Cognitive declines after deep brain stimulation are likely to be attributable to more than caudate penetration and lead location

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Sir, We have read the follow-up paper from the German multi-centre randomized deep brain stimulation (DBS) trial (Witt et al., 2013) with great interest. The authors conducted a study investigating the relationship between DBS lead trajectory and cognitive decline after surgery performed in patients with Parkinson’s disease. They concluded that penetration of the caudate nucleus was a risk factor for global cognitive decline, and that suboptimal placement of the electrode outside of the subthalamic nucleus (STN) also increased the risk of verbal fluency decline. These were interesting findings, however, we strongly suspect that these two issues make up only a subset of what is likely multiple factors affecting DBS cognitive outcome. The pathophysiology of cognitive decline in Parkinson’s disease is complex, and cognitive decline after STN DBS may be affected by baseline cognitive dysfunction, brain atrophy, and by surgical complications (e.g. intracranial haemorrhage).

To more closely examine this issue, we retrospectively reviewed the prospectively measured and documented cognitive function of our patients with Parkinson’s disease who underwent STN DBS and correlated them with the DBS lead trajectories. Patients in our cohort had a CT scan, T1-weighted MRI and the fast grey matter acquisition T1 inversion recovery (FGATIR) MRI sequence (Sudhyadhom et al., 2009) between July 2008 and December 2012. We included only patients with Parkinson’s disease who underwent STN DBS and completed pre- and postoperative cognitive tests without severe surgery-related adverse events such as intracranial haemorrhage. The outcome measures included the Dementia Rating Scale-II, Digit Span from Weschler Adult Intelligence Test-III (WAIS-III), delayed recall from two memory measures (Hopkins Verbal Learning Test-II, Logical Memory Stories from Weschler Memory Scale-III), Boston Naming Test, Controlled Oral Word Association Test, Trail Making Test, and Stroop Colour-Word Test. We reviewed the trajectory of each DBS lead using a CT-MRI fusion technique, and we identified patients with or without caudate penetration (Fig. 1). We then compared the extent of cognitive decline using hierarchical linear regression, controlling for baseline (pre-DBS) cognitive performance. Twenty-nine patients with Parkinson’s disease (24 males, five females) were included, and the DBS electrode penetrated the caudate nucleus in 12 cases. We classified these 12 cases into deep (n = 5) and superficial (n = 7) penetration groups. Deep penetration trajectory passed at least 3 mm medial to the lateral border of the caudate nucleus. The mean age was 63.9 years (standard deviation 6.6), and the mean follow-up period was 15 months. Although there was cognitive decline on some measures (i.e. fluency, digit span, executive function), this decline was unrelated to caudate penetration. There were no significant differences in cognitive outcomes between the two caudate penetration groups and the non-caudate penetration group (Table 1). Also, a medial trajectory with larger volume of caudate penetration was not associated with a worse outcome.

Although Witt et al. (2013) identified the lead trajectories in normalized brain space, we measured these using direct visualization of the DBS trajectory using an image fusion technique. Although the
described methods in the Witt et al. (2013) paper appeared to be valid, it might be meaningful to examine the original postoperative data in each case to confirm the accuracy of the lead trajectory. Most of the data from our series were derived from patients with unilateral DBS, but could be argued that unilateral cases may more accurately address the question, as only one trajectory would need to be considered as potentially causative. This would remove the ambiguity introduced in the cases of bilateral patients. It is also possible that the observed cognitive decline could have been because of the additive effect of the second lead (Alberts et al., 2008). In addition, a recent retrospective study revealed that transgression of the lateral ventricle was a risk factor for cognitive decline after STN DBS (Gologorsky et al., 2011). Trajectories with deep caudate penetration are obviously relatively medial, and more likely to transgress the lateral ventricle. Ventricular transgression might thus have contributed to the cognitive declines observed in the Witt et al. (2013) study. Taken together, these findings suggest that there are likely more factors that determine cognitive decline after DBS than caudate penetration and anatomic lead location.

Table 1 No difference in cognitive performance due to extent of caudate penetration

<table>
<thead>
<tr>
<th>Measure</th>
<th>No caudate penetration</th>
<th>Superficial caudate penetration</th>
<th>Deep caudate penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia Rating Scale-II</td>
<td>−0.175 (1.03)</td>
<td>0.240 (0.66)</td>
<td>0.0 (0.85)</td>
</tr>
<tr>
<td>Letter Fluency (COWA)</td>
<td>−0.434 (0.73)</td>
<td>−0.914 (0.77)</td>
<td>−0.260 (0.87)</td>
</tr>
<tr>
<td>WAIS-III Digit Span</td>
<td>−0.042 (0.75)</td>
<td>−0.616 (0.41)</td>
<td>−0.202 (0.55)</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>−0.119 (0.98)</td>
<td>0.343 (0.61)</td>
<td>0.220 (0.60)</td>
</tr>
<tr>
<td>Executive Function Composite</td>
<td>−0.200 (0.65)</td>
<td>−0.425 (0.79)</td>
<td>−0.460 (0.79)</td>
</tr>
<tr>
<td>Verbal Memory Composite</td>
<td>−0.152 (0.66)</td>
<td>−0.441 (1.01)</td>
<td>−0.134 (1.08)</td>
</tr>
</tbody>
</table>

Table shows z-score differences (mean = 0, SD = 1) of post-DBS minus pre-DBS cognitive scores. Standard deviations are in brackets.

No group differences were statistically significant based on hierarchical linear regression analyses using either two (caudate/non-caudate) or three group (non-caudate/superficial, deep) classification. Executive function composite is the average of Stroop Color-Word and Trail Making Test B z-scores. Verbal memory composite is the average of delayed recall scores from Logical Memory (WMS-III) and Hopkins Verbal Learning Test. COWA = Controlled Oral Word Association Test.

**References**


