LETTER TO THE EDITOR

Reply: The challenges for research on deep brain stimulation and memory

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Sir,

We thank Drs van den Noort *et al.* (2015) and Fried (2015) for their interest in our study (Miller *et al.*, 2015) reporting improvement in visual-spatial memory during theta burst deep brain stimulation of the fornix in four individuals with temporal lobe epilepsy, a translational study previously tested in rodents by our team (Sweet *et al.*, 2014). While echoing our cautionary statements regarding interpretation, Dr Fried (2015) applauded the use of a unique clinical opportunity to provide intriguing preliminary data. Dr van den Noort *et al.* (2015) describe the study as being ‘highly innovative’, ‘a promising direction for various disorders’ and ‘a pioneering study’, adding that ‘it is a strength that the authors of the present study use neuropsychological tests’. Their group also raised some concerns, so we appreciate this opportunity to respond.

Dr van den Noort *et al.* (2015) stated that ‘stimulation settings were different from previous studies, making comparisons... impossible.’ It would have been ideal to directly compare paradigms within the same sample, but that would have required electrode placements in different sites, which was not feasible. Using identical outcome measures would have facilitated comparisons, but measures were diverse across studies. Moreover, our design required four equivalent forms to be validated for measuring mesial temporal function and sensitivity to change. In spite of the differences, we achieved results similar to other studies; we believe the consistency among studies using different stimulation settings at different sites within this anatomical network adds robustness to the findings and supports the

potential of stimulating this system for treatment of memory disorders.

Dr van den Noort *et al.* (2015) criticize the study for having no statistical analyses and a small clinical sample. Our case series was small in this pilot because of the invasive nature of electrode implantation. While we could capitalize on this unique clinical opportunity, not all patients required placement at the precise target for our research study, limiting the number of potential participants to four, which did not satisfy the assumptions of even non-parametric statistics. To this end, we analysed our data qualitatively and provided full disclosure in tabular and graphic formats for the reader to scrutinize, taking care not to overstate our findings.

Dr van den Noort *et al.* (2015) were concerned that we misled the reader regarding verbal memory. In the sentence they quoted, we attempted to be very transparent: ‘Combining trials within each patient, on active stimulation one improved by 100% whereas the other three patients declined...’ (p. 1837). Furthermore, in the ‘Discussion’ section we concluded: ‘the effect of stimulation on other functions such as verbal memory and naming appears to be much more complex, with considerable variability among patients on stimulation. Therefore, we cannot exclude the possibility that burst stimulation may be detrimental to some types of function in certain individuals’.

Finally, Dr van den Noort *et al.* (2015) wondered why we analysed raw scores rather than standardized scores. Standardized scores show where a person scores relative to a reference group; in Table 1 we provided such scores

(IQ, Verbal Memory Index and Visual Memory Index) to describe cognitive and memory functioning. For the outcomes of stimulation, each person served as his or her own control when comparing sham versus active stimulation using an established within-subject crossover design (Louis *et al.*, 1984).

Nonetheless, we agree that when appropriate reference data are available, observed scores and change can be interpreted within a normative framework. Loring and Meador (2003) published reference data on the Medical College of Georgia Complex Figures in 162 patients who had medically refractory epilepsy and associated memory impairment. Our four participants showed expected epilepsy-associated memory impairment without intervention (sham stimulation, mean = 20.1) compared to the larger refractory epilepsy group [mean = 21.0; standard deviation (SD) = 7.4], proving to be typical of that population (46th percentile). On active stimulation, our four patients improved (mean = 25.8) compared to the epilepsy norm (retest mean = 21.0; SD = 7.4), rising to the lower margin of high average range (76th percentile). This improvement cannot be attributed to practice effects because the ordering of sham and active stimulation was randomized. Furthermore, Loring and Meador's patients also underwent repeat testing with alternate forms just like our patients but on stable treatment with 0% change ($n = 162$; mean = 21.0 on both exams; SD of the difference = 5.6), whereas our patients improved 28% during active stimulation compared to sham stimulation (mean = 25.8 active versus 20.1

sham; SD = 1.08; large effect size). These additional comparisons increase confidence that the improvement observed in our study is both reliable (statistically significant change) and also clinically meaningful (improving to a higher classification).

Therefore, although our study is preliminary, we believe that the promising results observed add safely to the recent evidence in this line of inquiry and encourage further study and development of these therapeutics.

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