Parkinsonism and Related Disorders 20 (2014) 554–557

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

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 transneuronal 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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http://dx.doi.org/10.1016/j.parkreldis.2014.02.020
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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 [1], 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^2, 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^2, 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 (0.05^8) 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^3, 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 en 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	*p*-Value	Right	Left	*p*-Value
SCP						
FA	0.33 (0.02)	0.36 (0.03)	**0.0046***	0.40 (0.04)	0.40 (0.03)	0.56
MD ($\cdot 10^{-3}$ mm^2/s)	1.38 (0.17)	1.26 (0.14)	**0.0004***	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^2/s)	0.78 (0.03)	0.81 (0.03)	0.14	0.71 (0.03)	0.71 (0.03)	0.89

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