

## Short communication

## Structural changes in cerebellar outflow tracts after thalamotomy in essential tremor



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## ARTICLE INFO

## Article history:

Received 18 September 2013

Received in revised form

30 January 2014

Accepted 24 February 2014

## Keywords:

Essential tremor

Thalamotomy

Diffusion tensor imaging

Tremor

Cerebellum

## ABSTRACT

**Background:** This study set out to determine whether structural changes are present outside the thalamus after thalamotomy in patients with essential tremor (ET), specifically in the cerebellorubrothalamic tracts. We hypothesized that diffusion tensor imaging (DTI) would detect these changes.

**Methods:** We collected DTI scans and analyzed differences in Fractional Anisotropy (FA) and Mean Diffusivity (MD) between the left and right superior and middle cerebellar peduncle in ET patients that have undergone unilateral, left, thalamotomy and ET patients that did not undergo thalamotomy (control group). We used classical ROI-based statistics to determine whether changes are present.

**Results:** We found decreased FA and increased MD values in the right superior cerebellar peduncle leading to the left, lesioned thalamus, only in the thalamotomy group.

**Conclusions:** Our study suggests long-term structural changes in the cerebellorubrothalamic tract after thalamotomy. This contributes to further understanding of the biological mechanism following surgical lesions in the basal ganglia.

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## 1. Introduction

Essential tremor (ET) is characterized by postural or kinetic tremor, and is the most common movement disorder in adults with an estimated prevalence between 0.4 and 0.9% in the general population, although the number seeking treatment is possibly lower [1]. Available studies on the pathophysiology of tremor in ET suggest that the cerebellum and the cerebello-thalamo-cortical pathway are involved in tremor generation [2]. Available oral medication for ET provides modest or insufficient benefit in some cases. Stereotactic ablation or stimulation of the nucleus ventralis intermedius (Vim), located in the ventrolateral thalamus [3], gives sustained satisfying tremor suppression in the contralateral

extremities in the majority of operated patients [4], suggesting a crucial role of this nucleus in the pathophysiological network of tremor. The Vim receives efferent input from the cerebellum through the superior cerebellar peduncle (SCP) and relays this input mainly to the primary motor cortex (M1) [3]. The effects of thalamotomy at the microstructural level have not been studied thus far. In other forms of ablation surgery, axonal and myelin degradation both upstream and downstream from the site of the lesion is observed [5]. After neuronal injury, the proximal axon ends 'die back' and do not regenerate, also termed retrograde trans-neuronal degeneration. The distal axon ends undergo Wallerian degeneration [6].

In order to quantify structural changes after thalamotomy, we performed MR diffusion tensor imaging (DTI) in a selected group of ET patients with prior successful unilateral left-sided Vim thalamotomy. DTI allows quantifying white matter by measuring diffusion of water molecules, and makes it possible to quantify white matter changes after thalamotomy in ET. Normally, axonal membranes and myelin pose barriers to water displacement, such that

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water preferentially diffuses along the direction of the axons [7]. The use of DTI in stereotactic neurosurgery is gaining increased attention, since the visualization of white matter tracts before surgery could help to better define the correct target, and subsequently improve clinical outcome [8]. We hypothesized that DTI would detect unilaterally changed diffusion values in the efferent tracts from the right cerebellum to the left, lesioned, thalamus.

## 2. Methods

### 2.1. Patients

Six ET patients who underwent unilateral, left-sided, successful thalamotomy between 1998 and 2008, as defined by a persistent reduction of at least 2 points on item 5 of the Essential Tremor Rating Scale (ETRS), which is scored during stretching of the right arm, were included in the study (five men; mean age 69 years, range 48–83, average time from surgery 7 years, range 4 months–10 years). To be able to objectify whether left/right differences were physiological or related to the thalamotomy, we also included a control group of 8 ET patients that did not undergo thalamotomy (four men; mean age 63 years, range 47–73 years). All participants fulfilled the consensus criteria for definite classic ET [11], had disease duration longer than 5 years, had symptoms onset before the age of 65, and had at least one affected first-degree relative. Furthermore, all participants were right-handed. Demographic and clinical characteristics are described in [Supplementary Table 1](#). Further details on the surgery have been described previously [9]. Written informed consent was obtained from all participants. The study was approved by the local medical–ethical board and was performed in accordance with the Declaration of Helsinki.

### 2.2. Data acquisition and analysis

DTI data were acquired by means of a spin-echo EPI sequence. The thalamotomy case images were acquired along 32 directions (TE 90 ms, TR 5758 ms, b0 1000 s/mm<sup>2</sup>, FOV 230 × 135, slice thickness 3 mm, voxel size 2 × 2 × 3 mm), control ET case images were acquired along 48 directions (TE 60/90 ms, TR 7294/8732 ms, b0 1000 s/mm<sup>2</sup>, FOV 224 × 224 × 112, slice thickness 2 mm, voxel size 2 × 2 × 2 mm). To prevent differences in scan parameters causing differences between groups, we solely assessed left–right differences within, and not between, groups. Furthermore differences in slice thickness could have caused partial volume effects. A simulation experiment showed that partial voluming leads to an underestimation of the effect at thicker 3 mm slices. In other words, left–right differences in the thalamotomy ET group could be underestimated compared to the control ET group (for details see [Appendix](#)).

Preprocessing was performed using in-house developed software, written in Matlab (The MathWorks, Natick, MA). The preprocessing was executed on the Dutch Grid using a web interface to the e-Bioinfra gateway (for details see [Appendix](#)) [10]. From the preprocessed datasets, Fractional Anisotropy (FA) and Mean Diffusivity (MD) images were computed. FA depicts the anisotropy of diffusion, ranging from 0 to 1, which is the normalized ratio of diffusion directionality. MD depicts the local average magnitude of diffusion in all directions. Both FA and MD are measures of white matter integrity. Bilateral superior (SCP) and middle (MCP) cerebellar peduncles were extracted to be used as regions of interests (ROI) from the ICBM DTI-81 Atlas, a validated stereotactic white matter atlas based on 81 healthy subjects [11]. ROI were inspected visually for correct inclusion of the SCP and MCP in all subjects. See [Supplementary Fig. 1](#) for an overview of the anatomy of the SCP and MCP. Mean FA and mean MD were calculated in these ROI using Matlab, and were averaged along the posterior–anterior axis to be able to visually determine at what location left/right differences are present. Calculating mean FA values was preferred over maximum FA since this is a more representative value for the entire ROI, as the maximum FA value would possibly more reflect the center of the structures. Two-sided Student's *T*-tests were used to test for left/right differences. An adjusted significance level of 0.00625 (0.05<sup>8</sup>) was calculated (Bonferroni method) to account for the increased possibility of type-I error due to multiple testing. Furthermore, we will

look at white matter integrity changes in relation to time elapsed from surgery and clinical outcome.

Additionally, to verify that the Vim nucleus was correctly targeted, high-resolution anatomical T1 3D SENSE images were obtained (echo time: 3.56 ms; repetition time: 9 ms; flip angle: 8°; field of view: 256 × 256 mm; voxel size 1 mm<sup>3</sup>, number of slices: 170) to determine the location of the lesion relative to the posterior commissure. The mean stereotactic coordinates of the lesion were 13.8 mm lateral (SD 1.7 mm), 8.1 mm anterior (SD 1.7 mm) and 0.7 mm superior (SD 0.8 mm) relative to the posterior commissure, which indicates correct targeting of the Vim nucleus [3].

## 3. Results

In the thalamotomy group, mean FA was significantly decreased in the right SCP (leading to the operated thalamus) compared to the left SCP (leading to the non-operated thalamus) ( $t[5] = 4.8564$ ,  $p = 0.0046$ ; [Table 1](#)). Mean MD was significantly increased in the right SCP compared to the left SCP ( $t[5] = -8.1762$ ,  $p = 0.0004$ ; [Table 1](#)). In the control ET group, there were no significant differences in mean FA and mean MD between the left and right SCP (mean FA:  $t[7] = -0.6108$ ,  $p = 0.56$ , mean MD:  $t[7] = 0.9162$ ,  $p = 0.39$ ; [Table 1](#)).

There were no significant differences in mean FA and mean MD between the left and right MCP, both in the thalamotomy and the control group (thalamotomy group: mean FA  $t[5] = 0.5838$ ,  $p = 0.58$ , mean MD  $t[5] = 1.767$ ,  $p = 0.14$ , control group: mean FA  $t[7] = -0.0356$ ,  $p = 0.73$ , mean MD  $t[7] = -0.1455$ ,  $p = 0.89$ ; [Table 1](#)).

FA differences in the SCP of the thalamotomy group did not correlate with time elapsed from surgery ( $r(4) = 0.52$ ,  $p = 0.29$ ) or with post-surgical tremor rating score improvement ( $r(3) = -0.24$ ,  $p = 0.69$ ).

[Fig. 1](#) provides an overview of FA and MD values along the posterior–anterior (*y*-axis) direction in the SCP and MCP.

## 4. Discussion

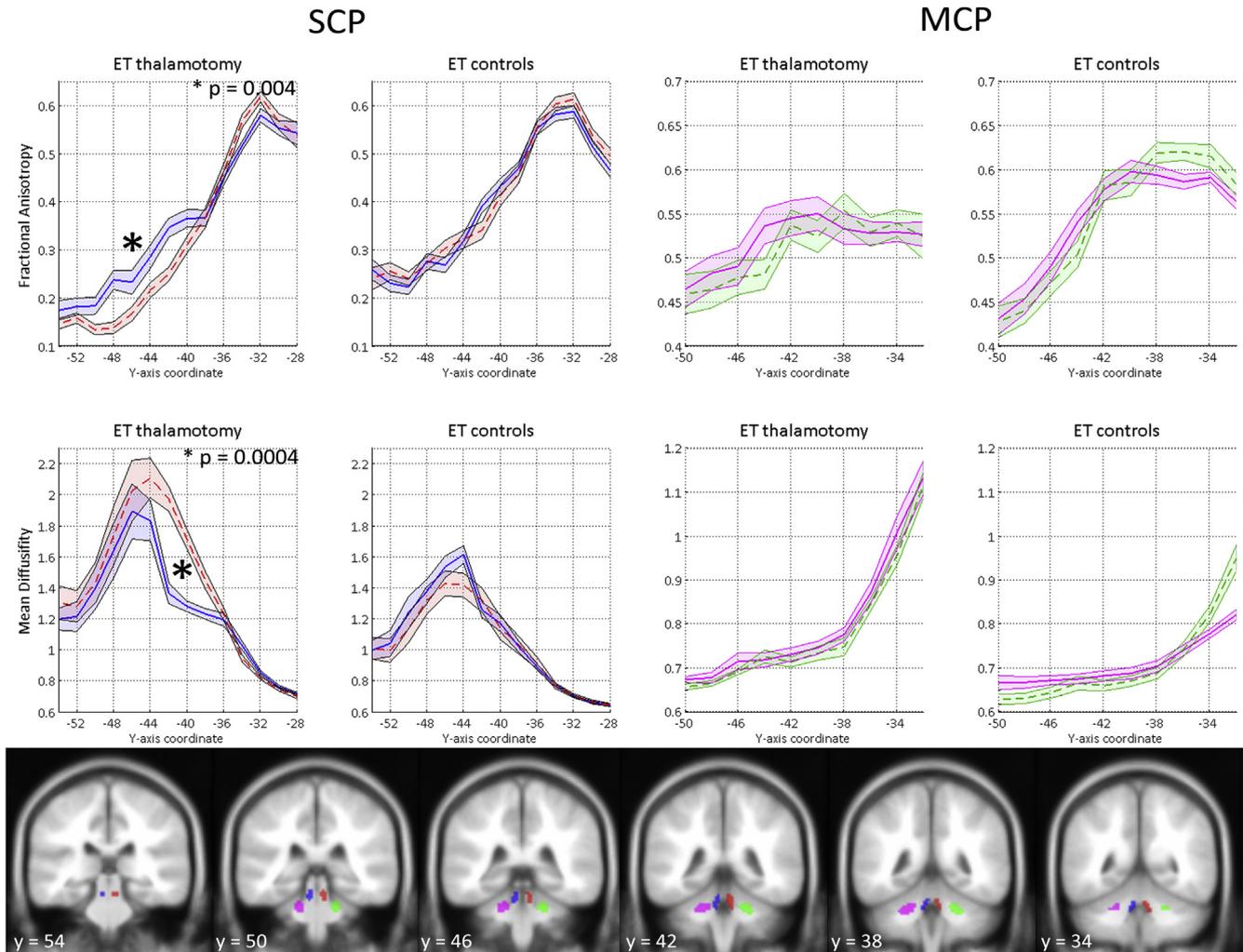
Our data are in agreement with the hypothesis that white matter integrity in the tracts leading from the cerebellum to the Vim is affected after thalamotomy, reflected in decreased FA and increased MD values in the right SCP, leading to the left, lesioned, Vim, after comparison of values for right and left SCP. This suggests that long-term structural changes after thalamotomy are not limited to the Vim, but are more widespread, possibly due to retrograde “dying-back” of axons leading to the lesioned Vim. Tracts leading from the Vim to the M1 were not assessed in this study. Unfortunately, it is troublesome to perform reliable tractography from the Vim to the M1 because of the small size of the Vim nucleus and the close proximity to other nuclei in the thalamus.

Axon and myelin density have been shown to negatively correlate with FA and positively correlate with MD values [12]. A DTI study by Concha et al. looking at the effects of corpus callosotomy in epilepsy patients found similar changes in FA values in

**Table 1**

Mean FA and MD in both groups in the SCP and MCP (standard error of the mean between brackets),\* significance threshold of  $p < 0.00625$  (Bonferroni method).

	Thalamotomy group ( $n = 6$ )			Control group ( $n = 8$ )		
	Right	Left	<i>p</i> -Value	Right	Left	<i>p</i> -Value
SCP						
FA	0.33 (0.02)	0.36 (0.03)	<b>0.0046*</b>	0.40 (0.04)	0.40 (0.03)	0.56
MD ( $\cdot 10^{-3}$ mm <sup>2</sup> /s)	1.38 (0.17)	1.26 (0.14)	<b>0.0004*</b>	1.04 (0.14)	1.07 (0.11)	0.39
MCP						
FA	0.51 (0.04)	0.52 (0.03)	0.58	0.54 (0.03)	0.54 (0.03)	0.73
MD ( $\cdot 10^{-3}$ mm <sup>2</sup> /s)	0.78 (0.03)	0.81 (0.03)	0.14	0.71 (0.03)	0.71 (0.03)	0.89



**Fig. 1.** Diffusion values together with confidence intervals in coronal slices (y-direction, MNI space) in the SCP and MCP in the thalamotomy and control group. Right SCP = red, dashed, left SCP = blue, solid, right MCP = green, dashed, left MCP = violet, solid. Lower image: ROI of SCP and MCP shown on coronal slices along y-axis (MNI space), colors correspond with the upper image.

axons further away from the lesion [5]. They observed DTI changes as early as 1 week post surgery. From our study, it is not possible to determine when the changes did occur in our patients. There was no correlation between FA changes and time elapsed since surgery. The mean follow-up time after surgery was 6 years. The shortest follow-up time after surgery in this series was 4 months. In this specific patient, a similar left-right difference was present as in the rest of our cases. This suggests that changes may occur before that time.

Tremor suppression occurs immediately after thalamotomy. It remains to be elucidated whether the observed degeneration in the SCP has a direct role in tremor reduction or is merely secondary to the thalamotomy. In our 6 operated cases, there was no relation between the degree of FA changes and clinical improvement. However, the spread of clinical improvement was small, since we have only included patients with relevant improvement. It would be interesting to repeat this study in a group of patients following Vim Deep Brain Stimulation, to compare changes in cerebellar outflow tracts. One would hypothesize that Vim Deep Brain Stimulation, which also reduces tremor, causes a 'functional' lesion of the cerebellorubrothalamic tracts, and in contrast to thalamotomy, not a structural lesion of the cerebellorubrothalamic tracts.

There is an ongoing debate regarding which thalamic subnuclei receive cerebellothalamic fibers [4,8]. Some authors suggest that

cerebellar fibers end in the posterior part of the Vop nucleus instead of the Vim nucleus. In our patients, the lesions are located in the Vim nucleus. This could implicate, that the observed changes in the SCP are related to lesioning of the Vim and not the Vop nucleus. However, the location of the lesions is based on long-term follow-up scans, and therefore not perfectly accurate.

In conclusion, our study shows long-term structural changes in the cerebellorubrothalamic tract after thalamotomy in patients with ET. This study contributes to further understanding of the biological mechanism following surgical lesions in the basal ganglia and could lead to a better understanding of the mechanisms of action of functional neurosurgery.

#### Financial disclosure/conflict of interest

None related to this manuscript.

#### Acknowledgments

This work performed computations using the e-bioinfra platform developed at the e-bioscience group of the Bioinformatics Laboratory of the AMC, using resources of the Dutch e-Science Grid, BiGGrid project, which is financially supported by the Nederlandse

Organisatie voor Wetenschappelijk Onderzoek (Netherlands Organisation for Scientific Research, NWO).

## Appendix

### Data acquisition and analysis

DTI data were acquired by means of a spin-echo EPI sequence. The thalamotomy cases and 6 control cases were acquired on a Philips Intera 3.0 T MRI scanner and data of 2 control cases were acquired on a Philips Achieva 3.0 T MRI scanner (Philips Medical Systems, Best, The Netherlands). Thalamotomy case images were acquired along 32 directions (TE 90 ms, TR 5758 ms, b0 1000 s/mm<sup>2</sup>, FOV 230 × 135, slice thickness 3 mm, voxel size 2 × 2 × 3 mm), control ET case images were acquired along 48 directions (TE 60/90 ms, TR 7294/8732 ms, b0 1000 s/mm<sup>2</sup>, FOV 224 × 224 × 112, slice thickness 2 mm, voxel size 2 × 2 × 2 mm). Differences in scan parameters could have caused biased diffusion parameter estimates between the two groups. Therefore, we did not compare the thalamotomy group with the control group directly, but solely assessed left-right differences within groups. Furthermore differences in slice thickness could have caused partial volume effects. A simulation experiment showed that partial voluming leads to an underestimation of the effect at thicker 3 mm slices. A slice thickness difference of 1 mm shows that a partial volume effect (CSF mixed with white matter) of 33% causes a larger difference in the control group (2 mm) compared to the thalamotomy group (3 mm) (see [Supplementary Fig. 2](#)). In other words, since the thalamotomy group was scanned using 3 mm slices, and the control group was scanned using 2 mm slices, and partial voluming is expected to underestimate differences with 3 mm slices more, the chance of left-right differences was higher a priori for the control group. Therefore, we expect that partial voluming did not significantly influence our results.

All data were anonymized prior to analysis. The preprocessing of the DTI data was performed using in-house developed software, written in Matlab (The MathWorks, Natick, MA). The preprocessing was executed on the Dutch Grid using a web interface to the e-Bioinfra gateway [[esupp ref 1](#)]. Head motion and deformations induced by eddy currents were corrected for by an affine registration of the Diffusion Weighted Images (DWIs) to the non-diffusion weighted image. The gradient directions were corrected by the rotation component of the transformation. The DWIs were resampled isotropically. Rician noise in the DWIs was reduced by an adaptive noise filtering method [[esupp ref 2](#)]. Diffusion tensors were estimated in a non-linear least squares sense. Datasets were non-rigidly registered to a population-based average template. Initially, to correct for anatomical variation outside white matter, non-diffusion weighted images were registered using DARTEL [[esupp ref 3](#)]. Diffusion tensor datasets were warped and tensors were reoriented accordingly. Subsequently, alignment within white matter was achieved by non-rigidly registering diffusion tensor datasets using the DTI-Toolkit (DTITK) [[esupp ref 4](#)]. From the warped datasets, Fractional Anisotropy (FA) and Mean Diffusivity (MD) images were computed. FA depicts the anisotropy of diffusion,

ranging from 0 to 1, which is the normalized ratio of diffusion directionality. MD depicts the local average magnitude of diffusion in all directions. Bilateral superior (SCP) and middle (MCP) cerebellar peduncles were extracted to be used as regions of interests (ROI) from the ICBM DTI-81 Atlas, a validated stereotactic white matter atlas based on 81 normal subjects [[esupp ref 5](#)]. ROI were inspected and visually for correct inclusion of the SCP and MCP in all subjects. The SCP is the ROI containing fibers leading from the dentate nucleus to the Vim. The MCP is used as a control ROI, as this peduncle contains afferent fibers leading from the cortex to the cerebellar cortex (see [Supplementary Fig. 1](#) for an overview of the anatomy of the SCP and MCP). FA and MD images were calculated using the ImCalc function of the Statistical Parametric Mapping software package (SPM8, Wellcome Department of Cognitive Neurology, London, United Kingdom; [www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). Furthermore, mean FA and mean MD were calculated in these ROI using Matlab, and were averaged along the posterior-anterior axis, to be able to visually determine at what location left/right differences are present. Calculating mean FA values was preferred over maximum FA since this is a more representative value for the entire ROI, as the maximum FA value would possibly more reflect the center of the structures.

### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.parkreldis.2014.02.020>.

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