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REPORT

Evidence for verbal memory enhancement with electrical brain stimulation in the lateral temporal cortex

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Direct electrical stimulation of the human brain can elicit sensory and motor perceptions as well as recall of memories. Stimulating higher order association areas of the lateral temporal cortex in particular was reported to activate visual and auditory memory representations of past experiences (Penfield and Perot, 1963). We hypothesized that this effect could be used to modulate memory processing. Recent attempts at memory enhancement in the human brain have been focused on the hippocampus and other mesial temporal lobe structures, with a few reports of memory improvement in small studies of individual brain regions. Here, we investigated the effect of stimulation in four brain regions known to support declarative memory: hippocampus, parahippocampal neocortex, prefrontal cortex and temporal cortex. Intracranial electrode recordings with stimulation were used to assess verbal memory performance in a group of 22 patients (nine males). We show enhanced performance with electrical stimulation in the lateral temporal cortex (paired t-test, $P = 0.0067$), but not in the other brain regions tested. This selective enhancement was observed both on the group level, and for two of the four individual subjects stimulated in the temporal cortex. This study shows that electrical stimulation in specific brain areas can enhance verbal memory performance in humans.

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Introduction

Deficits in memory and cognition present a major therapeutic challenge in a wide spectrum of brain disorders (Harrison and Owen, 2001). There is a need for new approaches to cognitive enhancement that would target specific brain regions and thus overcome limitations of current pharmacological and behavioural therapies (Sahakian *et al.*, 2015). Electrical stimulation of discrete areas in the brain has been applied to a range of neurological and neuropsychiatric disorders without a clear understanding of how it modulates electrophysiological activities (Johnson *et al.*, 2013), and little is known specifically about the effect of direct electrical stimulation of the brain on memory. Recent studies have reported mixed effects using various approaches to stimulation in mesial temporal lobe structures (Kim *et al.*, 2016), including the hippocampus (Coleshill *et al.*, 2004; Suthana *et al.*, 2012; Fell *et al.*, 2013; Jacobs *et al.*, 2016), entorhinal cortex (Suthana *et al.*, 2012; Fell *et al.*, 2013; Jacobs *et al.*, 2016), and fornix (Hamani *et al.*, 2008; Miller *et al.*, 2015). Positive effects reported in these studies were observed either in a single case study (Hamani *et al.*, 2008) or on the level of a group of patients stimulated in a specific brain region (Suthana *et al.*, 2012; Miller *et al.*, 2015). All of these studies investigated different memory functions using a variety of spatial and non-spatial tasks in patient population presenting a range of cognitive performances.

In this study we aimed to compare the effect of direct brain stimulation on memory performance in four brain regions supporting declarative memory (Eichenbaum, 2000), including two regions outside of the mesial temporal lobe: dorsolateral prefrontal cortex and lateral temporal cortex. Direct electrical stimulation of the lateral temporal cortex was previously shown to evoke multi-sensory experience of past events (Penfield and Perot, 1963), but was not explored in a paradigm to assess memory enhancement. We used classic tasks for verbal memory performance (Kahana, 2012) to study the effect of stimulation on memory in individual patients and across groups of patients stimulated in the four brain regions.

Materials and methods

The effect of stimulation on memory performance was investigated in epilepsy patients undergoing evaluation for resective surgery with intracranial subdural and depth electrode arrays in multiple cortical and subcortical brain regions. In this study we focused on 22 patients implanted in the four brain regions (Table 1) of the cortical-hippocampal declarative memory system (Eichenbaum, 2000). Basic clinical information together with the epilepsy pathology and verbal memory performance is summarized in Table 1. Following implantation, each patient participated in delayed free-recall memory tasks. The tasks were based on classic paradigms for probing verbal memory (Kahana, 2012), in which subjects learned lists of words for subsequent recall (Fig. 1A). Subjects were instructed to study lists of individual words presented sequentially on a laptop computer screen for a later memory test. Each word remained on the screen for 1600 ms, followed by a random jitter of 750–1000 ms blank interval between stimuli. Immediately following the final word in each list, participants performed a distractor task (20 s) consisting of a series of arithmetic problems. Following the distractor task participants were given 30 s to verbally recall as many words as possible from the list in any order. Each session consisted of 25 lists of this encoding-distractor-recall procedure.

Electrical stimulation was applied between pairs of adjacent electrode contacts in the specific brain regions during encoding of words for subsequent recall (Fig. 1A), using a fixed set of parameters (Table 1 and Supplementary material) taken from a recent report of memory enhancement (Suthana *et al.*, 2012). Only the amplitude parameter was varied within a fixed narrow range with respect to other clinical factors related to safety and patient treatment. Each patient was stimulated in one to two brain targets and here we focused on the targets localized in the four brain regions of the declarative memory system. Specific electrodes in the target brain region were selected based on the previously described subsequent memory effect (Kahana, 2006; Sederberg *et al.*, 2007) in the high gamma range (Supplementary material). Safe current amplitude for stimulation was determined for the chosen electrodes in a pre-test evaluation of after-discharges (Supplementary material). At least two stimulation sessions in one of the four brain regions studied were required to be included in the data analysis (Table 1) to ensure adequate number of samples to estimate mean performance on the non-stimulated lists ($n > 5$ lists). Additional data from single stimulation sessions were also compared as well as subset of data from stimulation of the language-dominant hemisphere (Supplementary material). In the studied group of 22 subjects there were seven stimulated in the parahippocampal region, six stimulated in the hippocampus, four stimulated in the temporal cortex, six stimulated in the prefrontal cortex, with one subject stimulated in two of these regions (Table 1). The number of sessions performed with each patient was determined by the length of seizure monitoring (range ~2–14 days) and willingness to participate in the study. The stimulation sessions were preceded by at least two record-only control sessions with no stimulation to familiarize subjects with the tasks and reduce potential learning effects. Subjects were instructed about the stimulation procedure but were blinded to the location of the stimulation site. Before starting any stimulation session the experimenter

Table 1 Summary of the patient clinical profiles and the stimulation experiments used to assess the effect on memory encoding

Subject	Age	Gender	Handedness	SOZ	MRI	Brain pathol.	Language laterality	Stim.	vIQ	Verbal	Sessions	Localization	Target region	Electrode type	Amp. (mA)	Freq. (Hz)	Pulse width (ms)	Duration (s)
1001	48	F	R	Right TC	Normal	Gliosis	L (fMRI)	-	81	None	2	Left HP	HP	Depth	1	50	0.3	4.6
1006	20	F	R	Right FC	MCD	Gliosis	L (fMRI)	-	91	None	2	Right HP	HP	Depth	1	50	0.3	4.6
1016	31	F	R	Left FC	Normal	Gliosis	-	None	71	None	2	Left PF	PF	Subdural	3.5	50	0.3	4.6
1018	47	M	L	Left FC, left FPC	Normal	-	L (fMRI)	-	85	None	2	Left PF	PF	Depth	1.5	50	0.3	4.6
1020	48	F	L	Right TC, right FC	Abnormal	Gliosis	L (fMRI)	-	98	Mild	4	Right HP	HP	Depth	1	50	0.3	4.6
1022	24	M	R		Atrophy, gliosis / encephalomalacia	-	L (fMRI)	-	81	None	2	Left HP	HP	Depth	1	50	0.3	4.6
1024	36	F	R	Right OPC	Normal	Gliosis	L (unknown)	-	100	None	3	Left HP	HP	Depth	1	50	0.3	4.6
1026	24	F	R	Left ATC, left OC	MTS, Gliosis	-	Bilateral (Wada)	-	112	None	4	Left EC	PH	Depth	0.5	50	0.3	4.6
1027	48	M	R	Right TC, right IC, right/left FC	Abnormal	-	L (fMRI)	-	93	None	2	Left HP	HP	Depth	1	50	0.3	4.6
1028	27	F	R	Right MTL	Abnormal	CD, Gliosis	L (Wada)	-	103	None	3	Right EC	PH	Subdural	1	50	0.3	4.6
1029	33	F	R	Left FC	Abnormal	-	-	-	108	Mild	2	Left PF	PF	Subdural	3.5	50	0.3	4.6
1030	23	M	L	Left MTL	Normal	Gliosis	L (fMRI)	-	106	None	4	Left PHC	PH	Depth	0.5	50	0.3	4.6
1031	24	M	R	Right FC, right TC	Abnormal	-	L (aphasia)	-	110	Moderate	2	Right PRC	PH	Depth	1.5	50	0.3	4.6
1033	31	F	R	Right TC	Atrophy	-	L (Wada)	-	85	None	2	Left PRC	PH	Depth	1.5	50	0.3	4.6
1036	49	M	L	Left ATC, left MTL	MTS	HS	Bilateral (Wada)	-	93	Moderate	4	Left PRC	PH	Depth	1	50	0.3	4.6
1042	27	F	L	Right TC	MCD	-	R (fMRI)	None	114	None	2	Right PF	PF	Subdural	1.5	50	0.3	4.6
1050	20	M	R	Left PC	Neoplasm	DNET	Bilateral (Wada)	None	95	Mild	2	Left TC	TC	Subdural	1.5	50	0.3	4.6
1060	36	F	R	Right TC	Normal	Gliosis	L (Wada)	-	95	Mild	3	Right PF	PF	Subdural	3	50	0.3	4.6
1069	26	M	R	Left FC	MCD	-	L (Wada)	-	-	Mild	2	Left PF	PF	Subdural	2.5	50	0.3	4.6
1111	20	M	R	Left TC, left OPC, left OC	Gliosis	Gliosis	L (fMRI)	-	108	None	3	Left PHC	PH	Depth	0.75	50	0.3	4.6
1176	41	F	R	Right MTL, right IC	MTS	-	L (Wada)	-	85	Moderate	3	Left TC	TC	Subdural	1.5	50	0.3	4.6
											3	Left TC	TC	Depth	1	50	0.3	4.6
1177	23	F	R	Left TC	TS	-	L (aphasia)	None	87	Moderate	4	Left TC	TC	Subdural	1	50	0.3	4.6

Analysis was focused on 23 subject experiments that had at least two sessions with any one stimulation target in four of the studied brain regions. Patient demographic data is presented together with clinical observations from structural MRI, clinically identified SOZs, pathology for those subjects who underwent resective surgery, hemispheric laterality of language functions together with the method of determination ('aphasia' means that the determination was done based on an identified lesion/pathology causing aphasia), overlap of the stimulating electrodes with the language areas for patients who have undergone cortical stimulation mapping ('-' indicates that the stimulation mapping was not performed or the report was not available), verbal IQ (vIQ), and the clinical qualitative description of verbal memory deficits as concluded in the neuropsychological assessment. Amp. = amplitude; aTC = anterior temporal cortex; CD = cortical dysplasia; DNET = dysembryoplastic neuroepithelial tumour; EC = entorhinal cortex; HP = hippocampus; FC = frontal cortex; FPC = fronto-parietal cortex; Freq. = frequency; HS = hippocampal sclerosis; IC = insular cortex; MCD = malformation of cortical development; MTL = mesial temporal lobe; MTS = mesial temporal sclerosis; OC = occipital cortex; OPC = occipito-parietal cortex; PC = parietal cortex; PF = prefrontal cortex; PH = parahippocampal region; PHC = parahippocampal cortex; PMG = polymicrogyria; PRC = perirhinal cortex; TC = temporal cortex; TPC = temporo-parietal cortex.
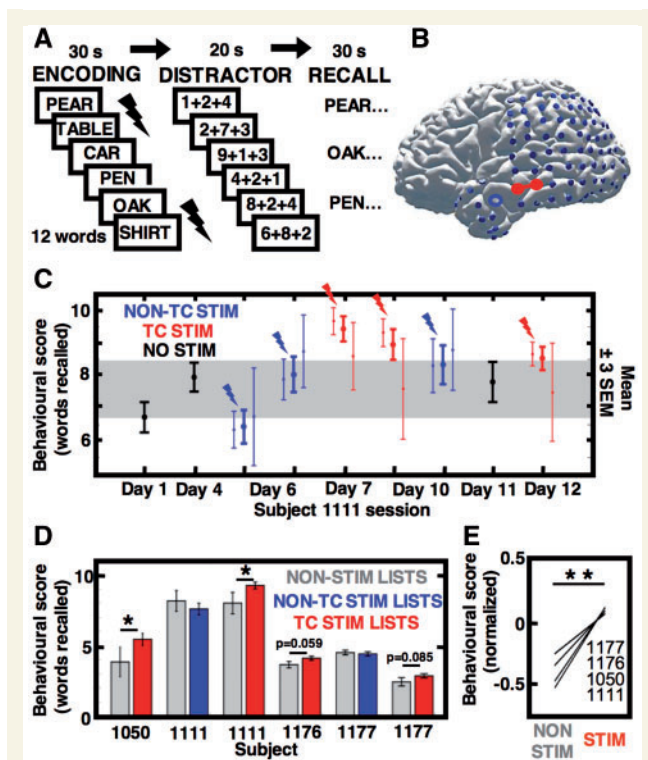
Figure 1 Stimulation in the temporal cortex enhances verbal memory performance. (**A**) Diagram of free recall verbal memory task design comprising three successive stages. (**B**) Stimulation site on the temporal cortex (red electrode pair) and in parahippocampal cortex (blue circle) used for Subject 1111. (**C**) Memory performance of Subject 1111 across all stimulation sessions. Overall session scores are in bold, broken down into scores on stimulated (left side thunderbolt) and non-stimulated word lists (right side). (**D**) Memory performance of all four subjects stimulated in the middle temporal gyrus and another target in two patients (*$P < 0.05$, permutation test). (**E**) Paired *t*-test comparison of subject memory performance on the stimulated and non-stimulated lists (**$P < 0.01$). All data are shown as mean ± standard error of the mean (SEM).

ensured that there were no after-discharges and no subjective experience of the stimulation.

All statistical tests were performed in MATLAB (MathWorks Inc.) using built-in and custom written codes. The effect of stimulation on memory performance in individual subjects (Fig. 1D) was assessed using a permutation test procedure—behavioural scores from all sessions with a given stimulation target were compared using difference in mean from the stimulated and non-stimulated lists, which was recalculated after randomly shuffling the list type labels 10 000 times to obtain a distribution of the shuffled difference scores. The permutation test was significant at $P < 0.05$ level if the original difference score without label shuffling was higher (enhancement) or lower (impairment) than 95% of the shuffled distribution scores. The same permutation procedure was used to compare the mean score obtained from the patients stimulated in the temporal cortex and the other brain regions. Paired *t*-test was used to compare normalized mean behavioural scores on stimulated and non-stimulated lists in the four temporal cortex subjects. ANOVA test was used to

compare the effect of stimulating in the four studied regions on memory performance with Tukey-Kramer *post hoc* comparison of the 95% confidence intervals (CIs) of the means. For more details see Supplementary material.

Results

Effect of stimulation in the lateral temporal cortex

First, we found that stimulation in the dominant lateral temporal neocortex of a subject with multiple stimulation sessions (Fig. 1B) increased the number of remembered words above the normal range, as compared to sessions with stimulation in parahippocampal region (Fig. 1C). In contrast to the parahippocampal region, memory performance within each session on the word lists with the temporal cortex stimulation was consistently higher than control lists without stimulation, and above the normal range (Fig. 1C). The same subject also reported subjective experience of improved mental 'picturing' of words during the temporal cortex stimulation sessions (Supplementary Video 1). Two of the four patients stimulated in the lateral temporal cortex showed a positive effect on memory recall; the other two patients showed a positive trend, which was not observed with stimulation in a different brain region (Fig. 1D). On the level of the whole group, memory recall of the stimulated word lists was significantly higher (paired *t*-test, $P = 0.0067$, $Df = 3$) than the non-stimulated lists (Fig. 1E). We noticed that the stimulation had a significant positive effect even in subjects with mild (Subject 1050) or no (Subject 1111) verbal memory deficits, as described in their respective neuropsychological assessments (Table 1).

Mapping stimulation sites to electrophysiological activity

Each experimental session comprised 20 lists with stimulation and five without (Fig. 1). Stimulation was applied during presentation of two consecutive words, followed by presentation of two other words without any stimulation to enable electrophysiological analysis without stimulus artefact. No difference in recall between stimulated words and the non-stimulated words (paired *t*-test, $P = 0.37$, $n = 4$, $Df = 3$) on the stimulation lists was observed (Supplementary Fig. 1) but the behavioural enhancement was observed on the level of the entire lists. This suggests that the positive effect of stimulation lasted beyond the period of electrical current administration (4.6 s) and modulated encoding of the entire stimulation list. To investigate this behavioural modulation further, we mapped spectral activities in the electrophysiological recordings induced during encoding of word lists (Fig. 2A and B). We focused on high gamma activities (62–118 Hz), which were previously associated with cognitive processing in humans (Kucewicz *et al.*, 2014) and are known to
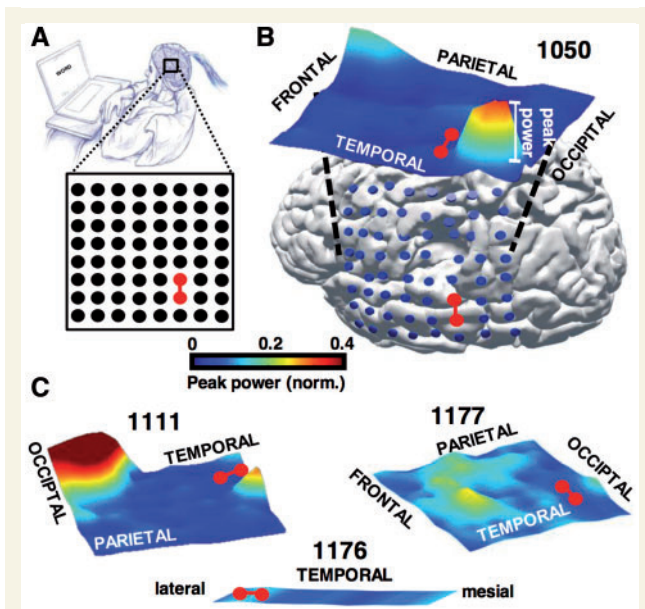
Figure 2 Localization of the temporal cortex stimulation sites relative to task-induced high gamma activity.
(**A**) Diagram of an example 8 × 8 grid of electrodes used to stimulate temporal cortex in Subject 1050 (red marks the stimulating electrode pair). (**B**) Surface plot displays peak power values of high gamma activity induced by presentation of words for memory encoding interpolated across all 64 grid electrodes on the underlying brain surface of Subject 1050 (electrodes are marked with blue dots). (**C**) Analogous surface plots are displayed for the remaining three patients (Subject 1176 was stimulated from a depth electrode). Notice that the stimulation sites (in red) localize in proximity to high gamma activity foci in the temporal cortex of Subjects 1050 and 1111.

predict successful memory encoding (Kahana, 2006; Sederberg *et al.*, 2007). In this *post hoc* analysis, we found that the stimulation sites in the left lateral temporal cortex were localized in close proximity to discrete foci of induced high gamma response to word presentation in Subjects 1050 and 1111 (Fig. 2B and C). The exact location of these high gamma response foci in the temporal cortex were subject-specific and not observed in Subjects 1176 and 1177. The high gamma activity foci were not only specific to the language-dominant hemisphere (Table 1 and Supplementary Fig. 2), suggesting activation of a widespread network engaged in these verbal memory tasks. They were not observed in proximity to the stimulation sites in the other three brain areas studied (Supplementary Fig. 2). The four patients were all stimulated in the left lateral temporal cortex that was language dominant (Table 2), although Subject 1050 was determined to have bilateral language localization by Wada testing (Table 1).

To assess the effect of temporal cortex stimulation on the spectral power, we used power across multiple frequency bands as features for a classifier (Supplementary material) to investigate further whether the amplitude and frequency parameters could potentially be adjusted for individual

patients stimulated in the temporal cortex. To do this we used the same target electrode to test a range of parameters in an additional experiment during quiet wakefulness outside of the task. The fixed parameters that we used in the memory tasks (50 Hz, 1.0–1.5 mA), taken from the previous study (Suthana *et al.*, 2012), were found to be optimal for only one of the four patients (Subject 1111) stimulated in the temporal cortex (Supplementary Fig. 3). In two of the four patients, higher frequencies (Subject 1050) or lower amplitudes (Subject 1177) were predicted to exert a greater effect on spectral power modulation and potentially on behavioural performance (not investigated in this study) than the fixed frequency and range of amplitude parameters used to assess the effect on memory encoding in this study. This suggests that stimulation patterns could be optimized to improve the modulatory effect on electrophysiological activity and memory performance.

Effect of stimulation across four regions of the human declarative memory system

Finally, we tested whether the behavioural effect of stimulation was specific to the lateral temporal cortex by comparing it to experiments with stimulating electrodes in one of the other three brain regions studied (Fig. 3A). Stimulation had a different effect on memory performance across the brain regions (ANOVA test, $P = 0.0019$, $F = 7.31$, $Df = 22$). The temporal cortex group was different from the other three brain regions stimulated ($P < 0.05$ Tukey *post hoc* comparison of 95% CI), showing the only positive effect on memory performance (Fig. 3B). The remaining three groups were not significantly different from each other. The same pattern was confirmed when data from patients, who completed only one session, were included in this analysis, or when data from patients stimulated in the non-dominant hemisphere were excluded (Supplementary Fig. 4)—only the temporal cortex stimulation group had a positive effect on verbal memory performance. Probability of obtaining a more positive mean effect using combinations of four randomly drawn scores from all 23 obtained was significantly below chance (permutation test, $P = 0.0003$) even when including the data with patients who completed only one session ($P = 0.005$; Supplementary material).

Discussion

Our findings show evidence that direct brain stimulation in the dominant lateral temporal cortex can enhance verbal memory in patients. Previous studies, which predominantly stimulated targets in the mesial temporal lobe structures, reported positive and negative effects in other verbal and non-verbal memory tasks (Suthana and Fried, 2014; Kim *et al.*, 2016). Here we focused on a specific task for verbal
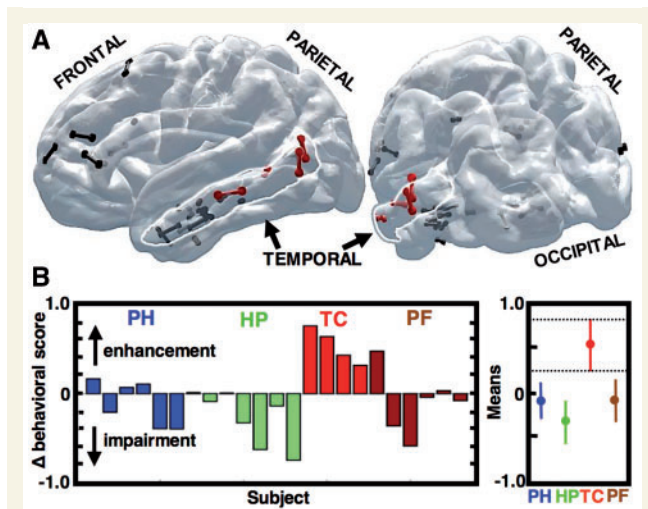
Figure 3 Stimulation-induced memory enhancement is specific to the temporal cortex. (**A**) Localization of four stimulation sites in the middle temporal cortex gyrus (red), which is highlighted with white lining, and 19 other sites tested (black) visualized in a unified transparent brain surface. (**B**) Stimulation enhances memory performance in the four subjects stimulated in the temporal cortex (TC; red bars; each bar is one subject) as compared to the other brain areas studied (PH = parahippocampal region; HP = hippocampus; PF = prefrontal cortex). Tukey-Kramer *post hoc* ANOVA comparison (right side) shows that temporal cortex means are significantly higher than parahippocampal region, hippocampus, prefrontal cortex ($P < 0.05$). Notice that only the temporal cortex group shows a positive effect of stimulation.

short-term memory given evidence from stimulation mapping studies, which suggested involvement of this region in the semantic brain network (Ojemann *et al.*, 1989; Tune and Asaridou, 2016). This region also overlaps with the cortical area mapped with sites where conscious memory experience was elicited in epilepsy patients (Penfield and Perot, 1963). Stimulation sites in our study were localized around the dominant middle temporal gyrus, which is associated with processing of semantic information (Binder *et al.*, 2009). Therefore, this brain region presents a viable target for exploring verbal memory enhancement. Its role in other non-verbal forms of declarative memory functions is not clear.

We found distinct areas within this region where word encoding induced high gamma activity, which may indicate more precise localization of information processing and thus map potential target sites for stimulation in this and possibly other regions in the temporal cortex. This activity was observed both in the language dominant and non-dominant hemispheres, and beyond the areas mapped during cortical stimulation mapping of language functions performed in a subset of patients. Hence, it is unlikely to be a biomarker of only verbal information processing in these tasks. High frequency activity in the gamma bands and above was previously associated with cognitive processing in human memory tasks in general (Kahana, 2006; Lachaux *et al.*, 2012; Kucewicz *et al.*, 2014) and proposed

to reflect the underlying activity of neuronal assemblies. Modulation of this activity with direct electrical stimulation presents one possible mechanism of the reported memory enhancement effect. In the current study, patients that were stimulated in the dominant lateral temporal cortex showed a positive modulation of memory performance. None of the patients were stimulated in the non-dominant temporal cortex, so it is not possible from our current data to determine if memory enhancement is possible with non-dominant temporal lobe stimulation. In the future, it would be ideal to incorporate *a priori* knowledge about the localization of language function when choosing the target stimulation areas activated in the tasks.

However, even with direct access of the implanted electrodes to the brain, understanding the electrophysiological effects of the stimulating current propagated over the cortical surface remains a major challenge (Borchers *et al.*, 2012). Hence, it is currently not known whether stimulating in the focus or perimeter of the foci of high gamma activity, on the gyrus or sulcus, from a depth and subdural surface electrode contact, or with different parameters would alter the reported effects. Ours as well as other stimulation studies with this patient population are restricted to a limited range of targets and parameters that can be explored, which is dictated by the clinical factors like the areas of epileptogenic or after-discharge activities. Nevertheless, we observed significant memory enhancement in subjects stimulated in proximity of the induced high gamma activity, providing a possible biomarker for the choice of target stimulation sites.

The mechanism of the stimulation's effect on electrophysiological activity and memory recall remains to be explored further. Direct brain stimulation is not necessarily the most appropriate technique for studying these mechanisms since it is thought to preferentially activate neuronal axons rather than cell bodies (Perlmutter and Mink, 2006) and thus exert effects across a whole network of local and distal brain connections. Hence, it is possible that the temporal cortex stimulation worked by activating a hub of the semantic brain network rather than a single brain region (Kim *et al.*, 2016). This hypothesis can be tested in animal models combining other techniques such as mapped calcium imaging exemplified in a study of micro-stimulation in rats, which showed a wide-spread activation of sparse assemblies of connected neurons instead of local populations surrounding the stimulating electrode (Histed *et al.*, 2009). Current human studies are limited to standard clinical macro-electrode contacts ($1-10\,mm^2$), which are separated by $5-10\,mm$. Using depth or subdural surface electrode contacts is another factor that may influence the modulatory effect of stimulation on neural activities. The spatial scale in either of these two electrode types is unlikely to be optimal for recording, stimulating and modulating neuronal assemblies underlying memory encoding and recall. We speculate that future studies utilizing high spatial resolution electrode arrays will advance the field (Worrell *et al.*, 2012).

Despite these mechanistic limitations, our study advances the field in several important aspects. First of all, this collaborative project overcomes the limit of small number of patients studied in the previous reports of memory enhancement ($n < 6$) from individual research groups (Kim *et al.*, 2016), making our larger dataset from multiple sites more reproducible. Second, we were able to test the effects of stimulation across four different brain regions. Lastly, the positive effect of stimulation was reported in individual patients tested across multiple days of stimulation sessions, on the level of the group of patients stimulated in the temporal cortex, and between the four groups stimulated in different brain regions. Previous studies reported the positive effects either as a single case study (Hamani *et al.*, 2008), or as a group effect without a significant enhancement in individual patients (Suthana *et al.*, 2012) or without statistical evaluation (Miller *et al.*, 2015). All of these studies including ours are limited to the number of patients available, variable clinical aspects in this patient population like individual case pathologies, medication and cognitive comorbidities, which need to be addressed by further increasing the number of subjects and assessing the effect of baseline deficits in verbal memory functions. Animal model studies are required to address these challenges. The other remaining issue in the field is elucidating the nature of cognitive processes modulated by the stimulation. The stimulation could enhance memory processing *per se*, or an associated process like attention and perception. Both have been proposed for possible functions of gamma oscillations (Tallon-Baudry and Bertrand, 1999; Jensen *et al.*, 2007), and all of these processes would contribute to the probability of recall. At this point it is not known whether the positive effect of stimulation in this brain region could generalize to other verbal and non-verbal memory functions, and whether stimulation in the non-dominant hemisphere would have a different effect.

Addressing these and other issues associated with direct brain stimulation for memory enhancement can potentially translate into clinical practice. For instance, the finding that electrical stimulation in the middle dominant temporal gyrus can enhance memory processes might provide a hint as to why some patients undergoing surgical removal of this region complain about verbal memory deficits. Knowledge about patient-specific brain areas involved in verbal memory processing can be used to guide resection surgery or promote alternative stimulation therapies. Finally, the reported memory enhancement effect may be particularly useful for developing new stimulation treatments for restoring memory functions and thus be applied in the emerging brain–machine interface technologies to treat memory and cognitive functions in humans.

Acknowledgements

Supplementary material

Supplementary material is available at *Brain* online.

References

Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb Cortex 2009; 19: 2767–96.

Borchers S, Himmelbach M, Logothetis N, Karnath H-O. Direct electrical stimulation of human cortex—the gold standard for mapping brain functions? Nat Rev Neurosci 2012; 13: 63–70.

Coleshill SG, Binnie CD, Morris RG, Alarcón G, van Emde Boas W, Velis DN, et al. Material-specific recognition memory deficits elicited by unilateral hippocampal electrical stimulation. J Neurosci 2004; 24: 1612–16.

Eichenbaum H. A cortical-hippocampal system for declarative memory. Nat Rev Neurosci 2000; 1: 41–50.

Fell J, Staresina BP, Do Lam ATA, Widman G, Helmstaedter C, Elger CE, et al. Memory modulation by weak synchronous deep brain stimulation: a pilot study. Brain Stimul 2013; 6: 270–3.

Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, et al. Memory enhancement induced by hypothalamic/fornix deep brain stimulation. Ann Neurol 2008; 63: 119–23.

Harrison J, Owen A. Cognitive deficits in brain disorders. 1st edn. London; Florence, KY: CRC Press; 2001.

Histed MH, Bonin V, Reid RC. Direct activation of sparse, distributed populations of cortical neurons by electrical microstimulation. Neuron 2009; 63: 508–22.

Jacobs J, Miller J, Lee SA, Coffey T, Watrous AJ, Sperling MR, et al. Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. Neuron 2016; 92: 983–90.

Jensen O, Kaiser J, Lachaux J-P. Human gamma-frequency oscillations associated with attention and memory. Trends Neurosci 2007; 30: 317–24.

Johnson MD, Lim HH, Netoff TI, Connolly AT, Johnson N, Roy A, et al. Neuromodulation for brain disorders: challenges and opportunities. IEEE Trans Biomed Eng 2013; 60: 610–24.

Kahana MJ. The cognitive correlates of human brain oscillations. J Neurosci 2006; 26: 1669–72.

Kahana MJ. Foundations of human memory. New York, NY: Oxford University Press, 2012.

Kim K, Ekstrom AD, Tandon N. A network approach for modulating memory processes via direct and indirect brain stimulation: toward a causal approach for the neural basis of memory. Neurobiol Learn Mem 2016; 134: 162–77.

Kucewicz MT, Cimbalnik J, Matsumoto JY, Brinkmann BH, Bower MR, Vasoli V, et al. High frequency oscillations are associated with cognitive processing in human recognition memory. Brain J Neurol 2014; 137: 2231–44.

Lachaux J-P, Axmacher N, Mormann F, Halgren E, Crone NE. High-frequency neural activity and human cognition: past, present and possible future of intracranial EEG research. Prog Neurobiol 2012; 98: 279–301.

Miller JP, Sweet JA, Bailey CM, Munyon CN, Luders HO, Fastenau PS. Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation with four cases. Brain 2015; 138: 1833–42.

Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 1989; 71: 316–26.

Penfield W, Perot P. The brain's record of auditory and visual experience. Brain 1963; 86: 595–696.

Perlmutter JS, Mink JW. Deep brain stimulation. Annu Rev Neurosci 2006; 29: 229–57.

Sahakian BJ, Bruhl AB, Cook J, Killikelly C, Savulich G, Piercy T, et al. The impact of neuroscience on society: cognitive enhancement in neuropsychiatric disorders and in healthy people. Philos Trans R Soc Lond B Biol Sci 2015; 370: 20140214.

Sederberg PB, Schulze-Bonhage A, Madsen JR, Bromfield EB, McCarthy DC, Brandt A, et al. Hippocampal and neocortical gamma oscillations predict memory formation in humans. Cereb Cortex 1991 2007; 17: 1190–6.

Suthana N, Fried I. Deep brain stimulation for enhancement of learning and memory. Neuroimage 2014; 85 (Pt 3): 996–1002.

Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, et al. Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med 2012; 366: 502–10.

Tallon-Baudry C, Bertrand O. Oscillatory gamma activity in humans and its role in object representation. Trends Cogn Sci 1999; 3: 151–62.

Tune S, Asaridou SS. Stimulating the semantic network: what can TMS tell us about the roles of the posterior middle temporal gyrus and angular gyrus? J Neurosci 2016; 36: 4405–7.

Worrell GA, Jerbi K, Kobayashi K, Lina JM, Zelmann R, Le Van Quyen M. Recording and analysis techniques for high-frequency oscillations. Prog Neurobiol 2012; 98: 265–78.