Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation with four cases

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Memory loss after brain injury can be a source of considerable morbidity, but there are presently few therapeutic options for restoring memory function. We have previously demonstrated that burst stimulation of the fornix is able to significantly improve memory in a rodent model of traumatic brain injury. The present study is a preliminary investigation with a small group of cases to explore whether theta burst stimulation of the fornix might improve memory in humans. Four individuals undergoing stereo-electroencephalography evaluation for drug-resistant epilepsy were enrolled. All participants were implanted with an electrode into the proximal fornix and dorsal hippocampal commissure on the language dominant (n = 3) or language non-dominant (n = 1) side, and stimulation of this electrode reliably produced a diffuse evoked potential in the head and body of the ipsilateral hippocampus. Each participant underwent testing of verbal memory (Rey Auditory-Verbal Learning Test), visual-spatial memory (Medical College of Georgia Complex Figure Test), and visual confrontational naming (Boston Naming Test Short Form) once per day over at least two consecutive days using novel test forms each day. For 50% of the trials, the fornix electrode was continuously stimulated using a burst pattern (200 Hz in 100 ms trains, five trains per second, 100 μs, 7 mA) and was compared with sham stimulation. Participants and examiners were blinded to whether stimulation was active or not, and the order of stimulation was randomized. The small sample size precluded use of inferential statistics; therefore, data were analysed using descriptive statistics and graphic analysis. Burst stimulation of the fornix was not perceived by any of the participants but was associated with a robust reversible improvement in immediate and delayed performance on the Medical College of Georgia Complex Figure Test. There were no apparent differences on either Rey Auditory-Verbal Learning Test or Boston Naming Test. There was no apparent relationship between performance and side of stimulation (language dominant or non-dominant). There were no complications. Preliminary evidence in this small sample of patients with drug-resistant epilepsy suggests that theta burst stimulation of the fornix may be associated with improvement in visual-spatial memory.

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Introduction

Memory loss associated with trauma or degenerative disease is a major public health problem and a source of considerable long-term morbidity, and even mild symptoms can be highly debilitating. In spite of many decades of research on memory loss, treatment is limited mostly to pharmacological stabilization of memory in some degenerative disorders or compensation of static deficits in cognitive rehabilitation but these interventions do not typically restore actual memory abilities in humans. Neuramodulation by deep brain stimulation of structures involved in memory processing has recently emerged as a potential strategy to ameliorate memory deficits in a variety of disease states, possibly by enhancing innate processing to unlock latent ability. There is strong evidence that the substrate for memory can be enhanced by indirect electrical stimulation of the hippocampus via its associated white matter tracts. In rodent models, 130 Hz stimulation of the entorhinal cortex (Stone et al., 2011) or fornix (Soriano-Mas et al., 2005; Hescham et al., 2013) is associated with significant improvement in spatial memory that is proportional to amplitude of stimulation, and 8 Hz stimulation of the fornix (McNaughton et al., 2006) or medial septal nucleus (Lee et al., 2012) is able to restore performance on spatial learning tasks and normalize search strategy after experimental lesions. In humans, stimulation of the fornix or perforant pathway has been shown to improve memory in one person with morbid obesity (Hamani et al., 2008) and in seven people with drug-resistant epilepsy (Suthana et al., 2012). A clinical trial in six people with Alzheimer’s disease has shown sustained increases in metabolism with continual stimulation over the course of a year and possible cognitive improvement or slowing of decline (Laxton et al., 2010; Smith et al., 2012). Another individual with Alzheimer’s disease showed similar results over the first year of stimulation (Fontaine et al., 2013).

The studies reported above used a range of stimulation targets, frequency and amplitude parameters, and temporal scales of the effect. Two other studies provide more direct evidence for the potential benefit of stimulation delivered to the hippocampus via the fornix. Shirvalkar et al. (2010) infused muscimol into the medial septum of Long-Evans rats to attenuate theta rhythm and impair memory for spatial episodes; they then stimulated the fimbria-fornix (FFx) to induce different oscillation patterns in the hippocampus, using three stimulation protocols: theta stimulation (7.7-Hz single pulses), 100-Hz stimulation (single pulses delivered at 100 Hz), and theta burst stimulation (7.7-Hz bursts off of single-pulse trains delivered at 500 Hz). Theta burst stimulation was the only stimulation protocol that improved spatial memory performance.

In addition, we have recently reported (Sweet et al., 2014) that fornix stimulation in a rodent model of traumatic brain injury has little effect on memory using standard and low-frequency stimulation. However, patterned stimulation using intermittent bursts in the theta range (five 50-ms trains per second) was associated with significant improvement in cognitively demanding tasks, possibly because it better replicates natural physiological activity in the hippocampus than tonic high-frequency stimulation (Sweet et al., 2014). If patterned stimulation of the fornix is capable of modulating memory processes, it might represent a novel therapeutic option for individuals who suffer from cognitive and memory disorders. An important first step is to establish the immediate effect of this paradigm on a variety of different memory functions. The present study is a preliminary clinical trial with a small case series to explore whether theta burst stimulation of the fornix might improve memory in humans.

Materials and methods

Participant population

Individuals undergoing implantation of stereo-EEG electrodes into the temporal lobe for evaluation of drug-resistant temporal lobe epilepsy were enrolled in the study. Each participant had undergone extensive preoperative testing, including video-EEG and comprehensive neuropsychological testing. Participants were excluded from the study if they had evidence of a structural brain lesion or general cognitive impairment, defined as full-scale IQ < 70 on preoperative neuropsychological testing. The study was reviewed and approved by our institutional review board. The subjects provided written informed consent to participate in the study.

Trajectory selection and electrode implantation

Depth electrodes (Integra Life Sciences) were implanted stereotactically using a Leksell frame and a volumetric CT scan coregistered to preoperative MRI. Each electrode consisted of 12 platinum-iridium cylinders measuring 1.1 mm in diameter and 2.3 mm in length, evenly spaced at 5-mm intervals. Trajectories were planned using the iPlan workstation (Brainlab). Electrode arrays were implanted into the head and body of the hippocampus via a lateral approach. An additional electrode array was targeted to the posterior fornix just behind the tail of the hippocampus, with the terminal electrode implanted into the dorsal hippocampal commissure and the next two electrodes parallel to and adjacent to the fornix (Fig. 1). Electrodes were implanted under general anaesthesia using stab incision and a 2.1 mm twist drill to make a small burr hole; intraoperative fluoroscopy was used to verify accuracy of placement, and stimulation of the fornix electrodes was performed intraoperatively to record evoked potentials in the hippocampal head and body. A volumetric CT was obtained to verify electrode location by co-registration with presurgical volumetric MRI (Fig. 1).
Evoked potential recording and theta burst stimulation

Starting on postoperative Day 2, participants underwent analysis of hippocampal-evoked potentials in the awake state followed by neuropsychological testing during theta burst stimulation. All procedures were performed in the epilepsy monitoring unit, and all stimulation was performed using a Medtronic External Neurostimulator Trialing Unit (Model 37022) controlled by the N’Vision Clinician Programmer (Model 8840) and interfaced with the intracranial electrodes via a screening cable with alligator clips (Model 3550-67). Bipolar stimulation (0.1 ms, 2 Hz) of two adjacent electrodes in the fornix electrode was performed at 0–10 mA and an

Figure 1 Targeting of fornix and hippocampus. (A and B) Preoperative MRI was used to identify a trajectory passing through the fornix and terminating in the dorsal hippocampal commissure. Fusion between preoperative MRI and postoperative CT was used to demonstrate electrodes located in the fornix on (C) coronal and (D) axial views, as well as electrodes in the hippocampal (E) head and (F) body. White arrows indicate the relevant electrode contact.
evoked potential was recorded in the hippocampus head and body to define an input-output curve. Theta-burst stimulation was performed using the same contacts using 0.1 ms pulses at 200 Hz in 100 ms trains, five trains per second, which was accomplished by setting the neurostimulator to cycle 0.1 s on and 0.1 s off (Fig. 2).

Neuropsychological testing paradigm

Each participant underwent repeated neuropsychological testing sessions on consecutive days. Active stimulation (7 mA) was delivered during half of the sessions and sham stimulation (0 mA) during the other half. Stimulation was activated at least 20 min before the beginning of the testing session. The order of active and sham testing was established by computer randomization, and the participants and examiners were blinded to whether stimulation was active or not. During each testing session, three neuropsychological tests were administered using alternate, equivalent forms to minimize potential retest/practice effects. The order of the tests was designed to allow a single 60-min testing session of both immediate and delayed memory (Fig. 3). Alternate, equivalent forms for each test (Medical College of Georgia Complex Figure Test, Rey Auditory Verbal Learning Test and Boston Naming Test) were randomized between active and sham stimulation trials a priori.

Rey Auditory Verbal Learning Test

In the Rey Auditory Verbal Learning Test (Rey, 1964), the examiner reads a 15-item word list at a fixed rate, and the examinee is asked to repeat as many words as he or she can remember after each of five presentations. The sum of the five trials provides a sensitive index of efficiency of acquisition. Recall (Immediate Free Recall) is tested again after the examinee is required to repeat a distraction list (List B) and again 20 min later (Delayed Free Recall), followed immediately by a Recognition Trial (discriminating the original 15 targets from 35 distractors). This test is especially sensitive to integrity of left mesial temporal networks (Loring et al., 2008). This study used six alternate forms developed by Fastenau (Fastenau et al., 2001, 2002; Fastenau, 2002), which have been shown to be equivalent to one another and resistant to retest effects in clinical trial paradigms in prior studies by Beglinger et al., 2003, 2005. Dependent variables include total words reported across the five learning trials (Sum of Trials I–V), Immediate Free Recall, Delayed Free Recall (long-term memory), and Recognition Accuracy. For this study, the primary outcome was defined as per cent retained at the Delayed Free Recall Trial (i.e. percentage of the original words learned that are correctly identified after the 20-min delay).

Medical College of Georgia Complex Figure Test

The Medical College of Georgia Complex Figure Test (MCG-CF; Loring and Meador, 2003) requires examinees to reproduce a complicated line drawing, first by copying freehand (Copy Trial) and then drawing it from memory immediately afterward (Immediate Recall) and again after 20–30 min (Delayed Recall). The MCG-CF has four alternate forms that have been shown to be equivalent to one another and resistant to retest effects (Yasugi and Yamashita, 2010) and have also been shown to be resistant to retest effects (Yasugi and Yamashita, 2010). All drawings were scored independently by two trained psychometrists and the average ratings were used for each drawing; the scoring system for the MCG figures was derived from the scoring for the Rey-Osterrieth Complex Figure Test, which has been shown to have excellent interrater reliability ranging 96–97 for copy and memory trials (Fastenau et al., 1996). Dependent variables include performance during the copy, immediate, and delayed recall phases. For this study, delayed recall was analysed as the primary outcome.

Boston Naming Test

The Boston Naming Test (Kaplan et al., 1983) is a test of visual confrontational naming that is used to identify potential language disturbance. The examinee is shown a series of line drawings of familiar objects, which increase in word-retrieval difficulty from beginning to end. The examinee is allowed 20 s to identify each one then semantic cue is provided (allowing another 20 s to retrieve the name of the object), and finally a
phonemic cue is provided if the examinee has not yet responded correctly. The full-length test consists of 60 items, but four 15-item short forms were developed and validated for retest protocols (Mack et al., 1992; Fastenau et al., 1998). During testing, the examiner records the response and the time required to generate each response; for this study, the times to give the initial responses (response latencies, maximum of 20 s per item) were summed across the 15 items as well as for the last three items (which are the three most difficult items on each alternate form). The primary outcome was defined as latency across the entire test.

Statistical analysis
Statistical analyses were performed using the Statistical Package for the Social Sciences v17.0 (SPSS). For each participant, performance during sham stimulation was used as a control. If more than one testing session was performed within a stimulation condition, the arithmetic mean of scores across the two sessions was used for analysis. The small sample size precluded use of inferential statistics; therefore data were analysed using descriptive statistics and graphic analysis.

Results
Study population
Four participants were enrolled in the study. Demographic, epilepsy, and preoperative neuropsychological data are shown in Table 1. There were two males and two females, average age 32.0 years, with an average duration of epilepsy of 20.5 years. On preoperative assessment, average Wechsler Adult Intelligence Scale Fourth Edition (WAIS-4; Wechsler, 2008) full-scale IQ was 88.3 [standard deviation (SD) = 11.0], and preoperative memory scores were 101.5 (SD = 6.2) and 97.5 (SD = 13.9) for the Wechsler Memory Scale, Third Edition (WMS-III; Wechsler, 1997) Delayed Auditory-Verbal Memory Index and Delayed Visual Memory Index, respectively. Because the experimental protocol did not allow for prolonged monitoring beyond what was necessary for clinical purposes of the epilepsy workup, one of the participants (Patient 3) underwent only two testing sessions (one active and one sham); the other three underwent four sessions (two active and two sham). All four participants underwent Wada testing that demonstrated left-sided dominance for both speech and memory.

Table 1 Baseline demographic and neuropsychological data

<table>
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<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Handedness</th>
<th>Dominant hemisphere</th>
<th>Side of implant</th>
<th>Full scale IQ</th>
<th>Verbal memory immediate</th>
<th>Verbal memory delayed</th>
<th>Visual memory immediate</th>
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Table 2 Neuropsychological testing data

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<td>97</td>
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Evoked potential recording and theta burst stimulation
In all cases, robust evoked potentials were recorded from the ipsilateral hippocampus head and body with stimulation of the fornix (Fig. 4A). Latency ranged from 6–20 ms, with earlier responses generally seen in the body than in the head, presumably because the recording electrode was closer to the stimulating electrode. Input-output curves (Fig. 4B) showed incremental increase in response with a plateau between 8 and 10 mA. All participants had excellent evoked potentials at 7 mA, which was the amplitude used for theta burst stimulation during testing. None of the participants were able to perceive either single pulse or theta burst stimulation. No after-discharges or seizures occurred during or immediately after stimulation, and no other adverse effects were noted. In addition, there were no clinical or electrophoretic seizures within 6 h before or after the testing sessions.

Neuropsychological testing
Neuropsychological testing data are presented in Table 2. In addition, they are depicted graphically in Figs 5 and 6.

For visual-spatial memory (MCG), active stimulation was associated with improvement in six of seven paired trials across the four patients; change was negligible on the seventh paired trial (Fig. 5A). Combining trials within each patient, all four patients showed improvement on active stimulation (range = +12% to +44%; mean = +28%, median = +29%) (Fig. 6A).

For verbal memory (Rey Auditory Verbal Learning Test), active stimulation was associated with decline in five of seven paired trials across the four patients; improvement was noted in the other two paired trials (Fig. 5B). Combining trials within each patient, on active stimulation 1 improved by 100% whereas the other three patients declined (−12% to −100%; for all patients, mean = 24%, median = −45%) (Fig. 6B).

For confrontational naming (Boston Naming Test), active stimulation was associated with shorter response latencies (faster retrieval) in four of seven paired trials and longer response latencies (slower retrieval) on three paired trials (Fig. 5C). Combining trials within each patient, on active stimulation two of four patients had shorter response latencies (52% faster for both patients), and two of the...
four patients had longer response latencies (+66% to +296%) (for all patients, mean = 64% longer response latencies, median = 7% longer response latencies) (Fig. 6C).

Discussion

This preliminary study with a small sample of four cases suggests that theta burst stimulation of the fornix using a paradigm that is feasible with commercially available implanted neurostimulator devices might produce reversible improvements in visual-spatial memory. Based on this initial pilot sample, it seems that this stimulation paradigm might be safe and well tolerated for short periods without discomfort or increase in seizures and might not worsen either verbal memory or naming.

Previous investigations into deep brain stimulation of structures that project to the mesial temporal lobe have addressed two distinct targets: the dorsal fornix and the perforant pathway. The dorsal fornix target was discovered serendipitously during a study of deep brain stimulation of the hypothalamus for obesity during which vivid memories were evoked due to inadvertent stimulation of the columns of the fornix, located just posterior to the hypothalamus (Hamani et al., 2008). Chronic stimulation at this location was associated with significant improvement in verbal memory compared with the preoperative state (Hamani et al., 2008). Based on these findings, several clinical trials have been launched using this target as a potential treatment for Alzheimer’s type dementia (Laxton et al., 2010; Smith et al., 2012; Fontaine et al., 2013). These studies have documented stabilization of memory scores and changes in metabolism after implantation, although the cumulative effect on cognitive testing was modest. Stimulation of the perforant pathway was examined in a study of seven individuals undergoing depth electrode evaluation for epilepsy using a spatial learning task that involved navigation of a virtual environment. Stimulation during the learning phase was found to produce significant improvement on performance of the task (Suthana et al., 2012). The mechanism by which these effects occur is not clear but may involve structural or synaptic changes,
Our stimulation strategy differs from previous studies in two important ways. First, we implanted electrodes quite posterior, in the crus of the fornix anterior to the splenium of the corpus callosum. The entry point required for this approach is in the posterior temporal lobe, distant from the classic bur hole used for deep brain stimulation. However, this target is larger and much closer to the hippocampus, so it may allow more specific activation of fibres for diffuse activation of the hippocampus. Second, unlike previous studies that have used stimulation parameters similar to what is used for treatment of movement disorders, we investigated patterned stimulation with five 0.1 s bursts per second. This decision was made based on our previous study on the analogous target in rats where we found that stimulation using a theta burst paradigm (200 Hz in five 50-μs trains per second) is superior to either high frequency (130 Hz) or low frequency (5 Hz) stimulation in improving performance on spatial tasks after traumatic brain injury (Sweet et al., 2014). This pattern replicates naturally occurring firing observed in the hippocampus, including complex spikes that fire in phase with theta rhythm, and has previously been shown to have widespread effects on cellular and network processes underlying memory (Diamond et al., 1988; Martin et al., 2000). In comparison with traditional stimulation methods, theta burst stimulation may have a more robust effect on intrinsic oscillation patterns, which might make the hippocampus more receptive to memory encoding (Winson, 1978; Larson and Lynch, 1986). Similarly, recent studies using patterned stimulation in spinal cord stimulation have shown promising results (De Ridder et al., 2010).

To our knowledge, this is the first study (albeit, small and preliminary) to use validated neuropsychological tests to demonstrate that brain stimulation might lead to improvement in memory in a blinded, sham-controlled manner. Our initial hypothesis was that stimulation on the dominant side would improve verbal memory and stimulation on the non-dominant side would improve visual memory. The finding that stimulation of either side improved figural memory likely reflects the role of both the right and the left hippocampus in spatial operations, especially for spatial relationships (Nadel et al., 2013), such as the relative locations of objects embedded within the MCG Complex Figures.

### Table 2

Impact of fornix theta burst stimulation on Rey Auditory Verbal Learning Test, Medical College of Georgia Complex Figures and Boston Naming Test scores

<table>
<thead>
<tr>
<th>Medical College of Georgia Complex Figures</th>
<th>Complex figures copy off</th>
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<th>Complex figures immediate off</th>
<th>Complex figures immediate on</th>
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<table>
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| Boston Naming Test                        | Naming off†              | Naming on†              | Naming (last 3) off          | Naming (last 3) on           |                               |                           |                           |
|------------------------------------------|--------------------------|-------------------------|------------------------------|-------------------------------|                               |                           |                           |
| Patient Side of implant                  |                          |                         |                              |                               |                               |                           |                           |
| 1                                         | D                        | 49.5                    | 82.5                         | 8.3                           | 15.0                          |                           |                           |
| 2                                         | D                        | 92.5                    | 42.0                         | 41.5                          | 19.0                          |                           |                           |
| 3†                                        | N                        | 26.0                    | 103                          | 11.0                          | 60.0                          |                           |                           |
| 4                                         | D                        | 37.5                    | 18.0                         | 4.7                           | 4.8                           |                           |                           |
| Average                                   |                          | 51.4                    | 61.4                         | 16.4                          | 24.7                          |                           |                           |

*Off* and *On* refer to sham (0 mA) and active (7 mA) stimulation, respectively. For side of implant: N = language non-dominant; D = language dominant. Average of two testing sessions is shown, except for one participant (†) who underwent a single testing session under each experimental condition. †Primary outcome measure.
Figures. The hippocampus is known to play a pivotal role in spatial learning and memory; our results suggest that spatial processing may be more amenable to neurostimulation than processing of verbal information. Previous studies have documented that stimulation of the perforant pathway produces improvement in spatial navigation and route learning, and this works equally well during stimulation of either the language-dominant or language non-dominant temporal lobe (Suthana et al., 2012). Future research with larger samples will help to refine the stimulation target and/or stimulation parameters, which may allow for targeting of additional regions and/or at alternate settings, possibly with a greater effect on spatial memory as well as other aspects of memory processing. Such research will be important for clarifying and enhancing clinical use.

There seemed to be a rather consistent and reversible improvement in visual-spatial memory with stimulation across all study participants in this small sample.
However, 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. In addition, the history of seizures in all participants and proximity of the epileptogenic zone may also play a role. Regardless of the cause, the beneficial effect of stimulation on figural memory appears to be at least as great as any potential deleterious effect on other functions.

There are several important limitations to the interpretation of the results of this study. First, the number of participants is very small. A larger cohort would be ideal, but this is an invasive neurosurgical procedure that is not without risk; thus, it cannot be carried out easily in large numbers of patients until pilot data—such as those we present here—help to justify continuing with further research. Nonetheless, even within this small, preliminary study there seems to be a pattern of improvement in visual-spatial memory scores during active stimulation across all four patients, which warrants further formal investigation with a larger sample. As an extension of the small sample size, both dominant and non-dominant sides were implanted but could not be compared; future research with larger samples could formally test outcomes by side of stimulation, as well.

Second, all of the individuals in this study had drug-resistant epilepsy arising from the ipsilateral hemisphere, which may have affected the physiology of the mesial temporal structures. On the other hand, most participants in this study also had memory scores in the normal range, which might have limited their potential for improvement. In our animal study of theta burst stimulation of the fornix, we identified the greatest impact when memory was most significantly impaired, and the effect in non-traumatized animals was fairly modest (Sweet et al., 2014). Third, because stimulation occurred continuously during testing, it is not possible to differentiate whether improvement was due to effects on encoding, retrieval, or both. Fourth, the stimulation settings we used were different from previous human studies, and this precludes direct comparison with prior work in this area. Finally, we cannot rule out that these findings might be an artefact of greater arousal generically rather than a specific effect on memory, although the fact that improvement was consistently seen in a single test (and not on measures of naming latency) makes it less likely.

### Conclusion

Stimulation of the fornix produces an evoked response in the hippocampus, and theta burst stimulation of this target appears to be associated with improvement in visual-spatial memory within this very small sample. These preliminary data support further study with larger samples to evaluate the utility of this strategy for the treatment of individuals who suffer from memory deficits due to brain injury or degenerative disease.

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