Stereotact Funct Neurosurg 2015;93:378–379
DOI: 10.1159/000440728

**Comment on the Article by Ledermann et al.
Entitled 'Effects of Cerebellothalamic Tractotomy
on Cognitive and Emotional Functioning in
Essential Tremor: A Preliminary Study in 5 Essential
Tremor Patients'**

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We read the paper of Ledermann et al. [1] with interest and congratulate the authors for focussing on neuropsychiatric, cognitive and personality outcomes following surgery to the cerebellothalamic tract. As indicated by Ledermann et al., the cerebellothalamic tract is one of the major ascending fibre bundles running through the posterior subthalamic area (PSA) which is the area below and behind the subthalamic nucleus and lateral to the red nucleus. The excellent motor and neurocognitive outcomes following cerebellothalamic tractotomy for essential tremor (ET) mirror our own experience of deep brain stimulation in this region which we published in 2013 [2].

In our study [2], 11 patients with pharmacologically resistant and disabling essential tremor were offered PSA deep brain stimulation (PSA-DBS). The mean age and tremor duration of our sample were 69.4 ± 13.1 years and 30 years, respectively. All patients underwent pre-operative diffusion tensor imaging and tractography (DTI-T) to delineate the cerebellothalamic tract. Patients were randomised into two groups. Group A patients (3 unilateral left PSA-DBS and 3 bilateral PSA-DBS) underwent electrode insertion in the conventional manner using anatomical targets indicated on the Schaltenbrand-Wahren atlas and on MR imaging [3]. In group B patients (3 unilateral left PSA-DBS and 2 bilateral PSA-DBS), the DTI-T images showing the cerebellothalamic tract were fused to axial T2-weighted images, then used to determine the target coordinates. Electrode insertion then proceeded in the standard manner. Optimal target location was confirmed with intra-operative testing and intra-operative MR scanning. The brain electrodes were then internalised and connected to a neurostimulator.

The DBS system was programmed postoperatively, and the patients were reviewed 6 weeks, 3, 6 and 12 months after surgery. Neuropsychological testing was performed before surgery and 6 months postoperatively with their stimulators switched on. Both the neurologist and neuropsychologist were blinded to which groups the patient belonged to until the end of the study period.

Our study differs from that of Ledermann et al. in regard to the following: the surgical target in their study was defined on ana-

tomical features and refined with micro-electrode recordings and macrostimulation. In ours, the target for group A patients was determined in a similar manner, and the postoperative target coordinates closely follow that of Ledermann et al. However, their paper assumes that the anatomical target corresponds to the cerebellothalamic tract. Our study used deterministic tractography (group B) to increase the probability that the targeted tissue is actually the cerebellothalamic tract. Additionally our study afforded longer neurocognitive (baseline and 6 months) and motor outcomes (3, 6 and 12 months) and a more varied sample to include unilateral and bilateral cases. Both neurologist and neuropsychologist were blinded to the grouping of patients until the end of the study, thereby reducing observer bias.

In our study, the average tremor improvement was 82 and 87% 3 and 12 months following surgery with no significant difference between the two groups. However, tremor control was obtained at lower stimulation frequencies in group B patients, suggesting that DTI-T-guided electrodes could be associated with a better outcome. This has been confirmed in subsequent studies, the results of which will be released later this year. Subtle declines in immediate memory and phonemic verbal fluency were noted in either group but did not reach statistical significance. There was a trend towards greater decline in semantic verbal fluency ($p = 0.052$) and clinically meaningful memory changes (defined as 40% decline from their baseline performance) in the conventional group only. There was no statistical difference in neurocognitive and psychological outcomes of patients undergoing uni- or bilateral electrode implantations but this may be a function of the small sample size. Stimulation parameters or demographics did not differ significantly between the two groups.

We are surprised to find that alterations in neurocognitive function were not observed in the patients of Ledermann et al. Postoperative cognitive declines particularly in verbal fluency and memory have been consistently reported following DBS in ET patients, and this is mirrored in our series. With respect to PSA-DBS there is emerging evidence of both transient and more lasting cognitive changes in a subset of patients [4, 5]. The former have been speculated to be attributable to microlesional/oedema effects and the latter to permanent changes to neuroanatomical structures. One difference between the two studies relates to stimulation effects, which were absent in the study of Ledermann et al. With thalamic DBS for ET, effects of stimulation have been postulated to account for postoperative memory [6] and verbal fluency [7] changes. Conclusions regarding stimulation effects on cognition in PSA-DBS ET patients are limited to one study at present which only analysed verbal fluency outcomes in 17 patients 3 days and 1 year after zona inserta DBS surgery [5]. These authors found no effect of stimulation on verbal fluency at either follow-up, concluding that a structural lesion is likely to account for the residual verbal fluency decrements in 24% of their sample at the 1-year follow-up. We did not compare performance on cognitive tests with stimulators switched on and

off and therefore cannot infer whether cognitive changes are attributed to stimulation, microlesioning or indeed a combined or selective cognitive effect. However, stimulation effects per se would not offer an explanation for the observation of greater semantic verbal fluency and memory decrements in group A versus group B in our study. We postulate that the use of DTI-T in electrode insertion may be associated with better cognitive outcomes by way of avoiding functional pathways along the cerebellothalamocortical networks involved in memory and verbal fluency skills.

An alternative explanation for the difference between our findings and those of Ledermann et al. may relate to differences in sensitivities of tests utilised and/or the method of data analysis. It is not clear from their paper whether they included measures of word fluency, given that the Frontal Lobe Score was utilised. Phonemic (letter) fluency has been found to be sensitive both to the effects of DBS surgery in ET patients and predictive of postoperative cognitive declines [7]. Ledermann et al. provide only group scores on the Frontal Lobe Score which may mask significant individual performance changes. It is only with scrutiny of individual test results before and after surgery that meaningful changes in a subset of patients are revealed; whether this reflects individual susceptibility (possibly due to age, disease severity and/or pre-operative cognitive impairment) or surgical technique is important to understand for DBS patient selection [8] and requires further investigation with larger sample sizes and detailed neuropsychological test batteries. Nevertheless, at least with respect to our preliminary findings, DTI-T offers the promise of a technique to ensure optimal neurocognitive outcomes following surgery for ET and confirms that stimulation or lesioning within the cerebellothalamic tract is safe.

References

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