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Short Communication

Memory modulation by weak synchronous deep brain stimulation: A pilot study

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ABSTRACT

Zero-lag phase synchronization of EEG activity has been reported to be a central mechanism accompanying long-term memory formation. In this pilot study, we examined the effects of synchronous low-amplitude stimulation of the rhinal cortex and the hippocampus in eleven temporal lobe epilepsy patients. The impact of in-phase stimulation (zero lag) on long-term memory encoding of words was contrasted with anti-phase (180° phase lag) and sham stimulation. We hypothesized more correctly remembered words for the in-phase compared to the sham condition and fewer correctly remembered words for the anti-phase vs. the sham condition. Indeed, we observed a trend for a linear condition effect for correctly remembered words, which is in accordance to our prediction (in-phase > sham > anti-phase). This finding suggests that even weak synchronous deep brain stimulation of rhinal cortex and hippocampus may modulate memory performance, while clear evidence for an enhancement of memory by this kind of deep brain simulation is still lacking.

Phase synchronization of EEG activity has been reported to be a central mechanism accompanying long-term memory formation [1,2]. In particular, zero-lag (in-phase) synchronization of gamma oscillations around 40 Hz between the rhinal cortex and the hippocampus, as well as within the hippocampus has been shown to be associated with successful memory encoding in humans [3] and macaques [4]. Two functions of gamma band synchronization may contribute to memory operations. On the one hand, it may promote neural communication between memory-relevant cortical areas [5]. On the other hand, gamma band synchronization may facilitate synaptic plasticity [1,2].

In this pilot study, we examined the effects of synchronous low-amplitude stimulation of the rhinal cortex and the hippocampus in humans. We applied sinusoidal currents with amplitudes of 0.01 mA corresponding to voltages in the mV range. These currents and voltages are much smaller than those used in other memory-related deep brain stimulation studies [6–8]. The motivation for this approach was to use stimulation patterns which more closely resemble physiological conditions. In fact, it has been demonstrated that in vitro stimulation in the mV range can guide neural network activity in a similar way as in vivo endogenous electric fields do [9]. The impact of in-phase stimulation (zero phase lag) on long-term memory encoding of words was contrasted with anti-phase (180° phase lag) and sham stimulation. Because in-phase synchronization is thought to facilitate and anti-phase synchronization to hinder memory formation [2,5], we hypothesized more correctly remembered words for the in-phase compared to the sham condition and fewer correctly remembered words for the anti-phase vs. the sham condition. Intrusions may be prevented by stronger encoding of words presented during the ongoing series (in-phase synchronization). Thus, we hypothesized fewer intrusions for the in-phase compared to the sham condition.

Materials and methods

Patients

Eleven temporal lobe epilepsy patients (five female, mean age: 37 ± 9 years, all right handed) undergoing presurgical evaluation participated in the study. These patients were implanted because the seizure onset zone could not be defined unequivocally by non-invasive means. In none of the patients seizures occurred within

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24 h before or after the experiment. The study was approved by the Ethics Committee of the University of Bonn and all patients gave written informed consent. The first six patients had been scheduled for hippocampectomy based on the outcome of clinical depth-EEG monitoring (all seizure focus and hippocampus sclerosis on the left side) and the stimulation protocol was applied to the pathological medial temporal lobe (left side). After surgical intervention the resected hippocampi underwent extensive histological examination. In the following five patients (pat7–pat11) the stimulation protocol was applied to the non-pathological medial temporal lobe (seizure focus on the right side in pat7, in all others on the left side; hippocampus sclerosis in pat8, grey-white differentiation disorder in pat9, no specific neural pathologies in the others).

Neuropsychological testing

For neuropsychological assessment of declarative memory, the verbal learning and memory test (VLMT [10,11]) was applied, which basically represents the German equivalent of the internationally well established Rey Auditory Verbal Learning Test. This test requires verbal serial list learning and was conducted in the patients before electrode implantation (i.e. several days before the deep brain stimulation experiment). A target word list ("list A") of 15 unrelated and frequent concrete nouns is to be learned across five learning trials, each followed by immediate free recall. This learning phase is followed by one learning trial of a distracter "list B" with 15 different words, again followed by immediate recall (trial 6). Thirty minutes later delayed free recall of "list A" is tested (trial 7). Finally, a recognition memory test is applied, which asks for the identification of "list A" items as targets out of an orally presented list which additionally comprises "list B" items as well as semantically and phonetically related words as distracters. The memory measures extracted from the verbal learning and memory test are: a) memory span: immediate recall after trial 1 (number of words correctly recalled); b) learning: immediate recall (sum) after trials 1–5; c) memory consolidation: memory loss over time (number of words recalled after trial 7 minus those recalled after trial 5); d) recognition memory: correctly recognized words minus false alarms.

Depth electrodes

The first nine patients were implanted with bilateral hippocampal depth electrodes from a posterior approach [12]. Electrodes consisted of 10 cylindrical platinum contacts with a diameter of 1.3 mm and a length of 1.6 mm, which were located along the longitudinal axes of the hippocampi with the anterior contacts reaching into the rhinal cortex. In the last two patients bilateral depth electrodes were implanted from a temporo-lateral approach targeting anterior hippocampus, rhinal cortex, parahippocampal cortex and amygdala. In all patients the placement of electrode contacts was ascertained by magnetic resonance images which were acquired after the implantation of electrodes (for an example see Fig. 1). Electrode contacts were localized based on the individual MRIs and comparison with standardized anatomical atlases [13]. The contacts selected for stimulation always fell within gray matter. In principle, the spatial resolution of these MRI data would allow one to distinguish between contacts located within the entorhinal and the perirhinal part of the anterior parahippocampal gyrus (as has been done, for instance, by Suthana and colleagues [8]). However, with the present stimulation protocol (bipolar stimulation between rhinal cortex and hippocampus in the in-phase condition, or between both regions and the mastoid in the anti-phase condition) the current flow cannot be regarded to be strictly confined to either the entorhinal or perirhinal subregion. This configuration is different from that used in Suthana et al. [8], where bipolar stimulation was delivered to electrode contacts only 1.5 mm apart within either entorhinal cortex or hippocampus. Thus, we denoted the anterior stimulation contact simply as localized within rhinal cortex.

Memory paradigm

During the different stimulation conditions patients (all except patient 1) performed a word list learning task with subsequent free recall [14]. In brief, series of 12 semantically unrelated German nouns were presented subsequently on a computer screen (stimulus duration: 400 ms, interstimulus interval: 2.5 s, interval between series: 10 s). In each series, different words were presented. Series were randomly assigned to the experimental conditions (sham, in-phase stimulation, anti-phase stimulation). After a distraction task (counting backward in steps of three, starting at a random number between 81 and 99, duration: 30 s), patients were asked to name the words they remembered (time limit of 2 min). For each stimulation condition four series of 12 words (i.e. in total 48 words) were presented (in pat2 only anti-phase and sham condition; in pat7 two blocks of 3 × 4 series; interval between

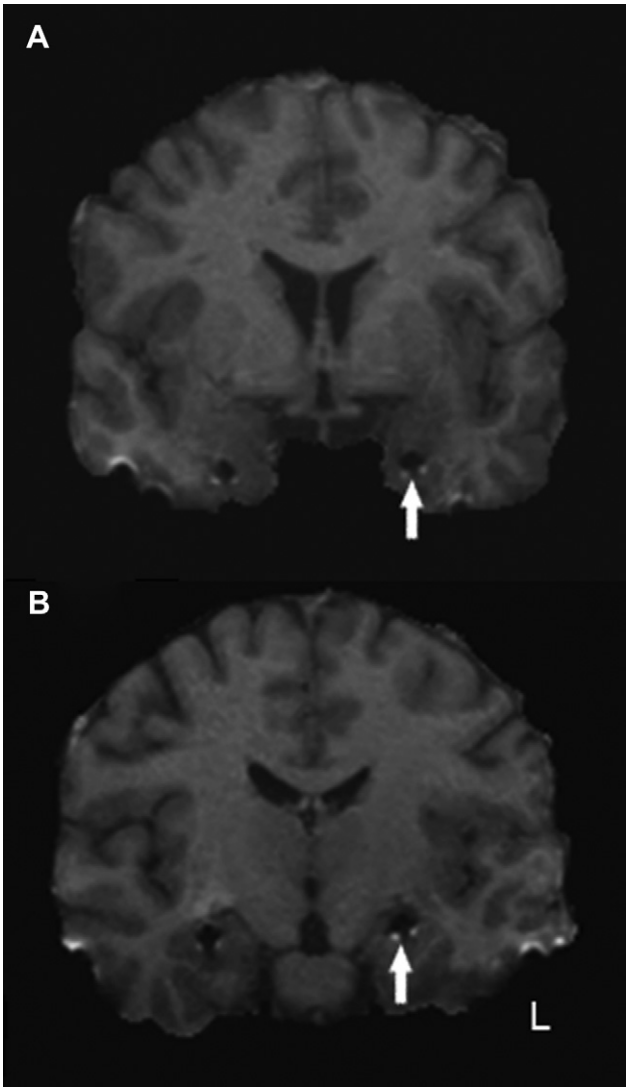

Figure 1. Localization of depth electrode contacts: two coronal MR images of a patient with bilateral depth electrodes in situ (radiological convention, L = left). (A) The white arrow indicates the chosen electrode contact within rhinal cortex. (B) The white arrow designates the chosen electrode contact within the anterior hippocampus.

stimulation conditions: 1 min). The order of stimulation conditions was randomly selected (through drawing lots) by the scientist preparing the stimulation (J.F.) and was unknown to both, the patient and the experimenter (N.A., B.S. or A.DL.). Statistical analyses were conducted for the group of nine patients, in which all three experimental conditions were completed (pat3–pat11).

Deep brain stimulation protocol

For all patients one electrode contact was chosen located within the rhinal cortex and one within the anterior hippocampus. Additionally, an Ag/AgCl surface electrode was mounted at the mastoid of the hemisphere chosen for stimulation. Inter-electrode impedances between the depth electrodes, as well as between the depth and the surface electrodes were between 5 kΩ and 25 kΩ. Bipolar stimulation was applied by the Twister neurostimulation apparatus (Dr. Langer Medical GmbH, Waldkirch, Germany) through the designated input channels of a Harmony EEG system (Schwarzer Medical GmbH, Heilbronn, Germany). The stimulation signal was a continuous sine wave with a frequency of 40 Hz and a current amplitude of 0.01 mA. Thus, the induced charge per half-wave amounted to 0.0796 μC with a charge density <1.25 μC/cm^2. These values are more than two orders below the recommended safety limits for chronical stimulation with implanted electrodes [15]. Three stimulation conditions were used: 1) anti-phase: rhinal vs. hippocampal contact (i.e. stimulation pole A = rhinal contact; stimulation pole B = hippocampal contact), 2) in-phase: connected rhinal and hippocampal contact vs. mastoid electrode (i.e. stimulation pole A = rhinal and hippocampal contact electrically connected via a bridge circuit; stimulation pole B = mastoid electrode), 3) sham (simulated initiation of stimulation). Stimulation was applied non-stop during the learning, distraction and recall phases of each condition.

Results

Side effects of deep brain stimulation

None of the patients and none of the experimenters noticed an effect of stimulation or could distinguish the active stimulation conditions from the sham condition. Besides the expected markers of hippocampus sclerosis, histological examination of the resected hippocampi did not reveal any signs related to the impact of electrical currents. Furthermore, no effects of the different stimulation conditions on the back-counting task were observed, i.e. during all three experimental conditions patients were able to perform the distraction task and they back-counted across similar number ranges.

Memory performance

The number of correctly remembered words and the number of intrusions during the three experimental conditions are listed in Table 1. These data were statistically evaluated by two-way ANOVAs with "stimulation condition" (in-phase, anti-phase, sham) as repeated measure and "stimulation side" (pathological hippocampus, non-pathological hippocampus) as between-subjects factor. For the number of correctly remembered words, no significant effect of condition ($P = 0.17$), but a trend for a linear effect ($F_{1,7} = 4.161$; $P = 0.081$) was observed, which is in accordance to our prediction (in-phase > sham > anti-phase). There was no interaction between the linear condition effect and stimulation side ($P = 0.63$), as well as no main effect for stimulation side ($P = 0.77$). For the number of intrusions, a significant condition effect was detected ($F_{2,14} = 4.044$, $P = 0.041$, Huynh–Feldt corrected). Again, no interaction between stimulation condition and stimulation side ($P = 0.25$), as well as no main effect for stimulation side ($P = 0.78$) were observed. A subsequent one-tailed *T*-test revealed a trend for a reduced number of intrusions during the in-phase compared to the sham condition ($P = 0.079$, $t_8 = 1.56$) in accordance to our prediction.

The results of the verbal learning and memory test (VLMT [10,11]) conducted in the patients before electrode implantation are reported in Table 2. Interestingly, in all patients showing no memory impairment in this test with respect to normative data (pat 4, pat7, pat9) the differences of correctly remembered words for the in-phase vs. anti-phase condition were in the predicted direction. On the other hand, for the patient with deficits in all four memory measures (pat5) the difference between correctly remembered words in the in-phase vs. anti-phase condition was opposite to the predicted direction.

Conclusion

Up to now, very few studies have addressed the potentiality of memory improvement by deep brain stimulation [6,7]. Recently, Suthana et al. [8] reported that stimulation of the entorhinal cortex during learning of destinations within virtual environments enhanced memory for this kind of spatial information.

In the present pilot study, weak deep brain stimulation was applied in epilepsy patients to the non-pathological, as well as pathological side. In the latter case stimulation was always on the left side. All patients were right handed suggesting regular language dominance, although functional reorganisation of cortical language distribution cannot be excluded [16]. Studies evaluating the neuropsychological consequences of hippocampal resections with varying extensions indicated that the left hippocampus significantly contributes to verbal memory even in case of hippocampal sclerosis on this side [17,18]. Electrophysiological data showed that hippocampal sclerosis is characterized by a reduced availability of neural assemblies recruitable for memory formation, but by preserved network functions [19]. In the context of clinical applications, it is therefore an important question whether residual memory functions of a pathological medial temporal lobe may benefit from deep brain stimulation.

In accordance to our predictions, we observed a trend for a linear effect of stimulation condition on the number of correctly remembered words (in-phase > sham > anti-phase), as well as a trend for a reduced number of intrusions during in-phase vs. sham stimulation. These findings suggest that even weak synchronous deep brain stimulation of rhinal cortex and hippocampus may modulate memory performance. However, clear evidence for an enhancement of memory by this kind of deep brain simulation is still lacking. The present data moreover suggest that memory modulation may only be possible in patients with

Table 1
Average number (across series of 12 words) of correctly remembered words and intrusions (false namings) for the three experimental conditions.

Condition	Correctly remembered words			Intrusions		
	In-phase	Anti-phase	Sham	In-phase	Anti-phase	Sham
pat2	–	0.667	0.667	–	1.333	2
pat3	5.25	4.25	5.4	0.5	0	0.8
pat4	2.333	1	1.5	0.333	0	0.25
pat5	1	1.333	2.333	1.667	1.333	1.333
pat6	2	2	2.2	2.4	2.2	3
pat7	4.125	2.25	1.875	0.125	0.25	0.5
pat8	5.5	3.5	3.5	2.25	2.5	3
pat9	1.5	1	2.25	0	0.5	0.25
pat10	1	1.5	1.5	1.5	1.25	1.75
pat11	2	1.75	0.75	0.33	0	0
Mean (pat3–pat11)	**2.745**	**2.065**	**2.368**	**1.012**	**0.893**	**1.209**
s.e.m	0.586	0.374	0.455	0.315	0.324	0.385

Table 2
Results of the verbal learning and memory test [11]. Test scores at or under the 10% range limit with respect to normative data of healthy controls [10] are shown in italics.

	Verbal learning and memory test			
	Recall trial1	Recall trial 1–5	Loss over time	Recognition
pat2	5	*43*	1	*−3*
pat3	5	*41*	*5*	*2*
pat4	7	54	3	14
pat5	*4*	*33*	*4*	*7*
pat6	*4*	*42*	2	10
pat7	6	47	−2	14
pat8	7	51	*5*	10
pat9	6	46	3	13
pat10	5	*29*	*5*	*6*
pat11	*4*	*41*	0	14
Mean	**5.3**	**42.7**	**2.6**	**8.7**
s.e.m	0.4	2.4	0.7	1.8
10% range limit	4	43	4	9

sufficient residual memory capacity (as assessed by the verbal learning and memory test). Further investigations should explore in greater depth the effects of stimulation loci, frequency, amplitude, phase-lag and timing.

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