Clinical outcomes after MRI connectivity-guided radiofrequency thalamotomy for tremor

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Word Counts Abstract: ~~200~~200

Figure: 4, Table: 1, Video: 0

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Key words

- Tremor
- Essential Tremor
- Parkinson's disease
- Connectivity-guided Stereotactic Neurosurgery
- Radiofrequency Thalamotomy

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Abstract

Objective: Radiofrequency-thalamotomy is an established treatment for refractory tremor. ~~Contemporary published data mainly report on MR-guided focused ultrasound thalamotomy outcomes~~It is unclear whether connectivity-guided targeting strategies could further augment outcomes. Our aim was to evaluate the efficacy and safety of MRI connectivity-guided radiofrequency-thalamotomy in severe tremor.

Methods: Twenty-one consecutive patients (14 essential tremor, 7 Parkinson's disease) with severe tremor underwent unilateral radiofrequency thalamotomy at a single institute between 2017 and 2020. Connectivity-derived thalamic segmentation was used to guide targeting. Changes in the Fahn-Tolosa-Marin rating scale (FTMRS) were recorded in treated and non-treated hands as well as procedure related side-effects.

Results: Twenty-three thalamotomies were performed (with two patients receiving a repeated intervention). The mean postoperative assessment timepoint was 14.1 months. Treated-hand tremor scores improved by 63.8% whereas non-treated hand scores deteriorated by 10.1% ($p<0.01$). Total FTMRS scores was significantly better at follow-up compared to baseline (34.7 vs 51.7; $p=0.016$). Baseline treated hand tremor severity (rho=0.786; $p<0.01$) and total FTMRS score (rho=0.786; $p<0.01$) best correlated with tremor improvement**.** The most reported side effect was mild gait ataxia (11 patients) which correlated with the percentage of thalamus lesioned (rho = 0.55, $p=0.029$)

Conclusion: Radiofrequency-thalamotomy guided by connectivity-derived segmentation is a safe and efficacious option for severe tremor in both PD and essential tremor.

Introduction

Tremor is a debilitating clinical manifestation of a range of conditions, including Parkinson's disease (PD) and essential tremor (ET)[1]. In medically refractory cases, surgery could be considered. Radiofrequency Thalamotomy (RF-T) of the ventrolateral motor thalamus has been widely carried out for this patient group[2,3]. Anecdotal evidence suggests good tolerability and acceptable outcomes though contemporary objective data is lacking[4]. It is also unclear if recent advances in imaging strategies used to refine ventral intermedius (Vim) nucleus targeting, such as connectivity-derived thalamic segmentation, could further augment outcomes[5]. This study explores the outcomes of complementing conventional targeting for RF-T with MRI connectivity targeting guidance in a cohort suffering from severe tremor, the hypothesis being that this approach would be safe whilst providing durable tremor amelioration.

Material and Methods

Patients

21 consecutive patients (14 males, 7 females, mean age: 66.8, Standard Deviation (SD):6.5) treated with unilateral MRI-guided RF-T for severe tremor related to PD (7 patients) or ET (14 patients) between January 2017 and February 2020 at the National Hospital for Neurology and Neurosurgery were enrolled. ET was defined according to the latest consensus for tremor classification[1,6] and PD according to the UK brain bank criteria[7]. Patients were eligible for surgery if their postural or intention tremor score was severe (score ≥2 on the Fahn-Tolosa-Marin rating scale (FTMRS)) and disabling (score of ≥2 on any item in the disability subsection of the FTMRS). This work was registered as a University College London Hospital audit (Registration number: 83-202021-TW-Thalamotomy) and assessments performed as part of standard care.

Surgical procedure

All patients underwent unilateral surgery. The thalamic region connected to the ipsilateral primary motor cortex (i.e. the ventrolateral thalamus), the thalamic region connected to the contralateral dentate nucleus (i.e. the Vim) and the region connected to the ipsilateral primary sensory cortex (i.e. the ventroposterior thalamus) were localized on preoperative 3T MRI using high-angular resolution diffusion imaging (HARDI) and probabilistic tractography, generally done the day before surgery as previously described (~~Supplementary~~ see reference for detals of image acquisition and processing)[5]. Surgery was performed under local anaesthesia using a stereotactic MRI-guided and verified approach. A Leksell frame (model G, Elekta Instrument AB, Stockholm, Sweden) was mounted on the

head and stereotactic pre-implantation MRI scans (T2, Proton Density, and T1-3D MPRAGE) were acquired and co-registered with the preoperative connectivity segmentation maps to localize the target. Two targets were then planned, one conventional atlas-based target using anterior commissure-posterior commissure (AC-PC) coordinates and a second target using connectivity. For both plans, depth was set at Z=0 (AC-PC level). The atlas coordinates were defined as: X = 12–14 mm; Y = (AC-PC length/3) − 2 mm anterior to PC, at Z = 0. As the connectivity target is influenced by thresholding value, as well as other limitations inherent to the technique[8] the final target was selected to encompass as much of the connectivity defined Vim as possible without encroaching on the sensory thalamus but also informed by the atlas target. In other words, the connectivity data was used to 'refine' the atlas target. A frontal burr hole around the coronal suture was placed in line with the planned trajectory and a 1.5 mm diameter, 2mm bare tip radiofrequency probe was advanced to the target using dynamic impedance recording. If introduction of the probe resulted in a stun effect and tremor disappeared, the patients were then "stressed", using verbal recollection and arithmetic tasks, to elicit the tremor. Stimulation was then performed up to 2 mA at 500µs, 133Hz to check on side effects and to estimate the degree of tremor suppression. In case of poor response or unacceptable side-effects, the probe was removed, and the process repeated following appropriate targeting adjustments. ~~The permanent lesion was then created using 70°C coagulation for 60 seconds at two or three locations 2mm apart along one or two adjacent parallel trajectories. Stereotactic MRI was obtained at the end of the RF coagulation to confirm lesion location.~~ Permanent lesions were created using 70°C coagulation for 60 seconds. Lesion size was a clinical judgement based on functional reserve, tremor response and side effect threshold. Patients with large amplitude tremor often saw significant tremor reduction with two lesions along the initial trajectory (1mm below and 1mm above the AC-PC plane but required a third one, or even additional lesions through an additional trajectory 2mm medial and 1mm anterior to the first, to eliminate tremor completely. Conversely, only one or two lesions were made in patients with low side effect thresholds on stimulation or with problematic balance or speech prior to the procedure. Stereotactic MRI was obtained at the end of the RF coagulation to confirm lesion location.

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Outcomes

Patients were evaluated before surgery and at one month, between three and six months, and between six and 36 months after surgery by a movement disorders neurologist. The FTMRS was used to quantify tremor severity[9]. The primary efficacy outcome was defined as the change in the FTMRS tremor score for the treated hand as compared to the non-treated hand between baseline and the last assessment time point performed between 6 and 36 months after surgery. Hand tremor scores (scored out of 12 points) were derived from adding resting, postural, and intention scores of the treated hand. Comparisons between baseline and long-term lateralized (scored out of 4 points for rest, postural and intention components plus handwriting, pouring, and drawing items), and disability (scored out of 28, including items 15-21) sub-scores as well as the total FTMRS score (scored out of 140) were secondary efficacy outcomes. In cases where FTMRS assessments were not available, a Clinical Global Impression (CGI) score was measured to estimate the surgery outcome[10].

Known RF-T side effects including gait, speech, or taste impairment as well as sensory or motor deficits were specifically screened for at each post-operative visit.

Imaging data processing

Diffusion sequences were acquired on a 3T Siemens Prisma system using multiband accelerated sequences developed at the Center for Magnetic Resonance Research (CMRR) at the University of Minnesota for the human connectome project (HCP) protocol version CCF_Prisma_VD13D_2016.07.14[11]. Image processing steps have been previously described[5]. The resulting connectivity segmentation maps from preoperative diffusion sequences acquisition were co-registered with the immediate postoperative stereotactic MRI 1.5mm^3 T1 MPRAGE and 1.0x1.0x2.0mm T2 sequences (1.5 T Siemens Espree) using the Medtronic FrameLink platform. Immediate postoperative MPRAGE and T2 acquisitions were used to segment the thalamotomy lesions. This was done manually first by an experienced functional neurosurgeon (HA) using ITK-SNAP[12] and confirmed by a second one (LZ). Lesion volumes in mm^3 were defined using the fslmaths tool[13]. Lesion locations in relation to the mid-commissural point (MCP) were evaluated using the post-op T2-weighted 1.5T scan on the Medtronic FrameLink platform. The target point at Z=0 (that is, at the level of the AC-PC plane) was selected along the trajectory. The MPRAGE scans were co-registered to the MNI152_T1_1mm template using a combination of linear (flirt tool) and non-linear (fnirt tool) registration steps[13]. The transformation warps were then applied to the segmented lesions which were thresholded by 50% to remove interpolation voxels and achieve transformed lesions with a volume as close as possible to the native space volumes. These were then used to generate a group average lesion map using fslmaths[13]. We measured both thalamotomy lesions with and without including perilesional oedema rim.

Statistical analysis

Comparisons between pre- and post-operative scores measured between 6 and 36 months after surgery were performed using the Wilcoxon signed rank-test. Correlations between baseline characteristics and the total FTRMS score, treated hand tremor score and tremor disability score were assessed using the Spearman rank test. Test were corrected for multiple comparison using the Bonferroni correction when required. p-values<0.05 were considered significant. All data were analyzed using the SPSS statistical package (SPSS, Release V.26.0 Chicago, Illinois, USA).

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Results

Twenty-one consecutive patients (14 ET, 7 PD) representing 23 thalamotomies (repeated for 2 patients) were included in this study. Baseline and follow-up FTMRS scores were available for 18 patients, corresponding to 20 thalamotomies (2 reinterventions). Three patients were seen in clinic but were not assessed using FTMRS. Five patients received thalamotomy after thalamic-DBS as a rescue option for insufficient tremor control. Baseline tremor scores and lesion characteristics are summarized in Table-1. Mean ACPC length was 24.8 mmm +/- 1,4 mm. The mean ±SD lesion coordinates in relation to midcommissural point (MCP), taken at the centre of the lesions were at X=14.3 ± 1.4 mm, Y=-6.3 ± 1.3 mm and Z=0 ± 0.4 mm. The mean and median difference between the

final Y coordinate and the atlas Y coordinate were 0 mm (SD=1.4). The mean and median of the absolute value of the ~~-~~difference between the final Y coordinate and the atlas Y coordinate were 1.2 and 1 respectively (SD=0.7). The mean and median difference between the final X coordinate and the atlas X coordinate (defined as 13mm on average) were 1.3 mm and 1.4 mm respectively (SD=1.6 mm).

The mean ± SD axial radius of the lesions in MNI, (if lesion volumes were converted into spheres) with oedema was 4.8 ± 0.7 mm, and without oedema was 2.3 ± 0.4 mm meaning a mean diameter of 9.6 and 4.6 respectively. Difference between final Y coordinates and atlas Y coordinates, ~~as well as~~ lesions' radius and deviation from atlas defined X and Y coordinates are depicted on Figure-~~1A and 1-B, respectively.~~1.

After a mean follow-up of 14.1 months, tremor improvement in the treated hand was significantly better than in the non-treated hand (63.8% vs -10.1%; p<0.01) (Figure-2A and 2-B). Tremor disability scores and total FTMRS scores were significantly better compared to baseline (7.55 ± 4.73 vs 13 ± 3.93, p<0.01, and 34.7 ±1 6.17 vs 51.65 ± 15.30, p=0.016, respectively) (Figure 2-C and 2-D). Lateralized sub-scores for intention, rest, and postural components of tremor as well as for drawing, pouring, handwriting, were all significantly lower at last evaluation (Figure-3). For the three patients without FTMRS assessments, two reported improvements (CGI score: 1 and 2) while one reported worsening (CGI score: 6). Two patients exhibited slight albeit non-clinically significant improvements (18% and 26%). These two patients were re-operated resulting in 37% and 63% improvement, respectively, compared to the score prior to the second surgery. Tremor improvement did not significantly differ between ET and PD patients (60.5% vs 70%, respectively p=0.13). Group average thalamic lesions including and not including oedema rim measurement are shown in Figure-4.

Patients' baseline tremor (Spearman rho=0.786; p<0.01) and total FTMRS scores (Spearman rho=0.64; p<0.01) correlated with tremor improvements at follow-up. In our cohort, no significant correlation was found between outcomes and gender, age at surgery, tremor aetiology, lesion size and location, or the reason for choosing thalamotomy, including patients with previous Vim-DBS failure. Lesion location on postoperative stereotactic MRI encompassed the intended target in all patients.

The most reported side effect was mild, transient gait ataxia (8 patients). Other transient side effects included upper limb paraesthesia (2 patients), mild dysarthria (4 patients), loss of the sense of taste (2 patients) and mild motor or sensory deficits (1 patient each). Persistent side effects included mild gait ataxia (3 patients), mild sensory deficit (1 patient) and paraesthesia (2 patients). No correlation was found between side effects and lesions size or location.~~We identified a positive correlation between gait ataxia (transient or persistent) and percentage of thalamus lesioned without inclusion of the oedema rim (Spearman rho = 0.55, p=0.029).~~

Discussion

This study explored the utility of an MRI connectivity-guided RF-T technique for management of intractable tremor. This paper is focused on the outcomes rather than the technicalities of using structural connectivity to define the target that has been reported in a previous publication[5].

Overall, the safety of this approach was acceptable with durable tremor efficacy, adding to the experience of previous thalamotomy studies[3,4]. Good outcome following RF-thalamotomy was indeed noticed for both treated hand total tremor scores as well as on rest, postural and intention components of tremor. FTMRS outcomes were similar to those obtained with other surgical techniques used to treat severe refractory tremor, including thalamic deep brain stimulation, gamma-knife or MR-guided focused ultrasound thalamotomy[4,14] confirming MR-guided RF-thalamotomy as a valid option in refractory tremor of PD and ET.

~~We examined the difference in the Y coordinates between the atlas-based target and the final target informed by connectivity. The reason for this is that the X coordinate is determined by the thalamic width and the thalamo-capsular border and can therefore be determined on conventional MRI using a proton density sequence while the Z coordinate is accepted to be at the AC-PC level (i.e. Z=0). The mean difference in the Y coordinates was 0. This was rather expected since on average, the atlas coordinates of the Vim provide an accurate targeting method. However, there was a standard deviation of 1.4 mm (and a wider spread, see Fig 1) between the atlas-defined Y and the final Y as refined by connectivity targeting. Additionally, the mean of the absolute value of the difference between atlas defined and the final Y coordinates was 1.2 mm, and 4 thalamotomies add a deviation above 2 mm. This indicates that connectivity targeting is useful in capturing the 'individual" anteroposterior variability of the Vim location, which may impact the clinical outcome among the minority of patients whose anatomy significantly differ from the atlas. Further prospective works comparing connectivity-based and atlas-based targeting are warranted to determine whether this difference might be clinically significant in terms of RF-T outcome.~~

We examined the difference in the Y coordinates between the atlas-based and final target informed by connectivity. This analysis was chosen because the X coordinate is determined by the thalamo-capsular border and can be determined on structural MRI using a proton density sequence while the Z coordinate for comparison was taken at the AC-PC level (i.e. Z=0). The mean difference in the Y coordinates was 0. This is expected since atlas coordinates are an average of the Vim location across subjects. However, the standard deviation between atlas defined Y and the final Y coordinate, as refined by connectivity targeting, was 1.4 mm (and a spread was wider, see Fig 1). Additionally, the mean of the absolute value of the difference between atlas defined and the final Y coordinates was 1.2 mm, and 4 thalamotomies had deviations above 2 mm. This indicates that connectivity targeting is useful in capturing the 'individual" anteroposterior variability of the Vim, which may impact the clinical outcome among patients whose anatomy significantly differs from the atlas. Further prospective works comparing connectivity-based and atlas-based targeting are warranted to determine whether this difference might be clinically significant in terms of RF-T outcome.

Early post-operative gait ataxia affected over 50% of our subjects though this was mild and transient in most cases. Other sensorimotor side effects noted were similarly mild and/or transient, suggesting

that the procedure was reasonably tolerated. This is consistent with reports from other Vim lesioning surgical techniques and presumably relate to the inadvertent disruption of established anatomically related pathways, such as the dentato-thalamic tract and fibres from the ventral posterolateral thalamus[4]. We also noted dysgeusia following thalamotomy, an adverse event that has been reported following MR-guided focused ultrasound thalamotomy and presumably due to lesions overlapping with the solitario-thalamic gustatory fibers[15]. Our patients who experienced taste impairment had fully recovered six months after the intervention.

Baseline tremor severity predicted RF-T outcomes which may be clinically useful information for future patient selection. Previous DBS failure was not negatively correlated with outcomes. Although only five patients received RF-T for this indication, this finding potentially provides support for RF-T as a 'rescue' option for tremor that does not respond adequately to DBS[16]. Since those patients did not receive connectivity-guided DBS, it is unclear whether this additional benefit rely on the targeting strategy or the RF-T itself. Prospective controlled trial comparing Vim-DBS and RF-T using connectivity-guided targeting might allow to answer this question. Two patients required two thalamotomies because of insufficient initial benefit, with a good and long-lasting effect noted after the second intervention that occurred 14 and 23 months after the first one. This suggests that RF-thalamotomy can be safely repeated in cases of insufficient tremor control or early recurrence, as previously reported with MR-guided focused ultrasound thalamotomy[17].

~~We examined the difference in the Y coordinates between the atlas-based target and the final target informed by connectivity. The reason for this is that the X coordinate is determined by the thalamic width and the thalamo-capsular border and can therefore be determined on conventional MRI using a proton density sequence while the Z coordinate is accepted to be at the AC-PC level (i.e. Z=0). The mean difference in the Y coordinates was 0. This was rather expected since on average, the atlas coordinates of the Vim provide an accurate targeting method. However, there was a standard deviation of 1.4 mm (and a wider spread, see Fig 1) between the atlas defined Y and the final Y as refined by connectivity targeting. This indicates that connectivity targeting is useful in capturing the 'individual" anteroposterior variability of the Vim location. Further prospective works comparing connectivity-based and atlas-based targeting are warranted to determine whether this difference might be clinically significant in terms of RF-T outcome.~~

Conclusion

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To conclude, RF-T guided by a novel MRI connectivity technique appears to be safe and efficacious in the treatment of severe tremor related to PD and ET. Exploring these findings in larger cohorts comparing surgical modalities and exploring individual and lesion predictive characteristics will be of value in determining the exact role of this approach in tremor management.

~~This research study was supported by researchers at the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre.~~

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~~**Table-1: Baseline characteristics of the patients**~~

Figure-1: Box Plots showing the difference in the final Y coordinate from the atlas target (A), the radius of the lesions assuming perfect spheres (B) and X and Y deviation from the atlas coordinate for each thalamotomy (C)

Figure-2: Radiofrequency thalamotomies outcome.

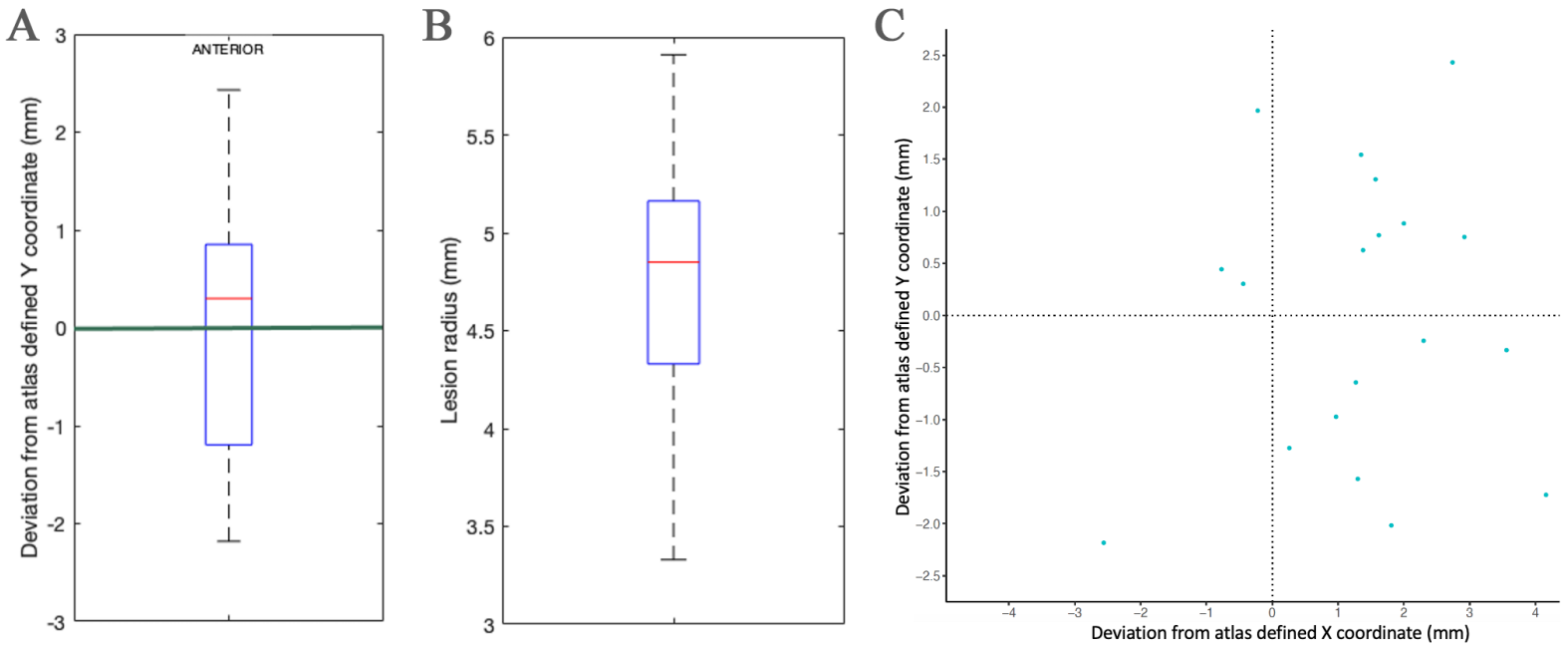
A: Evolution of treated hand tremor score, B: Evolution of non-treated hand tremor score, C: Evolution of tremor disability score, D: Evolution of total Fahn-Tolosa-Marin rating scale score

Figure-3: Evolution of the different lateralized subscores. Drawing A: drawing within a large spiral template, Drawing B: drawing within a tight spiral template, Drawing C: drawing lines inside a linear template; for comparison between baseline and long-term assessment performed between 6 and 36 months after the surgery: * $p<0.05$, ** $p<0.01$

Figure-4 Group average lesion (MNI) with and without oedema. 4 lesions were performed on the right thalamus while 14 lesions were performed on the left thalamus.

Figure 1. Box Plots showing the difference in the final Y coordinate from the atlas target (A), the radius of the lesions assuming perfect spheres (B) and X and Y deviation from the atlas coordinate for each thalamotomy (C)

Figure 1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Deviation from atlas defined Y coordinate (mm)
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B
Lesion radius (mm)
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C
Deviation from atlas defined Y coordinate (mm)
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−2
−1
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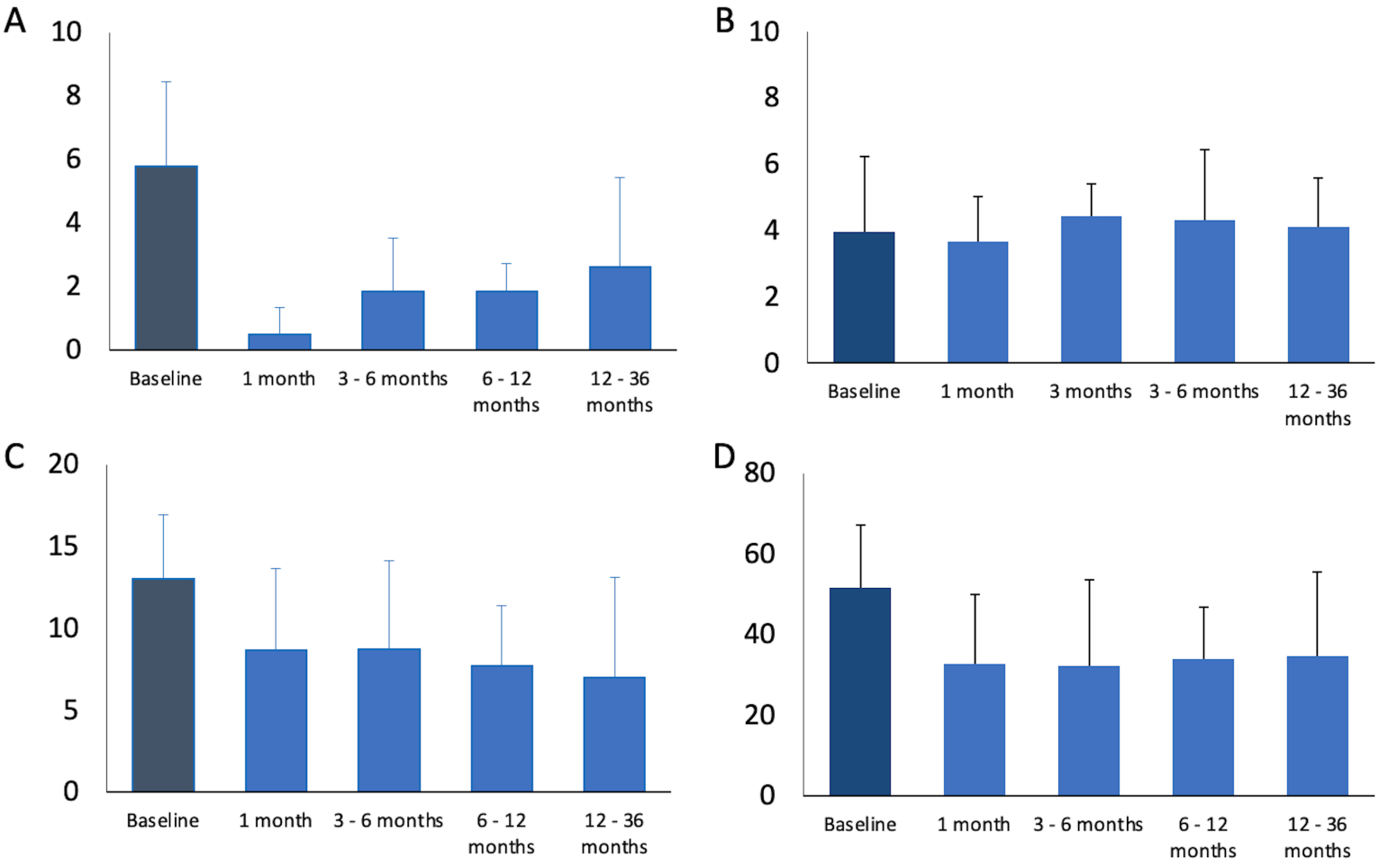
4
Deviation from atlas defined X coordinate (mm)

Figure 2. Radiofrequency thalamotomies outcome. A: Evolution of treated hand tremor score, B: Evolution of non-treated hand tremor score, C: Evolution of tremor disability score, D: Evolution of total Fahn-Tolosa-Marin rating scale score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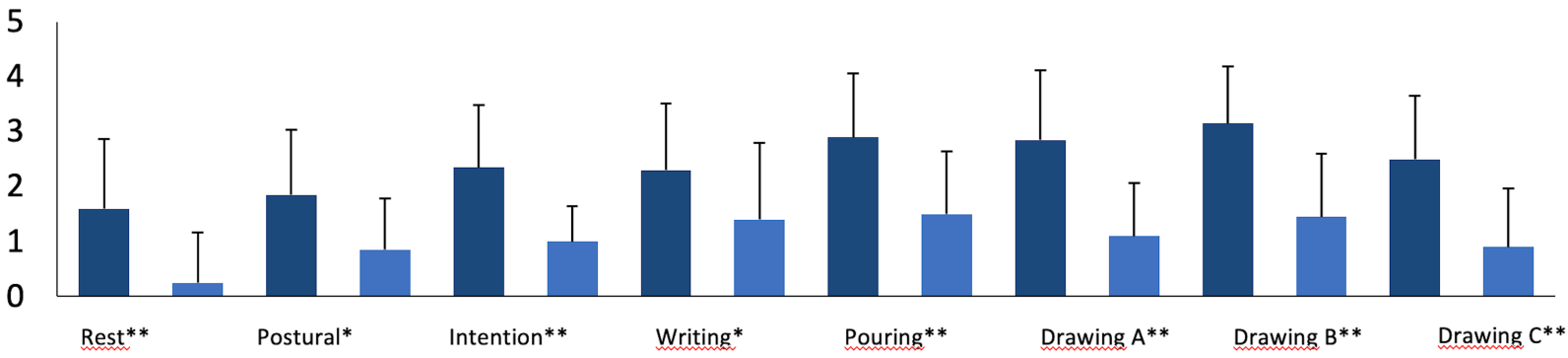
6 - 12 months
12 - 36 months

Figure 3. Evolution of the different lateralized subscores. Drawing A: drawing within a large spiral template, Drawing B: drawing within a tight spiral template, Drawing C: drawing lines inside a linear template; for comparison between baseline and long-term assessment performed between 6 and 36 months after the surgery: * $p<0.05$, ** $p<0.01$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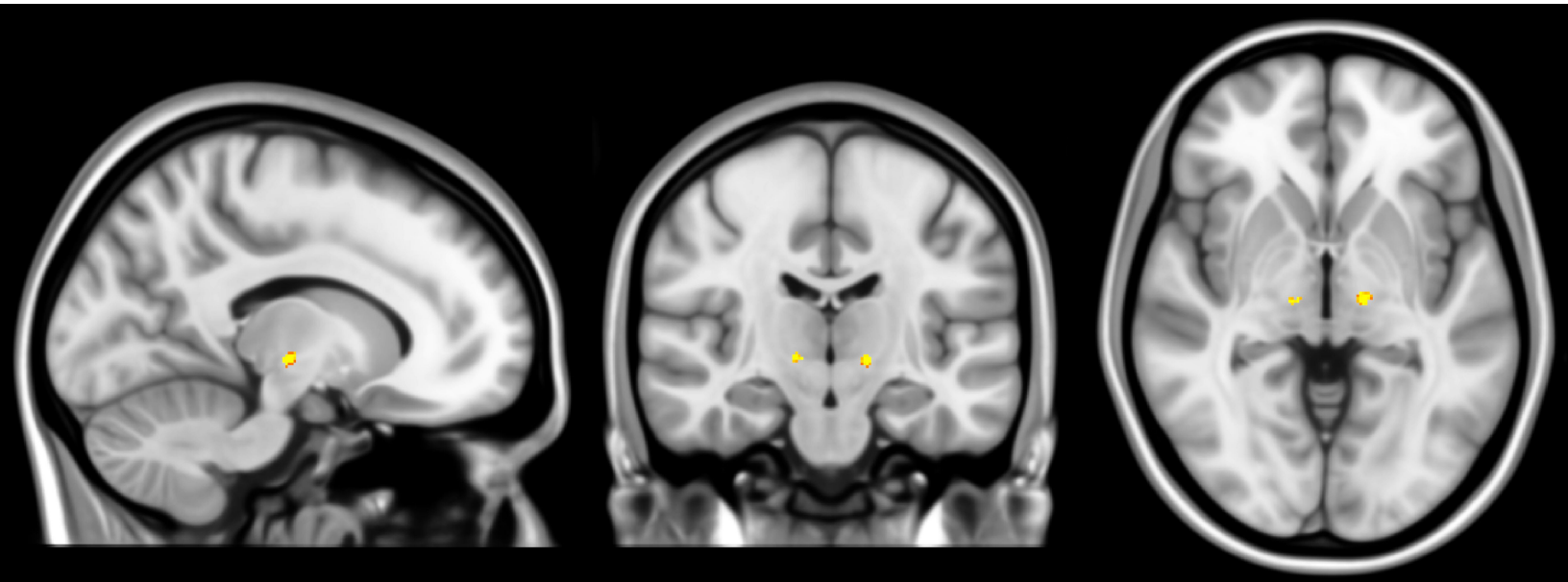
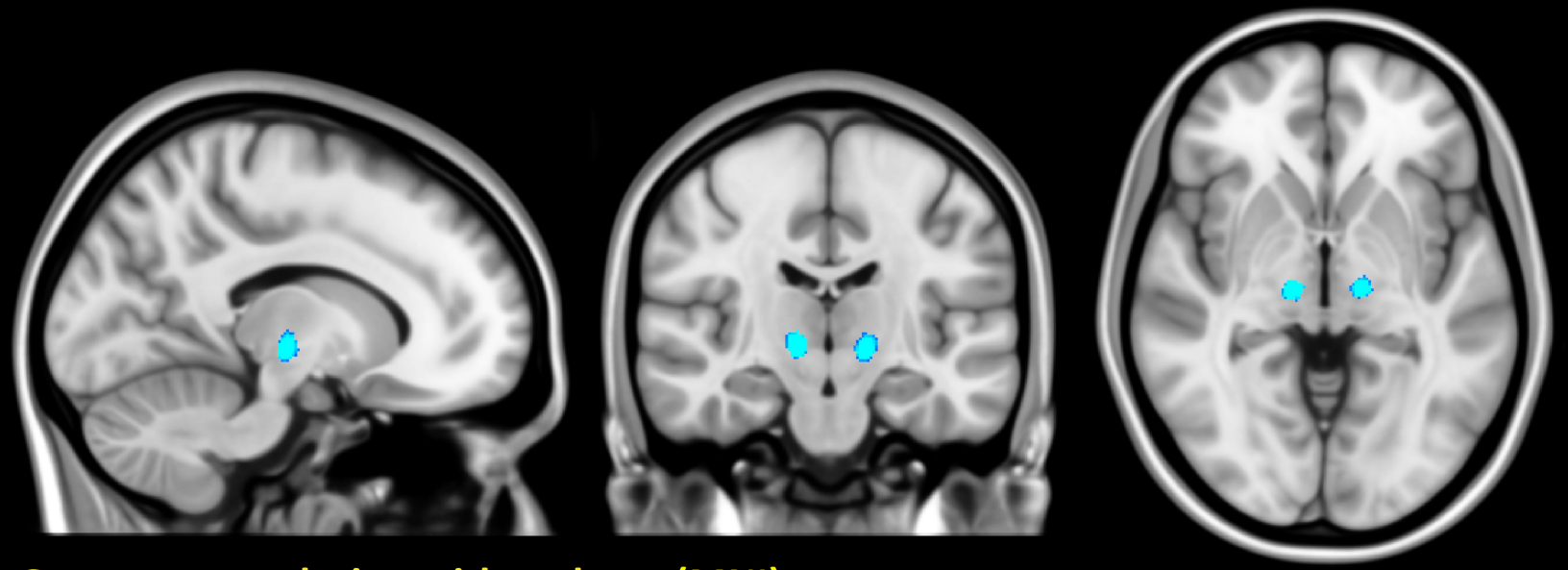
Rest**
Postural*
Intention**
Writing*
Pouring**
Drawing A**
Drawing B**
Drawing C**

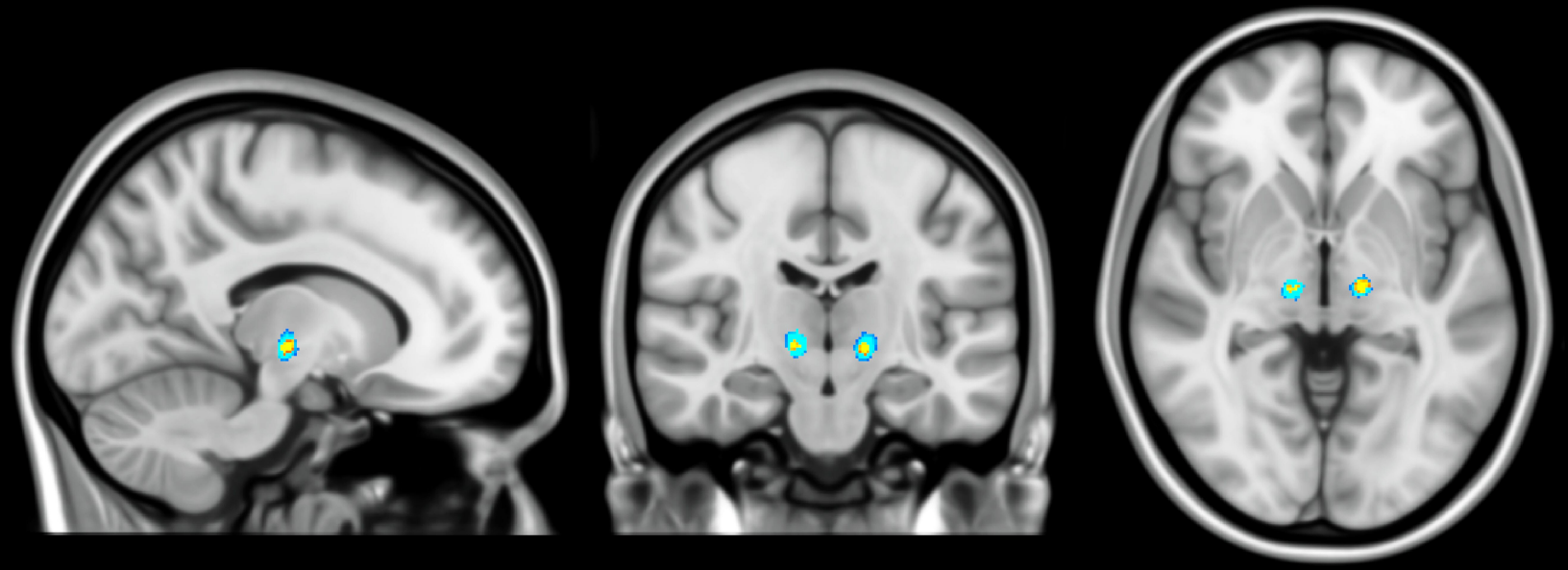
Figure 4. Group average lesion (MNI) with and without oedema. 4 lesions were performed on the right thalamus while 14 lesions were performed on the left thalamus.



Group average lesion without oedema (MNI)



Group average lesion with oedema (MNI)



Group average lesion with (blue) and without (yellow) oedema (MNI)

Table-1: Baseline characteristics of the patients

	Patients and thalamic lesion characteristics	
No of patients	21	
No of thalamotomies	23	
Gender	Male: 14	Female: 7
Handedness	Right: 17	Left: 4
Treated Vim	Right: 5	Left: 16
Aetiology of tremor	ET: 14	PD: 7
Age at Thalamotomy (years)	66.8 +/- 6.5	
Follow-up duration (months)	14.1 +/- 9.4	
Baseline treated hand tremor score	5.8 +/- 2.7	
Baseline tremor disability score	13 +/- 3.9	
Baseline total FTMRS score	51.7 +/- 15.3	
Factor influencing choice of RF-T over DBS	DBS failure	5
	Patient's preference	9
	Advanced age or medical comorbidities	7
Thalamotomy Volume with oedema (MNI) mm3	474.3 +/- 184	
Thalamotomy Volume without oedema (MNI) mm3	55.4 +/- 34.5	
Lesion/thalamus volume with oedema (%)	6.04 +/- 1.96	
Lesion/thalamus volume without oedema (%)	0.85 +/- 0.38	
MCP coordinates, centre at Z=0 (mm)	X (Lateral)	14.3 +/- 1.6
	Y (Posterior)	6.3 +/- 1.3

Legend: ET Essential Tremor, PD Parkinson's disease, MCP MidCommissural point, FTMRS: Fahr Tolosa Marin Rating Scale