LETTER TO THE EDITOR

The challenges for research on deep brain stimulation and memory

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Sir,

With great interest, we read the article on the use of theta burst stimulation of the fornix to improve memory functions in four patients suffering from drug-resistant temporal lobe epilepsy (Miller *et al.*, 2015) and the commentary by Itzhak Fried (2015) on the possible applications of this new clinical intervention technique. Miller *et al.* (2015) conclude that the preliminary results of their small sample of patients with drug-resistant epilepsy suggest that theta burst stimulation of the fornix may be able to improve visual-spatial memory performance.

First, we want to complement Miller *et al.* (2015) on their highly innovative study and we agree with them that the use of deep brain stimulation of the fornix to improve memory functioning seems to be a promising direction for various disorders (Hamani *et al.*, 2008; Suthana *et al.*, 2012). Of course, we understand that a pioneering study like this has methodological shortcomings (mainly due to practical reasons, e.g. no statistical analyses, small clinical sample, stimulation settings different from previous studies making comparisons with previous results impossible, etc.). However, although it is a strength that the authors of the present study use neuropsychological tests, the way they interpret the neuropsychological data and the conclusions that are drawn based on these data, are, unfortunately, inadequate, and in some cases even misleading, as we will illustrate below.

The authors, for instance, report that there were no apparent differences on the Rey Auditory-Verbal Learning Test. However, if we take a closer look at those results (see Table 2 in their paper), we see clear differences between the sham and active stimulation condition. The average group result for the short-term retention is 76% for the sham condition versus 63% for the active stimulation condition; moreover, the scores of the long-term retention show a similar pattern, 68% for the sham condition versus 40% for the active stimulation condition. In our opinion, their remark that ‘combining trials within each patient, on active stimulation 1 improved by 100%’ is misleading, because the overall trend in their data (i.e. of the other three individuals) is clearly in the opposite direction and is even more in support of the hypothesis that burst stimulation of the fornix seems to be contraindicated for the auditory memory domain. Moreover, note that the authors use no statistical analyses to prove their conclusions and therefore it is especially important to discuss and interpret the observational data in an adequate and cautious manner (e.g. Vandembroucke *et al.*, 2007) and not to focus solely on the part that is in line with the hypothesis.

Furthermore, the reason the authors decided not to report and compare their results using the official clinical norm scores of their neuropsychological tests is unclear. For example, the authors write ‘For this study, the primary outcome was defined as per cent retained at the Delayed

Free Recall Trial' (i.e. does this mean the percentage of the original words learned that are correctly identified after the 20-min delay?). Note that a critical concept in neuropsychological testing is the use of norm scores (Harvey, 2012). To apply deep brain stimulation clinically for the improvement of memory functioning and to draw clinical conclusions using the clinical norm scores of the neuropsychological tests instead of raw/percentage scores is a requirement, as otherwise it is impossible to interpret and compare patient data (Harvey, 2012).

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