LETTER TO THE EDITOR

Reply: 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 thank Dr Morishita and colleagues (2014) for their interest and valuable contribution. Many studies report a slight decline in cognitive functioning after subthalamic nucleus (STN) stimulation for Parkinson’s disease (Parsons et al., 2006; Witt et al., 2008). The observed neuropsychological sequelae are likely caused by several independent factors: first, there is a patient-inherent risk profile including age, impaired attention, higher antiparkinsonian medication, higher scores on axial motor symptoms and a lower L-DOPA response before surgery (Smeding et al., 2009; Daniels et al., 2010). However, these patient-related factors explain only 23% of the variance of postoperative decline (Daniels et al., 2010). In our study we found penetration of the caudate nucleus to be associated with an increased risk for a decline in global cognitive functioning and working memory abilities (Witt et al., 2013). Furthermore, we were able to show that an additional factor is the placement of the stimulated electrode contact. We concluded, that besides the well-known inherent risk factors (age and disease progression), the electrodes track and the placing of the active electrode contributes significantly to the cognitive changes reported after STN-deep brain stimulation (DBS) for Parkinson’s disease.

Morishita et al. (2014) performed a retrospective analysis in 29 patients with Parkinson’s disease after unilateral STN-DBS. In 12 of these patients the lead of the electrode passed the caudate nucleus. The authors failed to show significant neuropsychological changes in association with the caudate lesioning and asked if a ventricular transgression might be the cause of cognitive changes in our study. None of our cases had a ventricular transgression, which can be avoided during surgical planning. Therefore this reason cannot account for the differences. The question may be asked why they failed to find this effect, which was so strong in our cohort. Several differences limit the comparability of both studies: (i) they included only 25 patients in their analysis and no controls. Our final analysis included 62 patients with Parkinson’s disease with 31 operated patients. The 31 control patients served to disentangle the effect of DBS surgery from the natural disease progression, which was not possible in Morishita et al.’s study; (ii) they observed 25 unilateral DBS patients, whereas in our study observed only one unilateral DBS patient (3%), but 30 (97%) bilateral DBS patients were analysed. Twelve patients showed bilateral caudate nucleus lesions, seven unilateral right-sided and seven patients unilateral left-sided lesion. We assume that it is important if the caudate is penetrated bilaterally; (iii) it is not reported where the caudate lesions were placed in the cohort of Morishita et al. They only show one example with a lesion in the body of the caudate whereas all of our cases had a penetration of the head of the caudate (at height $z=16$ in normalized brain space; see Fig. 2 in Witt et al., 2013), while the body of the caudate was nearly unaffected (see Fig. 1, showing all of our trajectories at normalized MNI coordinate $z=23$). Both tail and head of the caudate nucleus have different cortical projections and different cognitive functions (Cincotta and Seger, 2007; Grahn et al., 2008) and notably the head of the caudate is associated with working memory function (Grahn et al., 2008). Thus anatomical reasons may add to the difference; and (iv) in our study a deterioration in cognitive performance was defined as a decrease in task performance of >1 standard deviation (SD) compared with the control group. We choose this criterion because most of the cognitive changes after STN-DBS are mild, demonstrating a decline between 1 and 2 SD
compared to baseline performance. Morishita et al. performed statistical tests based on a hierarchical linear regression analysis which may limit the sensitivity of testing.

But despite the differences between the two studies, a closer look at the results of Morishita et al. (Table 1) showed that letter fluency and WAIS-III Digit Span Test worsened in the range between 1 and 2 SD in patients with a superficial caudate penetration, comparable with our results. This result closely resembles the cognitive deficits in the working memory domain in our results. Therefore the difference may disappear if controls, cohort statistical testing similar to ours were used. Because of the slight but significant changes of overall cognitive decline these are critical factors that must be controlled.

Finally our study does not claim that all cognitive decline after DBS is a result of the caudate penetration and lead location. The evolution of cognitive changes seen after STN-DBS is the result of a complex interplay of risk factors. In our study the penetration of the head of the caudate and the precise position of the active electrode are two determinants in this complex interplay that seem to be responsible for cognitive changes after STN-DBS. We are glad that our article has stimulated discussion and are convinced that a multicentre study is needed to consolidate and further elucidate the role of this important and completely preventable risk factor for cognitive decline following STN stimulation.

References


Morishita T, Okun MS, Jones JD, Foote KD, Bowers D. Cognitive declines after deep brain stimulation are likely to be attributable to more than caudate penetration and lead location. Brain 2014. Advance Access publication, February 11, 2014, Doi: 10.1093/brain/awu008.


