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RAPID COMMUNICATION

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Memory encoding-related anterior hippocampal potentials are modulated by deep brain stimulation of the entorhinal area

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Abstract

Background: Deep brain stimulation (DBS) of the human entorhinal area using 50 Hz pulses has revealed conflicting results regarding memory performance. Moreover, its impact on memory-related hippocampal potentials has not yet been investigated.

Methods: We recorded data from seven epilepsy patients implanted with depth electrodes in the entorhinal cortex, hippocampus, amygdala, and parahippocampal cortex. Entorhinal DBS (bipolar, biphasic 50 Hz pulses, on- and off-cycles of 15 s) was applied with low amplitude (0.1 mA) to resemble physiologic conditions. During DBS on- and off-periods, patients learned noun-color associations that were later tested.

Results: During entorhinal DBS we observed more positive deflections of event-related potentials (ranging from 700 to 950 ms) in the anterior hippocampus for the on- vs. off-condition. We detected no effects in the amygdala, mid hippocampus and parahippocampal cortex. On the behavioral level, no differences in memory performance (item and source memory) were apparent in the on- vs. off-condition, neither across all trials nor across patients.

Discussion: Our findings indicate that entorhinal DBS with low amplitude has an impact on memory encoding-related potentials within the anterior hippocampus, but not on memory performance per se.

KEYWORDS
anterior hippocampus, associative memory, deep brain stimulation, entorhinal area, event-related potentials

1 | INTRODUCTION

The entorhinal cortex acts as a "functional gatekeeper" between hippocampus and neocortex during memory operations (Basu et al., 2016; Fernandez and Tendolkar, 2006) and plays a role in the encoding of words and objects (de Vanssay-Maigne et al., 2011; Keene et al., 2016). Thus, deep brain stimulation (DBS) of the entorhinal area may provide a promising therapeutic approach to alleviate impaired memory functions (e.g., Laxton, Lipsman, & Lozano, 2013; Lee, Fell, & Axmacher, 2013). Indeed, entorhinal DBS with biphasic pulses of 50 Hz has been reported to improve memory performance in a virtual navigation paradigm (Suthana et al., 2012). However, a reduction in spatial and verbal-episodic memory performance was recently demonstrated using a similar protocol (Jacobs et al., 2016). Neither of those studies investigated hippocampal event-related potentials (ERPs). Aside from the conflicting behavioral results reported in previous studies, the question remained as to whether entorhinal DBS has an effect on memory-related potentials within the hippocampus.

To address this issue, we applied entorhinal DBS to presurgical epilepsy patients using a similar design to those of previous studies (Jacobs et al., 2016; Suthana et al., 2012). However, the memory paradigm, as well as the timing and intensity of stimulation were different, so that we could not directly address the controversy regarding the valence of stimulation on memory performance. One major difference

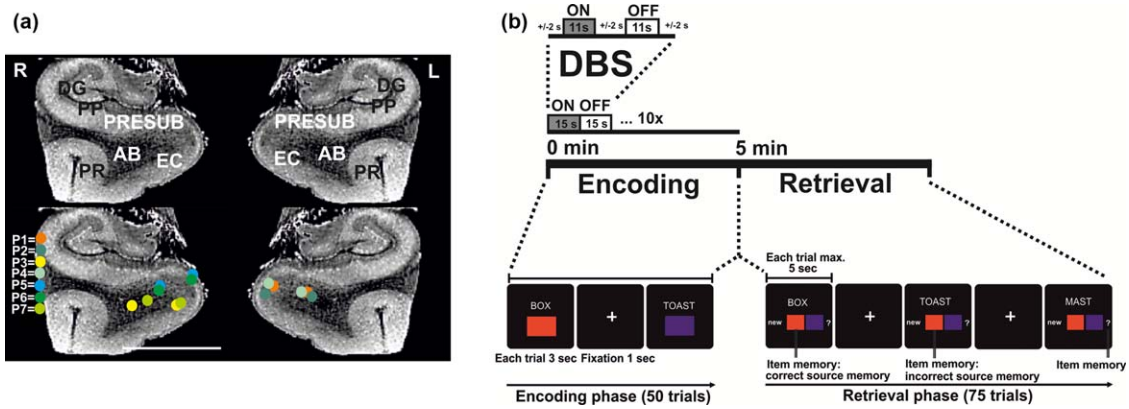

FIGURE 1 **(a) Localisation of stimulation contacts in the entorhinal area.** Postimplantation MRIs of each patient were mapped onto a representative MRI figure showing different subregions of the hippocampal formation (MRI figure adapted from Augustinack et al., 2010 with permission). The localisation of the stimulation contacts in the entorhinal area is indicated by dots with different colors, each patient corresponding to a different color. The scale bar corresponds to 1 cm. AB = angular bundle, EC = entorhinal cortex, DG = dentate gyrus, L = left side, R = right side, P 1–7= patient 1–7, PP = perforant path, PRESUB = presubiculum, PR = perirhinal cortex. **(b) Associative memory task and DBS scheme.** The upper part of the figure shows how we defined the EEG time periods for the on- and off-condition trials. Patients were asked to perform the associative memory task, during which electrical stimulation was applied throughout the encoding phase at consecutive 15 s on/off intervals across 50 trials. Responses to noun stimuli occurring within 11 s intervals during the on-off periods (+/− 2 s gaps) were analyzed. During the encoding phase patients were presented with a noun and an associated color. They were instructed to indicate whether the noun/color combination was plausible or not. In the retrieval phase consisting of 75 trials, we tested differences in item and source memory. Previously learned nouns were presented among new nouns. Patients were asked to indicate with a button press whether they recognized a previously displayed noun as old or classified it as new, and in case of an old decision, whether they could correctly recognize the color that was previously associated with the noun [Color figure can be viewed at wileyonlinelibrary.com]

was that we used stimulation currents with lower amplitude (0.1 mA), while Suthana et al. (2012) and Jacobs et al. (2016) applied currents between 0.5 and 1.5 mA, near to the individual thresholds for afterdischarges. The application of a low current amplitude of 0.1 mA is closer to physiologically occurring spontaneous currents (e.g., Fröhlich & McCormick, 2010), avoids possible side effects, and may be more suitable for therapeutic long-term stimulation. During the intermittent on–off stimulation periods, patients learned noun-color combinations, and had to subsequently recall the learnt nouns and associations (Staresina Fell, Do Lam, Axmacher, & Henson, 2012). We selected such an associative memory task as it particularly depends upon processes within the anterior hippocampus, and allowed us to distinguish between item and source memory. However, aside from relying on the hippocampus, this associative memory task cannot directly be compared to the virtual navigation tasks used by Suthana et al. (2012) and Jacobs et al. (2016), which are more continuous in nature.

Seven patients (mean age 39.5 ± 8.7 years, ± s.d., five females) suffering from temporal lobe epilepsy underwent implantation of depth electrodes within mesiotemporal structures to determine the seizure-onset zone after inconclusive noninvasive EEG monitoring, for possible epilepsy surgery. In all seven patients bilateral depth electrodes were implanted. The invasive EEGs revealed a temporomesial seizure-onset zone in all patients (left: $n = 3$, right: $n = 3$, bilateral: $n = 1$). The study was approved by the local ethics committee of the Medical Faculty of the University of Bonn. All patients gave informed consent to participate in this study.

The depth electrodes (three cylindrical platinum contacts, diameter: 1.3 mm; length: 1.6 mm) bilaterally targeted entorhinal area, amygdala, anterior and mid hippocampus, and parahippocampal cortex via a temporo-lateral approach. In two patients only unilateral electrodes were implanted in the anterior hippocampus, and in one patient a unilateral electrode was implanted in the amygdala. Electrode locations were verified via magnetic resonance imaging using an anatomic brain atlas (Duvernoy, Cattin, & Risold, 2013). Intracranial EEG data were recorded at a sampling frequency of 1024 Hz referenced against linked mastoids. Bipolar stimulation was applied to two neighboring contacts within the entorhinal area (distance: 3 mm in five patients; 4.5 mm in two patients), with one contact approximately located in the angular bundle and one contact in the entorhinal cortex (see Figure 1a). For illustrative purposes, these contacts were mapped onto a single coronal MRI image showing different subregions of the hippocampal formation (adapted from Augustinak et al., 2010, see Fig. 1a). This was done using a visual/manual procedure, i.e. each patient's contacts were identified in the individual coronal MRI slices and then transferred to the representative MRI image based on the relative contact positions (medial–lateral, superior–inferior), within the entorhinal cortex and angular bundle. In all seven patients stimulation was applied to the presumably nonpathological side (left $n = 3$, right $n = 4$). Results of presurgical evaluation confirmed that this was the case in six patients, whereas in one patient a bilateral pathology was diagnosed. In accordance with Suthana et al. (2012) and Jacobs et al. (2016), we used a 50 Hz stimulation frequency consisting of biphasic rectangular pulses (pulse width: 300 μs) administered via a SD-LTM neurostimulation device (Micromed S.p.A, Treviso, Italy). However, a lower stimulation current of 0.1 mA was used (vs. 0.5–1.5 mA in Suthana

et al., 2012 and Jacobs et al., 2016). Stimulation was applied during the encoding periods (each approximately 5 min) of an associative memory paradigm (Staresina et al., 2012) with alternating on- and off-cycles of 15 s duration (vs. around 5 s in Suthana et al., 2012 and Jacobs et al., 2016) (Figure1b).

In a previous study we measured the impedances between electrode contacts in patients implanted with the same depth electrodes (Fell et al., 2013). In this study, impedances between depth contacts were always below 10 kΩ (values reported referred to the stimulation contacts, which consisted of a rhinal, hippocampal, and scalp contact). Accordingly, the voltages delivered to the neighboring contacts in the present study were likely well below 1 V. The delivered charge was 0.03 μC per phase and the delivered charge density was 0.5 $\mu C/cm^2$ per phase. These values are more than two orders below the recommended safety limits for chronic stimulation with implanted electrodes (Grill, 2008).

During the encoding phase, object (noun)—color combinations were presented to the patients on a laptop screen, who then had to indicate via button-press whether these combinations were plausible or not (Staresina et al., 2012) (Figure 1b). During the subsequent retrieval periods the same nouns were presented together with 50% new nouns. Patients were asked to make an old/new decision and in case of an old decision, had to indicate the previously associated color. If they were unable to remember the associated color, they were instructed to select the question mark (Figure 1b). Encoding and retrieval periods were separated by a time gap of 1.4 ± 0.24 min (mean ± s.d. across patients) to avoid working memory effects. From the behavioral data we extracted the following measures separately for the on- and off-stimulation periods: percentage of hits (percentage of correct old responses, i.e. item memory), percentage of correct source memory (percentage of correctly associated color, out of total hits), adjusted source memory (percentage of correctly minus percentage of incorrectly associated color, out of total hits). Differences between on- and off-periods were evaluated by MANOVAs across all three measures and additionally using paired *t*-tests for the individual measures, separately across all experimental runs (3/3/3/4/5/6 runs per patient; 24 in total) and across patients. Behavioral data from one patient (with complete bilateral implantations) were excluded from statistical analysis as they performed only one run, and in case of total hits mostly chose the question mark (17/19), so that source memory could not be reliably accessed.

ERPs were evaluated for the five patients with bilateral implantations in the anterior hippocampus. EEG data underwent initial analysis via BrainVision Analyzer software (Brain Products GmbH, Gilching, Germany). Raw EEG data were visually inspected and epileptic potentials (e.g., spikes or sharp waves) or other artefact events were excluded. The on- and off-stimulation periods were curtailed by cutting 2 s at the start-/endpoint of the 15 s time intervals (Figure 1). Baseline normalization was performed by subtracting the average values in the time interval from −200 ms to stimulation onset of the individual trials. ERPs were filtered with a 0.53 Hz high-pass and a 40 Hz low-pass (second-order Butterworth). The mean amplitudes of ERPs across patients elicited by the noun/color stimuli were calculated in each patient based on the averaged recordings from two neighboring contacts located within the same anatomical structures, which were the anterior hippocampus, mid hippocampus, amygdala, and parahippocampal cortex, separately for on- and off-periods, as well as for the ipsilateral and contralateral sides to stimulation. Neighboring contacts were averaged because of their proximity (3–4.5 mm), and as they were both located within the same anatomical structures.

ERP amplitudes were evaluated using a two-way repeated measures ANOVA comprising the factors STIMULATION (on vs. off) and SIDE (ipsilateral vs. contralateral). Additionally, ERPs for the on- vs. off-condition were compared via nonparametric label permutation statistics (Maris and Oostenveld, 2007). In brief, paired *t*-tests were computed for each time point, and neighboring time points were clustered according to significant results from the *t*-tests ($p < 0.05$). Then the sum of *t*-values was calculated for each cluster. Afterwards condition labels (on/off) were permuted on the group level and again paired *t*-tests were calculated, clusters were determined and the sum of *t*-values within the new clusters were computed. Finally, for each permutation the cluster with the maximum sum of *t*-values was selected. The original cluster values were then compared to the maximum cluster values resulting from the permutations and a *p*-value for each cluster was calculated according to the rank position (31 possible permutations, min. *p*-value = 0.032).

Suthana et al. (2012) reported an increased intertrial phase locking in the theta range (3–8 Hz) for the on- vs. off-condition. To examine the influence of DBS on stimulus-related phase locking in our data, we analyzed phase locking values from anterior hippocampal EEG channels on each side. In accordance with Jacobs et al. (2016) the signals were filtered from 3 to 8 Hz with a second-order Butterworth filter for the time interval between 500 and 2000 ms with regard to stimulus onset. Phase values were extracted using a Hilbert transformation. The analyzed time intervals were cut from 0 to 1600 ms after stimulus onset to avoid edge effects. Phase locking values were quantified across trials via calculating circular variance (e.g. Lachaux, Rodriguez, Martinerie, & Varela, 1999). Differences in phase locking between on- versus off-stimulation conditions were tested via nonparametric label permutation statistics (Maris & Oostenveld, 2007) as described above.

On the behavioral level, we found no differences in averaged responses for hits (percentage of correct old responses), source memory (percentage of correct noun/color associations) and adjusted source memory (percentage of correct minus percentage of incorrect associations) across all experimental runs in the on- vs. off-condition (MANOVA: $F_{3,44} = .122$; Wilks $\lambda = .992$; $p = 0.947$; paired *t*-tests across 24 runs, each $p > 0.5$, each $T_{23} < 0.6$; see Figure 2a). Moreover, no significant differences were observed in averaged responses between the on- vs. off-condition for hits, source memory, and adjusted source memory across patients (MANOVA: $F_{3,8} = .052$; Wilks $\lambda = .981$; $p = 0.983$; paired *t*-tests across patients ($n = 6$), each $p > 0.6$, each $T_5 < 0.6$; see Figure 2b). There were no consistent unidirectional changes (i.e. either increases or decreases) for any of the patients, or for any of the evaluated behavioral measures (hits, source memory, adjusted source memory) across experimental runs.

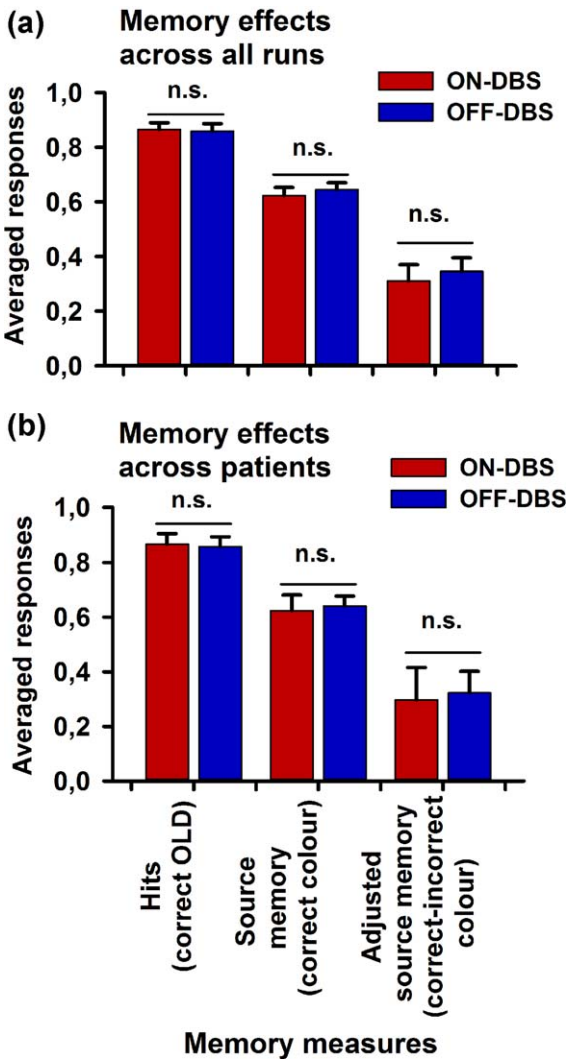

FIGURE 2 Deep brain stimulation effects on memory measures (a) Averaged responses for memory measures are shown for DBS-on vs. off trials. Hits (percentage if correct responses to studied nouns, item memory), source memory (percentage of correct color/noun combinations) and adjusted source memory (percentage of correct color/noun combinations minus percentage of incorrect combinations) averaged across all experimental runs. (b) Hits (item memory), source memory and adjusted source memory averaged across patients. Error bars indicate standard error of mean (SEM) [Color figure can be viewed at wileyonlinelibrary.com]

Additionally, we investigated whether there were behavioral effects related to the timing of the stimulation, or any that could be attributed to the aftereffects of the stimulation. For this purpose, we analyzed the behavioral responses for the first noun/color stimulus (1.off) and the first two noun/color stimuli (1.2.off) occurring immediately after the offset of the 15 s stimulation periods. Furthermore, we reanalyzed the behavioral responses for the off-condition after excluding the first stimulus (off-1.) and the first two stimuli (off-1.2.) occurring immediately after each offset. We compared the different behavioral measures (hits, source memory, and adjusted source memory) between the newly defined conditions and the on-condition (on) using paired two-tailed *t*-tests across runs and across patients. In all, we calculated six comparisons for each of the behavioral measures: 1.off vs. off-1.; 1.2. off vs. off-1.2.; 1.off vs. on; 1.2.off vs. on; off-1. vs. on; off-1.2. vs. on. None of these comparisons revealed a statistically significant difference, neither across runs (each $p > 0.28$), nor across patients (each $p > 0.22$). Accordingly, we observed no evidence for a behavioral effect related to the timing of stimulation.

Anterior hippocampal ERP responses to noun/color stimuli were characterized by a positive component in the time range between 200 and 1000 ms corresponding to the P600 component, which has been reported to be a hippocampal correlate of memory encoding of words (e.g. Guillem, Rougier, & Claverie, 1999; Klaver et al., 2005; Ludowig et al., 2008). During entorhinal DBS, more positive ERP amplitudes were elicited in the anterior hippocampus by the noun/color stimuli in the time range between 700 and 950 ms compared to the off-condition (ANOVA, $F_{1,4} = 10.4$, $p < 0.05$; Figs. 3a, b). No significant interaction between the factors SIDE (ipsilateral/contralateral to stimulation) and STIMULATION (on/off) for these mean ERP amplitudes was detected (ANOVA, $F_{1,4} = 2.02$, $p = 0.23$). To corroborate these findings, we applied nonparametric label permutation statistics to the ERPs. These statistics revealed a significant difference ($p = 0.031$) between the on- and off-condition on the ipsilateral side in the time range between 711 and 865 ms (entrance threshold: $p = 0.05$; with entrance threshold $p = 0.1$ significant ($p = 0.031$) between 709 and 922 ms). No significant difference was detected for the contralateral side. Moreover, no significant differences in mean ERP amplitudes for the on- vs. off-condition were found for the mid hippocampus, the amygdala, and parahippocampal cortex. For the anterior hippocampus, we additionally analyzed whether intertrial phase locking in the theta range between 3 and 8 Hz differed during DBS compared to the off-condition, using a similar approach to that of Jacobs et al. (2016). No statistically significant differences in intertrial phase locking were detected for the on- vs. off-condition ($p > 0.72$).

In the present study, we applied a DBS protocol with a stimulation locus, frequency, and pulse characteristics similar to those used by Suthana et al. (2012) and Jacobs et al. (2016), but with a lower stimulation amplitude and longer stimulation periods. In addition to item memory for nouns, we investigated, for the first time, the effect of DBS on associative memory encoding. We observed no significant effects on long-term memory performance in terms of item and source memory, neither when evaluated across all experimental runs, nor across patients. Thus, our findings indicate that the stimulation protocol we applied is ineffective with regard to the goal of memory enhancement (and also with regard to memory suppression). One reason for the discrepancies between this and previous studies using similar stimulation protocols, could be the variation in memory paradigms used: Suthana et al. (2012) implemented a different virtual navigation task (taxi driver) to that of Jacobs et al. (2016) (arena environment), who also used a verbal memory task (which may correspond to the item memory aspect of our task). Moreover, the low stimulation amplitude applied and the small number of subjects in the present study could have impeded a behavioral effect. Furthermore, a different subset of neurons activated via fibers more likely in the perforant than the alvear pathway, as

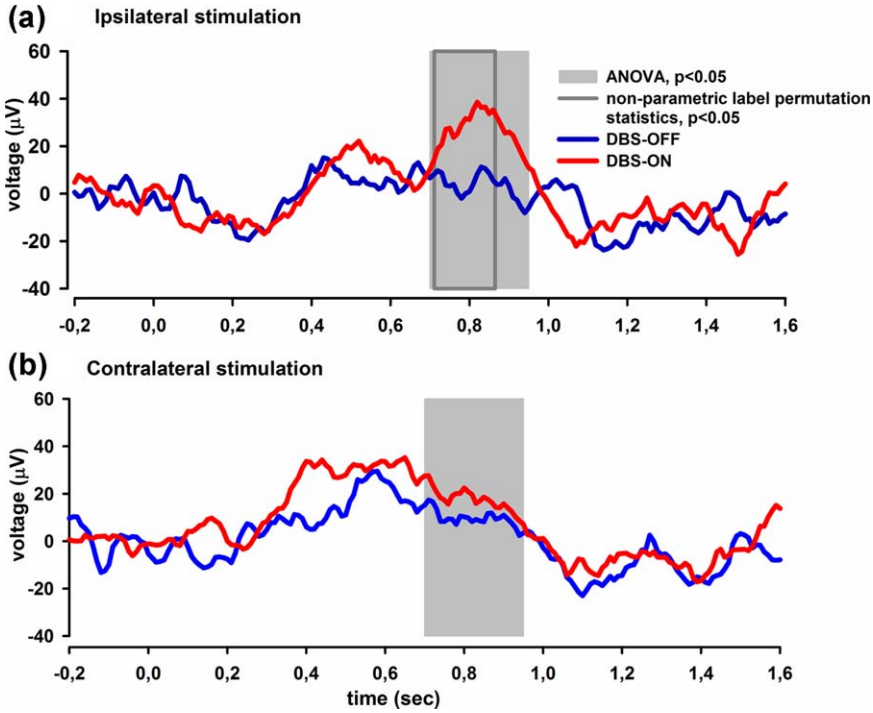

FIGURE 3 Mean amplitudes of event-related potentials within the anterior hippocampus during DBS on- vs. off-condition. An ANOVA revealed more positive amplitudes of ERPs in the anterior hippocampus (in each patient recorded from two neighboring contacts) for the 700–950 ms time window during entorhinal DBS. Nonparametric label permutation statistics confirmed this effect for the 711–865 ms time window on the ipsilateral side [Color figure can be viewed at wileyonlinelibrary.com]

reported by Suthana et al. (2012), could have influenced the behavioral outcome.

However, two factors argue against this explanation. First, the behavioral results are far from significant. Behavioral changes are not even consistent across experimental runs for any of the patients on an individual level. Second, in a previous study implementing in-phase vs. anti-phase rhinal-hippocampal 40 Hz stimulation with an even lower amplitude (0.01 mA), we observed a trend for memory modulation in the hypothesized direction (Fell et al., 2013). Nevertheless, as we investigated only seven patients, we cannot claim with any certainty that the statistical power was sufficient to exclude a possibly weak stimulation-related memory effect. It can only be stated that we did not observe any indication of such a memory effect in our small sample of patients.

Despite the clear absence of any behavioral effect, we found an effect of entorhinal DBS on anterior hippocampal ERPs. During DBS, the P600 component was more positive in the time range between 700 and 950 ms compared to the off-condition. This effect indicates that entorhinal stimulation with 50 Hz is, in principle, able to alter memory-related anterior hippocampal ERPs. The entorhinal area is connected to anterior hippocampal subfields such as the dentate gyrus via the perforant path originating from the angular bundle (Augustinack et al., 2010; Witter, 2007). Since in each patient one stimulation contact was approximately located in the angular bundle, stimulation very likely reached the perforant path. Thus, a possible candidate mechanism of enhanced ERPs observed in the DBS-on condition, is that entorhinal DBS may have stimulated afferents of the perforant path, which likely lead to a potentiation of synaptic responses as demonstrated in rodent experiments (Chen et al., 2010; Hansen & Manahan-Vaughan, 2015). Interestingly, an increased amplitude of the P600 potential was found in a previous study comparing processing of words with high vs. low imaginability (Klaver et al., 2005). As hypothesized, highly imaginable words were better remembered than words with a low imaginability. This behavioral effect may have been mediated by the increased P600 amplitude (e.g. Guillem et al., 1999; Klaver et al., 2005; Ludowig et al., 2008). Thus, the ERP effect observed in the current study does not rule out a potential positive influence on memory performance. Our study, however, did not reveal any indication for such a behavioral effect. Possibly, the stimulation amplitudes and resulting ERP effects were too small to result in statistically significant behavioral changes. Moreover, no effect of entorhinal DBS on intertrial phase locking in the theta range was observed, which is in accordance with the findings of Jacobs et al. (2016).

In conclusion, we provide evidence for a modulation of memory encoding-related potentials in the anterior hippocampus because of entorhinal DBS. However, we did not observe any effect of entorhinal DBS on memory performance. We cannot exclude that the lower stimulation amplitude and the differences between our memory paradigm and those of Suthana et al. (2012) and Jacobs et al. (2016), or the small sample size precluded detection of a behavioral effect. In light of the persistent controversy regarding the valence of entorhinal DBS on memory performance, other stimulation protocols, for instance, those targeting rhinal and hippocampal phase dynamics (Fell et al., 2013; Höhne, Jahanbekam, A., Bauckhage, C., Axmacher, N., & Fell, 2016), may be more promising with regard to a therapeutic enhancement of memory functions.

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