between network 13 and the left supplementary motor area (SMA) (Figure 3, 3.2., with the SMA cluster in axial, coronal, and sagittal planes; 3.2, lower part, scatter plot, with the confidence interval). In HCs, IC in this

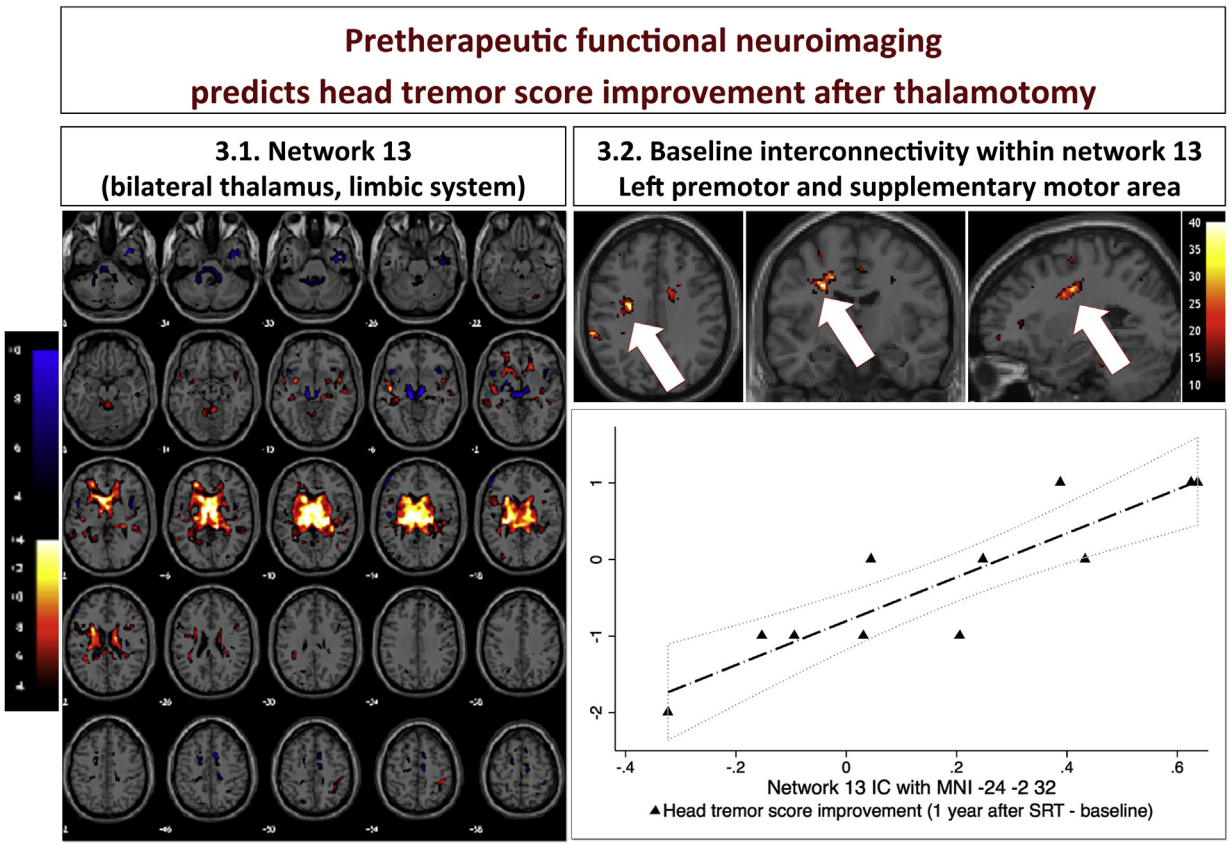

Figure 3. In 3.1., pretherapeutic functional neuroimaging predicts head tremor score improvement after thalamotomy: illustration in axial plane of the statistically significant main network 13, with bilateral thalamus and parts of the limbic system. In 3.2., upper part, the relevant cluster, left supplementary motor area (*arrows* pointing toward the left SMA in axial, coronal and sagittal plane, respectively), interconnected with network 13, cluster displayed in axial (left), coronal (middle) and sagittal (right) planes; lower part, the scatter plots, with confidence interval, showing the IC values correlated with head tremor score improvement. IC, interconnectivity; MNI, Montreal Neurological Institute; SRS-T, stereotactic radiosurgical thalamotomy.

Longitudinal study of interconnectivity changes after thalamotomy within network 13

4.1. Healthy controls (n=12)	4.2. Essential tremor, with head tremor, *before* thalamotomy (n=11)	4.3. Essential tremor, with head tremor, *after* thalamotomy (n=11)
mean 4.6 median 3.8 std dev 3.8 range 0.09-11.3	mean 0.1 median 0.2 std dev 0.3 range -0.3->0.6	mean -0.2 median 0.09 std dev 2.9 range -6->6

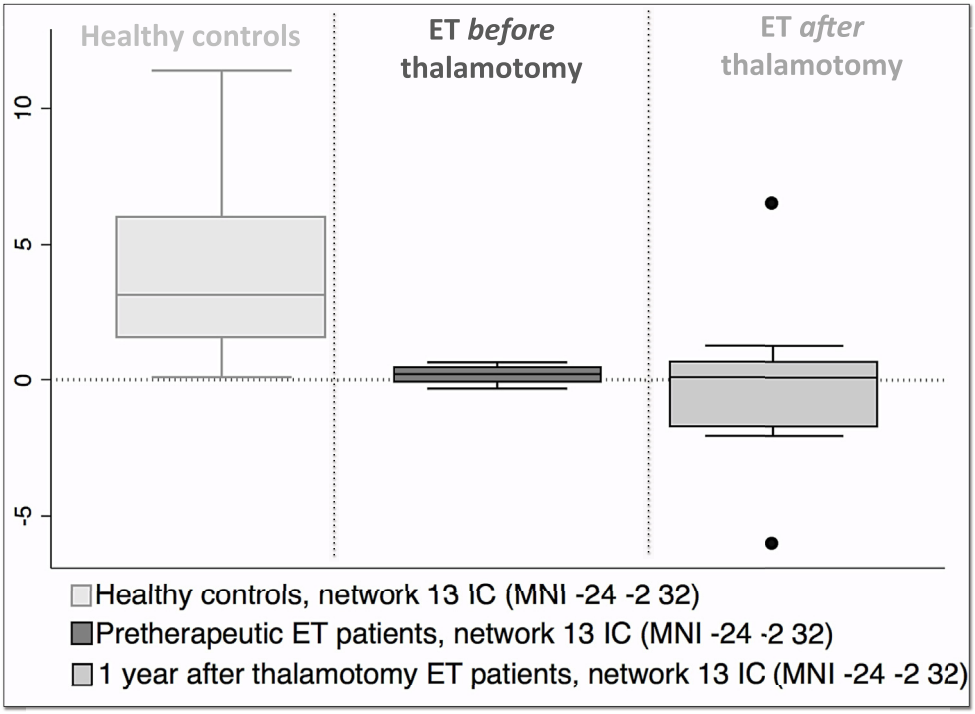

Figure 4. Longitudinal study of IC changes after thalamotomy within network 13; the mean, median, minimum, and maximum values and the corresponding boxplots (and their median values) are displayed for healthy controls (4.1.), pretherapeutic state (4.2.), and postherapeutic state (4.3.). ET, essential tremor; SD, standard deviation; IC, interconnectivity strength; MNI, Montreal Neurological Institute.

cluster of the network was strongly positive (Figure 4, 4.1.) (mean, 4.6; median, 3.8), it dropped in the pretherapeutic stage (Figure 4, 4.2.) (mean, 0.1; median, 0.2), and even became negative in the posttherapeutic stage (Figure 4, 4.3.) (mean, −0.2; median, 0.1); for further details please see Figure 4 (with the respective boxplots and mean, median, and minimum and maximum values). Patients with largest difference in IC with respect to HCs did have the largest benefit in head tremor improvement from the thalamotomy; however, their IC at follow-up changed the least.

The mean time to tremor improvement was 3.32 ± 2.7 months (median, 3; range, 0.5–10). There was no correlation between head tremor improvement and 1-year MRI signature volume (Spearman correlation coefficient = 0.57).

Assessment of Potential Confounders

The mean MRI signature volume 1 year after SRS-T did not show a statistically significant relationship with IC values within the relevant cluster ($P > 0.05$). Furthermore, it did not relate to head tremor arrest ($P > 0.05$).

The IC values within network 13 did not correlate with age or duration of symptoms ($P > 0.05$).

The upper limb tremor score improvements are presented in Table 1. Their correlations with the functional neuroimaging are beyond the purpose of this report.

DISCUSSION

In this study, we focus on the correlation between pretherapeutic functional rs-fMRI with baseline head tremor presence and/or further improvement 1 year after SRS-T. We used a standard data-driven approach, implying no a priori hypothesis, by generating 20 large-scale brain networks on pretherapeutic neuroimaging. We hypothesized that head tremor presence and/or improvement after SRS-T would be related to an altered IC between the tremor network and other sensorial systems. Of note, none of these networks showed significant IC for presence of pretherapeutic head tremor (n = 17). We further projected the 1-year SRS-T rs-fMRI time points on the same, previously generated, 20 large-scale brain networks. In patients with pretherapeutic head tremor (range, 1–3; n = 11), the network that included the bilateral thalamus and limbic system with left SMA was the only one that related in a statistically significant way to head tremor arrest after SRS-T. In HCs, IC in this cluster of the network was strongly positive, it dropped in the pretherapeutic stage, and even became negative in the posttherapeutic stage (mean, −0.2; median, 0.1). Patients with largest difference in IC with respect to HCs did have the largest benefit in head tremor improvement from the thalamotomy; however, their IC at follow-up changed the least.

The SMA is known as a cortical part that contributes to movement control,[36] including by neurons that directly project to the spinal cord. Four main functions of the SMA have been proposed: 1) coordination of temporal sequences of actions, 2) control of postural stability during stance or walking, 3) bimanual coordination, and 4) initiation of internally generated (as opposed to stimulus driven) movement. An important aspect is related to positional movement of head and eyes, by a relatively anterior part. The SMA is interconnected with numerous structures, by both efferent (including multiple basal ganglia structures: putamen, caudate, ventrolateral and ventral anterior thalamus [targeted in our patients]) and afferent (basal ganglia [ventral lateral and anterior thalamus], insula, midbrain, etc.) connections. Parts of the former are nicely revealed within network 13 of the present report, as part of the limbic system.

The cluster reported in this study somatotopically corresponds to the region of the SMA involved in head rotation, just superior to the one related to the contralateral eye movement fields. This is anatomically relevant in the context of a head tremor evaluation. We additionally postulate that head rotation area within the SMA, interconnected with the regions belonging to network 13, previously underlined, might be involved as a pacemaker generator in head tremor genesis.

We have revealed, for the first time, to our knowledge, a correlation between functional neuroimaging and head tremor arrest after SRS-T and thalamotomy in general. Baseline measures of IC between the bilateral thalamus and limbic system with the left SMA may predict head tremor arrest after thalamotomy. However, related to this particular symptom and the statistically significant network, SRS-T did not significantly normalize the abnormal connectivity after intervention. We postulate that the SMA is modulating head tremor appearance by altered IC with the thalamolimbic system in ET. Head tremor drop after SRS-T is related to more abnormal functional pretherapeutic profile compared with HCs. This abnormal profile does not seem to functionally respond to lesioning procedures, such as SRS-T, in this small cohort of patients. The exact reasons for this resistance remain to be established by further studies, but several hypotheses could explain our findings. Firstly, it is well known that similarities between the SMA and basal ganglia lesioning suggest their intimate relationship, by their structural cortico-basal ganglia loops in diseased patients. In Parkinson disease, at the cortical level, decreased activity of the SMA has been well recognized[37] and can be improved by DBS of the subthalamic nucleus.[38] In fact, animal studies done in 1888 by Horseley and Schafer[39] have already advocated that direct SMA stimulation in monkeys elicits movements that would appear in trunk, proximal upper extremity, and head. Secondly, the SMA is even more active than the primary motor cortex in certain demanding motor tasks. In head tremor, because of a more difficult visuomotor coordination, some of these motor tasks would become even more challenging than in healthy subjects. Moreover, movements evoked in the SMA are much more complex than those in the primary motor cortex. Thirdly, functional studies[40] have additionally determined that the SMA was strongly activated during reaching to different visual targets, comparable with the one of the motor cortex. We conclude that the SMA is involved in visually guided movements, of interest in ET context.

Few studies have specifically addressed treatment of head and voice tremor.[41] It has been previously stated that pharmacologic management of essential head and voice tremor is less efficient than the pharmacologic management of hand tremor.[42] Usually, propranolol and primidone, used alone or in combination, have been recommended for essential head tremor, but there is insufficient evidence in the current literature.[41] Botulinum toxin injections produce good relief in head tremor in the context of ET.[43] DBS is also effective, but bilateral Vim stimulation is frequently needed for severe head tremor.[44,45] In conclusion, there is a certain resistance of head tremor to the conventional pharmacologic agents, in the sense of a clinical response, which is less evident compared with that of hand tremor, with a need—in case of surgery—for bilateral stimulation to obtain better alleviation. It might also be possible that procedures such as SRS-T, because of a particular altered functional connectivity profile, cannot significantly normalize this abnormal profile after the intervention.

The current report analyses rs-fMRI data, which comes with the advantage of non-invasiveness and minimal patient compliance, to study both the radiobiology of SRS-T for tremor, and the pathophysiology of ET in general. Past reported histologic evidence of SRS-T has been essentially limited to very few studies, of whom one is the historical series of Gamma Knife thalamotomy performed by Leksell, in other indication (intractable pain) and further reported by Steiner et al.[46] The second histologic report by Kondziolka et al.[47] evaluated the effect of a 100-Gy irradiation dose in baboon, and suggested that radiosurgery of this dose (e.g., lower than in current clinical practice in SRS-T) generates focal necrosis and axonal degeneration of the thalamus (6 months after the procedure). We do think that neuroimaging in general and rs-fMRI in particular, with its recent advances, could provide new insights, with the use of powerful analytical tools, to better understand the radiobiology of SRS-T. Besides functional imaging, additional analysis of routine structural imaging (e.g., the T1-weighted MRI sequence) could be of great benefit. We have recently published 2 different reports evaluating pretherapeutic and/or longitudinal changes in gray matter density, using voxel-based morphometry,[48] as related to the final clinical effect 1 year after SRS-T.[49,50]

This study has several potential limitations. The first limitation is the small number of subjects. The second limitation, related to study design, is the use of rs-fMRI analysis, which might not be directly related to motor performance; however, we aimed to study brain network changes in the absence of any task (see the Introduction section). A third limitation is that the neurologic evaluation was not blinded (performed by the same neurologist, T.W., both in pre- and postherapeutic states). The fourth is that at the specific time when SRS-T induces these changes within the brain networks remains unknown; we have decided to perform rs-fMRI analysis after a period of 1 year after SRS-T because this is the final clinical and radiologic effect in our previously published experience.[51] The fifth limitation is the lack of data on longitudinal changes (at baseline and 1 year) in the HC group; however, current studies have sustained the reproducibility of functional networks across numerous sessions, including 1 year apart.[52]

CONCLUSIONS

The SMA plays a leading role in normal and abnormal motor system homeostasis, including of the head. Furthermore, altered IC strength between the left SMA with the bilateral thalamus and limbic system is correlated with head tremor arrest after thalamotomy. Why a more altered connectivity state compared with HCs is related to better improvement after the intervention remains to be elucidated by further studies. We currently are continuing our research protocol, aiming to provide a better understanding of the radiobiology of SRS-T for tremor and ET in general.

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