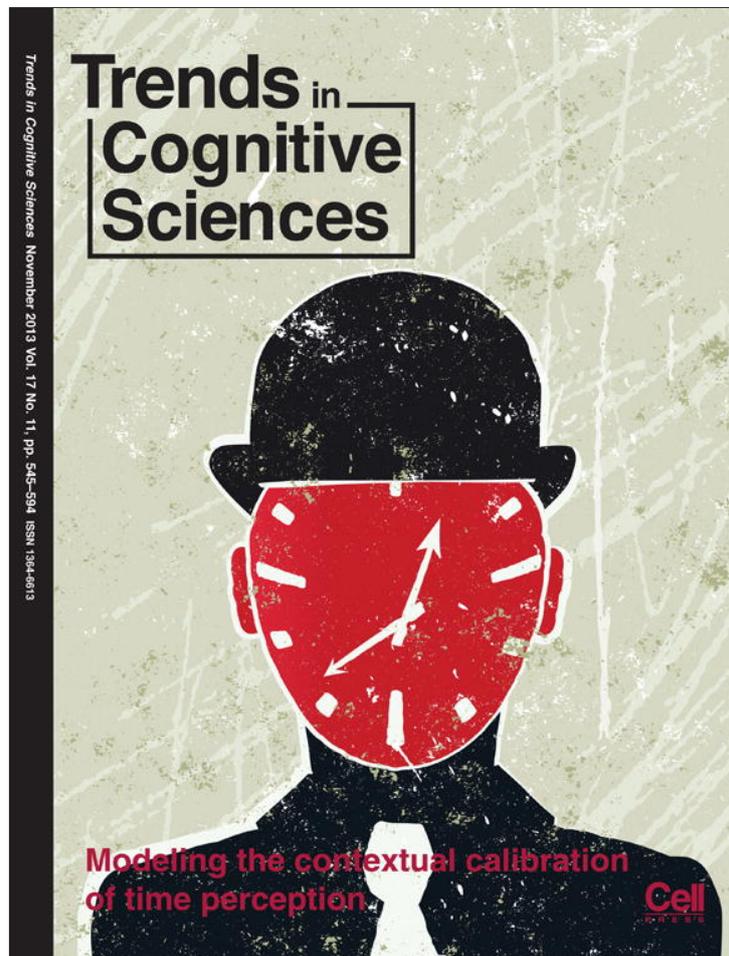


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Electrical engram: how deep brain stimulation affects memory

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Deep brain stimulation (DBS) is a surgical procedure involving implantation of a pacemaker that sends electric impulses to specific brain regions. DBS has been applied in patients with Parkinson's disease, depression, and obsessive-compulsive disorder (among others), and more recently in patients with Alzheimer's disease to improve memory functions. Current DBS approaches are based on the concept that high-frequency stimulation inhibits or excites specific brain regions. However, because DBS entails the application of repetitive electrical stimuli, it primarily exerts an effect on extracellular field-potential oscillations similar to those recorded with electroencephalography. Here, we suggest a new perspective on how DBS may ameliorate memory dysfunction: it may enhance normal electrophysiological patterns underlying long-term memory processes within the medial temporal lobe.

Investigating brain oscillations to guide DBS for memory dysfunction

Deep brain stimulation (DBS; see [Glossary](#)) has been applied to ameliorate symptoms in patients who do not respond to conventional pharmacological treatments in the context of disorders such as Parkinson's disease (PD), depression, obsessive-compulsive disorder, and temporal lobe epilepsy (TLE) [1]. More recently, DBS has been applied in patients with Alzheimer's disease (AD) [2–4]. AD patients are characterized behaviorally by significant progressive memory loss and cognitive decline, particularly with respect to learning new facts, forming new episodic memories, memory recall, and problem-solving. Hence, for DBS to be successfully implemented, it is crucial to map the dysfunctional neural mechanisms associated with the disease and identify the areas optimal for intervention. Furthermore, it is also critical to establish how DBS affects the disease and the specific type of electrical signaling pattern that yields the most effective therapeutic response [5].

In this review, we propose a new perspective on how DBS of the medial temporal lobe (MTL) and/or brain systems projecting to the MTL might be utilized to ame-

liorate memory dysfunction in AD patients. Specifically, we propose that identifying the normal neural oscillatory pattern underlying long-term memory (LTM) encoding and retrieval, and introducing this electrical pattern via DBS either to the MTL itself or to brain systems that project to the MTL, can improve memory deficits in AD patients [6]. Central to this proposal is the idea that identifying the normal physiological patterns underlying LTM processes is necessary for optimizing DBS to ameliorate memory dysfunction.

To address this new proposal, we focus on three inter-related questions:

- (i) How are neural oscillations related to long-term memory?
- (ii) How does DBS affect memory?
- (iii) How does DBS affect neural oscillations?

Throughout the review, we attempt to address these questions by integrating results from various fields of

Glossary

Coherence: this term is often used as a synonym for the term synchronization. Spectral coherence is a synchronization measure derived from the fast Fourier transform (FFT), which reflects the frequency-dependent correlation of both phase angles and amplitudes between two brain regions.

Cross-frequency coupling: interactions between certain characteristics (e.g., amplitude, phase, dominant frequency) of oscillations in different frequency ranges (typically extracted from broadband signals).

Deep brain stimulation (DBS): surgical procedure involving implantation of a brain pacemaker that sends electric impulses to specific regions of the brain.

Déjà vu: French for 'already seen'.

Déjà vécu: French for 'already lived'.

Flashback: involuntary immersion in a previous experience.

Illusions and hallucinations: perceptions of unreal phenomena as if they were real.

Inter-trial phase coherence: at certain time points within trials, certain phase angles of the neural oscillation preferentially occur. This is reflected by divergence of the distribution of phase angles at a certain time point across trials from a uniform distribution. Sometimes the term inter-trial phase-locking is used as a synonym.

Jamais vu: French for 'never seen'.

Optogenetics: method that uses light to control the electrical activity of genetically modified neurons.

Neural oscillations: rhythmic, wave-like neural activity that is generated by intrinsic neural mechanisms and by interactions between neurons.

Phase resetting: event-related reordering of the phase angles of an oscillation, in the sense that at a certain time point after the event, a certain phase value occurs with increased probability.

Phase synchronization: correlated occurrence of the phase angles of neural oscillations in two brain regions. This is reflected by divergence of the distribution of phase differences between the two regions from a uniform distribution.

Reminiscence: sudden involuntary recollection of a past memory.

Spike-field coherence: increased probability that action potentials (spikes) will occur at certain phase angles of local field-potential oscillations (and decreased probability that they will occur at other phase angles).

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Box 1. LTM processes and functional subdivision of the MTL

Declarative LTM can be investigated using a variety of different tasks that probe either free or cued recall, or recognition. Traditionally, it was believed that the MTL provides a unitary memory system that supports all declarative LTM processes, but does not play a role in short-term memory processes or non-declarative forms of LTM. More recent neuropsychological and neuroimaging studies, however, have suggested that the different subregions of the MTL are relevant for different memory processes [47]. According to this now prevailing view, the hippocampus proper is most relevant for encoding and retrieval of relational [70] and source memory (i.e., a stimulus together with a context) and for recognition based on recollection [71]. By contrast, adjacent structures in the parahippocampal gyrus, including parahippocampal cortex, entorhinal and perirhinal cortices (Figure 1), underlie encoding and retrieval of individual items and recognition based on familiarity [72]. According to a slightly different perspective, both the hippocampus and the adjacent perirhinal cortex may support associative memory, depending on the content of information [14]. These functional differences during normal memory processes may explain why stimulation of the hippocampus, compared to adjacent structures in the parahippocampal gyrus, leads to different memory-like phenomena.

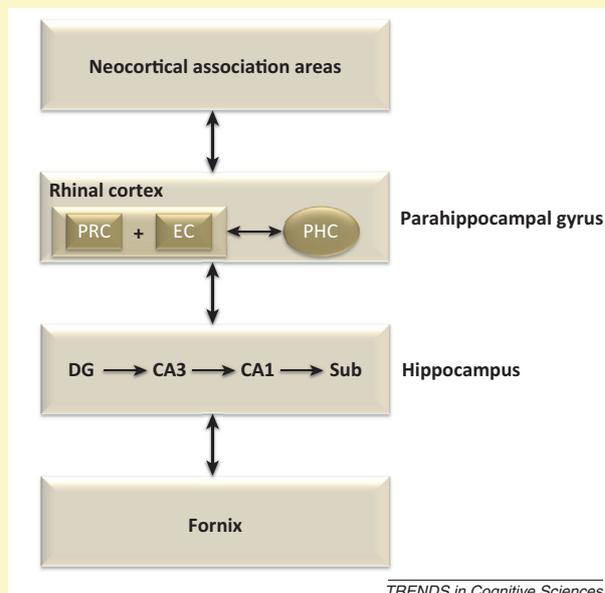


Figure 1. Schematic representation of subregions of the medial temporal lobe. PRC, perirhinal cortex; EC, entorhinal cortex; PHC, parahippocampal cortex; DG, dentate gyrus; CA3, cornu ammonis area 3; CA1, cornu ammonis area 1; Sub, subiculum.

research encompassing intracranial electroencephalography (EEG) studies on the oscillatory correlates of memory processes, work on *déjà vu* and *déjà vécu*, and electrical stimulation studies. At the end of the article, we provide some preliminary answers regarding the new proposal of using electrical stimulation parameters that mimic normal physiological LTM processes to enhance memory functions. We also suggest directions for future research that will enable a more complete account.

How are neural oscillations related to long-term memory?

Recent research suggests that different subregions of the MTL are relevant for different memory processes (Box 1). In what follows, we examine the role of neural activity in two frequency bands (gamma and theta, 30–100 and 3–8 Hz, respectively) in the context of the functions performed by different MTL structures.

Neuroelectrical correlates of MTL-based long-term memory: the role of gamma-band activity

Retrieval of declarative long-term memories has been characterized as ‘mental time travel’ back to the situation when an episode was initially encountered, or, in other words, as a reinstatement of encoding-related contents and brain activity patterns. This view is supported by several functional magnetic resonance imaging (fMRI) studies showing similar MTL blood oxygenation-level-dependent (BOLD) patterns during encoding and retrieval (for example, [7]). However, because DBS consists of the application of repetitive electrical currents, its effects can be most directly investigated by analysis of endogenous repetitive electrical currents – i.e., of EEG oscillations. Unfortunately, it is very difficult to investigate EEG oscillations within deep

brain regions such as the MTL with recordings from the scalp, and source reconstructions necessarily remain ambiguous (see [8] for recent advances using magnetoencephalography). By contrast, intracranial EEG recordings are ideally suited to explore oscillations within the MTL during LTM encoding and retrieval [9]. Indeed, results from several studies have shown that similar oscillations occur during encoding and retrieval. These effects have predominantly been observed in the high (gamma) frequency range, similar to the typical stimulation frequencies used in DBS studies: enhancements of hippocampal gamma-band activity have been described in word list-learning tasks with free recall during both successful encoding and retrieval [10,11]. In addition to enhancements of gamma power within the hippocampus, phase synchronization and similar bivariate (interaction) metrics have been analyzed during LTM processes. These studies showed that interactions between high-frequency activity in rhinal cortex and hippocampus appear to be similar during encoding and retrieval. Notably, given the close proximity of entorhinal and perirhinal cortices within the parahippocampal gyrus (see Figure 1 in Box 1), these regions are collectively labeled as ‘rhinal’ in many studies. Increases in stimulus-related gamma-band phase synchronization have been described during successful memory encoding within the MTL in relation to both free recall [12] and recognition memory [13]. During source memory retrieval, gamma coherence in the MTL was also enhanced [14]. Gamma-phase synchronization may support memory formation because action potentials occur predominantly during excitable phase ranges of these oscillations (spike-field coherence) [15], so that the synchronization of phases across regions leads to a stable temporal relationship among action potentials. As a result, phase synchronization may induce spike-timing-dependent synaptic plasticity [16].

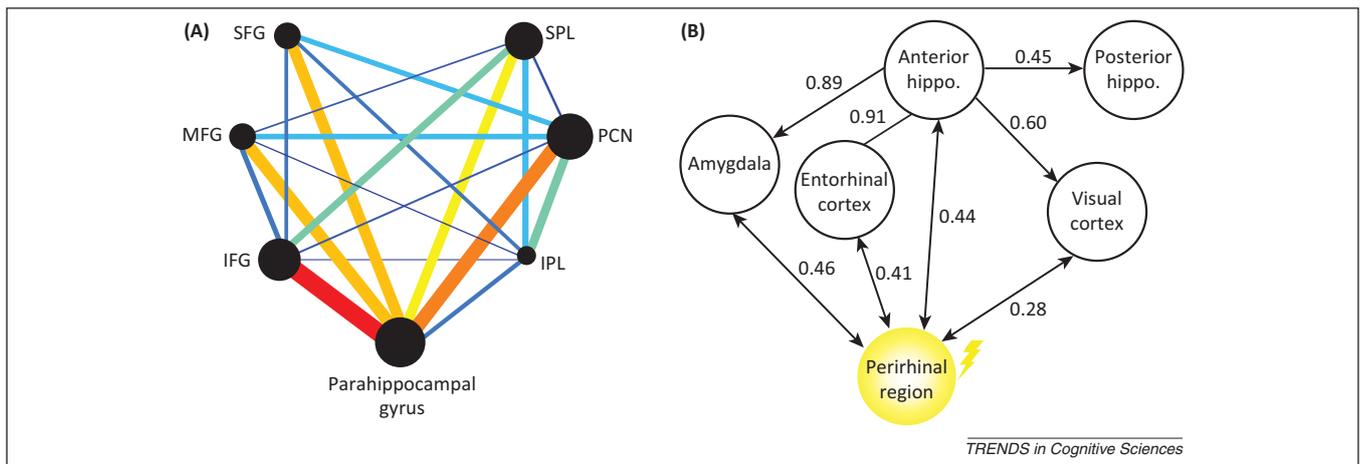


Figure 1. Synchronization effects related to long-term memory retrieval. **(A)** Using a graph theory approach, brain regions were treated as nodes in a network that were functionally connected via coherence during correct memory retrieval in the theta band. Warmer colors represent greater connectivity and the radius of each node denotes the relative number of connections in a specific network. As depicted, strong functional connectivity between parahippocampal gyrus (PHG) and prefrontal regions (SFG, MFG, IFG), PHG and precuneus (PCN), and PHG and superior parietal lobule (SPL) were observed during long-term memory retrieval. Reproduced with permission from [27]. **(B)** Functional coupling in the theta frequency range between brain regions involved in epileptic after-discharges. The arrows indicate the direction of causal relationships between the brain regions. Double arrows indicate that the two brain regions alternately take the lead. Numeric values represent the correlation coefficient, and the red lines represent significant correlation coefficients. As depicted, those stimulations of the perirhinal region at 2 mA that induced *déjà vu* experiences were associated with a strong connectivity in the theta range between medial temporal regions and with the visual area. Reproduced with permission from [28].

The functional role of gamma synchronization during retrieval is less clear within this framework, however. One possibility is that gamma synchronization serves to bind several smaller groups of neurons that each represent parts of previously learned information [17]; in other words, gamma synchronization supports an integrated representation of items that have been presented together in an associative learning experiment. Enhancements of gamma synchronization during retrieval could thus reflect the reinstatement of a previously learned association. It is still unknown, however, if high-frequency DBS actually induces activity in the gamma frequency range in downstream regions or oscillations with a lower frequency [18,19].

The role of theta oscillations in memory processes

Work in rodent electrophysiology suggests that apart from gamma-band activity, theta oscillations in the MTL also play a crucial role in LTM processes. Theta oscillations appear to be correlated with gamma-band activity [16,20–22]. Theta oscillations may be relevant because they provide a temporal framework for the representation of episodes and sequences [16,22]. In view of this extensive theoretical background, intracranial EEG evidence of a supportive role of theta oscillations in the hippocampus for LTM is surprisingly scarce. Several studies reported a reduction in theta power in the hippocampus during memory encoding in putatively hippocampus-dependent paradigms [11,13,23], and this effect may be particularly pronounced if the context differs between encoding and retrieval [24]. Furthermore, it has been suggested that the human correlate of rodent theta oscillations in the hippocampus is in the delta (1–3 Hz) frequency range [21,25–27]. In contrast to the reduced theta activity in the hippocampus during encoding, theta-phase synchronization between rhinal cortex and hippocampus increases during memory encoding [13], and neocortical regions become synchronized with the MTL during memory retrieval [27].

Figure 1A shows this increase in theta coherence with the parahippocampal gyrus during successful retrieval of spatial environments. This is in line with observations that induction of memory-related phenomena by electrical stimulation is accompanied by increased theta synchronization in the hippocampus and neocortical regions (see next section) [28]. As shown in Figure 1B, functional connectivity in the theta frequency range between the perirhinal region (part of the parahippocampal gyrus) and adjacent regions significantly increased during perirhinal stimulations that were followed by *déjà vu*.

In addition, certain phase-based characteristics, such as inter-trial phase coherence (also called inter-trial phase locking), appear to be relevant for LTM encoding. An increase in inter-trial phase coherence within the rhinal cortex and hippocampus, most prominently in the alpha and beta range, accompanies LTM formation and represents the most predictive measure of successful encoding [13]. Rhythmic stimulation via DBS likely induces both power effects and phase resetting, and phase resetting effects may also be relevant for facilitation of memory functions in animals [29] and humans [30].

Theoretically, memory retrieval should not only reinstate encoding processes (and therefore be similar to neural activity during encoding) but should also exhibit clear differences to encoding-related activity. It has been suggested that at a psychological level, encoding and retrieval occur during specific ‘modes’ that are mutually exclusive. Computational models of MTL function and empirical research suggest that encoding relies on pattern separation, that is, distinct storage of neural stimulus representations to avoid interference, whereas retrieval depends on pattern completion, which is the matching of an event to a similar but not identical previous experience [31]. Although gamma and theta oscillations appear to play a role in both processes (see above), more subtle differences (e.g., in the relative timing of

action potentials with regard to the theta phase) may distinguish encoding and retrieval [32].

How does DBS affect memory? *Déjà vu* and *déjà vécu*

The idea of applying electrical stimulation to the MTL to manipulate memory processes is not new. In the following, we describe studies showing that stimulation of the MTL in TLE patients evokes memory-related phenomena such as *déjà vu* and *déjà vécu*.

Spontaneous seizures and stimulation of the temporal lobe evokes memory-related phenomena

The idea that dreamy states (i.e., vivid recollections of past memories and *déjà vu* experiences) can be elicited via electrical stimulation of the MTL in TLE patients was first tested by Wilder Penfield (1891–1976). Prior to temporal resection to treat TLE, Penfield and colleagues observed that direct electrical stimulation (at frequencies above 40 Hz) of the lateral superior temporal lobe elicited ‘dreamy states’ similar to experiences reported prior to spontaneous seizures [33]. Penfield expanded the definition of ‘dreamy states’ to include *déjà vu*, *déjà vécu*, *jamais vu*, flashbacks or reminiscences, illusions, and hallucinations, and termed them experiential phenomena.

In addition to replicating Penfield’s results, subsequent studies found that these experiential phenomena depend on stimulation of the MTL rather than of the lateral temporal neocortex [34,35]. Notably, the discrepancy in results between Penfield’s and other studies can be explained by the fact that after-discharges of the electrical stimulation of lateral superior temporal lobe can spread towards the MTL and thus elicit experiential phenomena [36] (for a discussion of current spread, see Box 2). Table 1 summarizes the brain regions that evoke memory-related phenomena following electrical stimulation.

Interestingly, *déjà vu* and *déjà vécu* can also be observed in healthy populations [37]. The main difference between the two phenomena is the account of their experience: subjects who report *déjà vécu* tend to have more contextual details compared to those who report *déjà vu*. (For a description of *déjà vu* and *déjà vécu*, please refer to [38].) *Déjà vécu* experiences are reminiscent of observations in patients who suffer from confabulation [39]. Furthermore, whereas *déjà vu* does not lead to any behavioral impairment, *déjà vécu* is associated with impaired cognitive behavior that accompanies the sensation of errant recognition, as in cases of older adults with dementia [40]. In addition to the stimulation studies mentioned above, neuroimaging techniques have been used to validate the role of MTL in *déjà vu* and *déjà vécu*, including 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) [41,42] and single-photon emission computed tomography (SPECT) [43,44].

Regional and electrophysiological basis of *déjà vu* and *déjà vécu*

Although the above-mentioned studies amply demonstrate the relevance of the MTL for the induction of *déjà vu* and *déjà vécu*, it is still an open question as to whether these phenomena rely on distinct processes, which may then also be supported by different brain structures, or if they

Box 2. To what degree do electric fields induced by DBS spread to neighboring and related brain systems?

A crucial issue in DBS is the spread of current and how the volume of tissue activated by DBS (VTA) can be estimated. A variety of factors contribute to current spread, including the location and shape of the electrodes, stimulation parameters, whether monopolar or bipolar stimulation is applied, tissue conductivity, properties of the electrode–tissue interface, the orientation of neurons and neural layers, and neural connections. Several efforts have been undertaken to predict VTA based on volume conduction models and neuronal cell models [73]. For subthalamic nucleus stimulation in PD patients, finite element modules incorporating individual anatomical and diffusion tensor magnetic resonance data have been used [74]. It has been shown, for instance, that clinically effective stimulation parameters result in activation of myelinated axons over a volume that spreads outside the borders of the STN [75], and that side effects of STN stimulation on cognitive-motor performance can be minimized by choosing stimulation parameters based on computational modeling [69].

For DBS of the MTL, the issue of current spread is still unresolved. In general, current spread is less probable if stimulation amplitudes are low [6] and in bipolar stimulation with close-by electrode contacts [30], but cannot be excluded completely. In some cases, current spread is actually intended, for instance, in the case of fornix stimulation for activation of hippocampal neurons [2,3]. In other cases, current spread may be unintended but likely. For example, stimulation of the rhinal cortex probably activates hippocampal neurons because of the dense monosynaptic connections between the rhinal cortex and hippocampus [30]. Thus, caution is required when deducing functional dissociations of MTL subregions from DBS data or when interpreting memory enhancement effects based on stimulation of specific subregions. Computational modeling studies, similar to those for DBS of the STN, are necessary and desirable to estimate VTA via DBS of specific MTL loci with different stimulation settings.

represent only two different levels of magnitude of the same process. Three different theoretical accounts have been offered. First, several studies suggest that 50-Hz stimulation of the rhinal cortex induces *déjà vu* (but not *déjà vécu*), whereas the opposite is true after stimulation of the hippocampus [45,46]. It is then believed that *déjà vu* is due to impaired familiarity, whereas it is proposed that *déjà vécu* is generated by an erroneous sense of recollection [40]. More specifically, this model hypothesizes that abnormal theta oscillations in the hippocampus, which signal encoding and retrieval simultaneously, disrupt the process of encoding novel information, and thus generate *déjà vécu*. This is in line with results emphasizing the difference rather than the similarities between encoding and retrieval processes, in particular with regard to theta oscillations [32]. Together, these studies suggest a double dissociation between *déjà vu* and *déjà vécu*: the former results from disruption of the rhinal cortex, whereas the latter is due to compromised processing in the hippocampus. They are reminiscent of a theoretical framework that proposes a qualitative distinction between memory processes supported by the hippocampus and those that rely on regions within the parahippocampal gyrus (Box 1) [47].

Second, other studies suggest that *déjà vu* relies on an impairment of rhinal cortex processing that interacts with an intact hippocampus: According to this view, *déjà vu* is generated by erroneous activation of the rhinal cortex (resulting in an inappropriate feeling of familiarity) that interacts with an intact (hippocampus-dependent)

Table 1. Summary of brain regions in which memory-related phenomena could be elicited in TLE patients^a

Refs	Patients	Stimulation						Brain region stimulated	Effects ^b
		Pulse type	Pulse duration (ms)	Stimulation duration (s)	Frequency (Hz)	Voltage (V)	Current (mA)		
[36]	16	Rectangular, unidirectional	1	5	50	–	2–12	Hippocampus, amygdala, PHG, temporal neocortex	Dreamy states
[28]	1	Square waves with alternating polarity	1	5	50	–	1.5–2.5	Perirhinal	Experiential
[45]	24	Bipolar	1	5	50	–	1.37	Entorhinal, terirhinal	<i>Déjà vu</i> (EC), <i>déjà vécu</i> (PRC)
[46]	7	Bipolar	1	5	50	–	0.5–2	R entorhinal, L entorhinal, L perirhinal	<i>Déjà vu</i> (EC), <i>déjà vécu</i> (PRC)
[76]	35	Square, bipolar	0.5	–	–	–	0.5–4	Hippocampus, amygdala, PHG	Experiential
[77]	36	Lilly waves with alternating polarity	–	0.1	~10	5	≤10	Hippocampus, amygdala	Experiential
[78]	1	Biphasic	0.3–0.6	1–2.8	50	–	–	Left inferior temporal lobe	Vivid recollection of past memories
[33]	69	Square	2–5	–	40–100	1–5	0.005–0.5	Lateral and superior surfaces of the FTC, mainly R hemisphere	Experiential
[35]	16	Biphasic rectangular	1	5	50; 1 (P10)	2.5–6 (P1–P5)	1.5–3 (P6–P15)	Hippocampus, amygdala, PHG	Dreamy states

^aAbbreviations: –, data not available; P, patient; L, left; R, right; EC, entorhinal cortex; PRC, perirhinal cortex; PHG, parahippocampal gyrus; FTC, first temporal convolution.

^bIf no region is indicated, there is no specific information in the paper. Note that only some studies made clear indications of the memory-related phenomena associated with specific stimulated regions.

recollection process, resulting in a correct subjective evaluation that the seemingly familiar experience is actually new [48]. In other words, the hippocampus is required to ‘monitor’ the dysfunctional rhinal activity. Indeed, it was found that stimulation of the rhinal cortex only elicited *déjà vu* if the stimulation was followed by enhancement of theta-phase synchronization within the MTL [28], suggesting that an interaction between the rhinal cortex and hippocampus is necessary for *déjà vu* experiences (Figure 1B). Again, this result fits in the framework of a double dissociation between the memory functions of the subregions of the MTL [47]. More specifically, it suggests that interactions with parahippocampal structures in the theta frequency range are relevant for both pathological (*déjà vu*) and veridical retrieval (Figure 1A) [27].

Third, there are results suggesting a continuity of *déjà vu* and *déjà vécu*. According to this view, they reflect the same neural mechanisms and *déjà vécu* is merely an extension of *déjà vu* [35]. *Déjà vu* is then supposed to be generated by a low-level abnormality of familiarity processes that is closely linked to activity within the rhinal cortex, whereas additional recruitment of other parts of the MTL, such as the hippocampus, leads to the stronger phenomenon of *déjà vécu* [39]. This view fits in the framework of a qualitative continuity of memory processes supported by different subregions of the MTL (Box 1). Despite differences in the proposals regarding the induction of *déjà vu* and *déjà vécu*, these studies provide converging evidence that stimulation of the rhinal cortex and hippocampus induces memory-related phenomena. Nevertheless, the proposals reflect different views in the ongoing discussion on whether the MTL is a unitary memory system or whether there are qualitative differences between

hippocampus-dependent and -independent memory functions. Even so, these findings only demonstrate that memory functions can be specifically disrupted by electrical stimulation of the MTL subregions. By contrast, results from DBS studies in PD and TLE patients have provided evidence that MTL memory functions are typically negatively influenced by stimulation of the basal ganglia, but not by stimulation of the MTL itself.

How does DBS affect memory? Incidental memory effects

To understand how DBS affects memory, it is crucial to examine the effects of DBS in specific brain regions with respect to memory functions. In what follows, we examine the memory effects that result from stimulation of the basal ganglia in PD patients and of the fornix or the MTL in TLE patients. These results are summarized in Table 2.

DBS of the basal ganglia

Overall, although DBS has been successfully applied to the basal ganglia to alleviate motor dysfunction in PD patients, it appears to impair verbal memory in these patients, and the verbal memory impairment persists across long periods of time (Table 2). This was also supported by meta-analyses of DBS of the subthalamic nucleus (STN) in PD patients [49,50]. These studies consistently and reliably demonstrated memory decline in the verbal domain in spite of reduced patient dependence on levodopa therapy and behavioral benefits observed in the motor domain [49,50]. This effect may be related to mutual inhibition of memory systems within basal ganglia and the MTL [51]: if DBS in PD patients normalizes cognitive

Table 2. Overview of DBS studies reporting the impact of stimulation of the subthalamic nucleus (STN) in PD patients, or the MTL or fornix in TLE patients^a

Refs	Patients	Stimulation parameters				Brain region stimulated	Verbal memory	Nonverbal memory	Executive functions
		Pulse width (µs)	Frequency (Hz)	Voltage (V)	Current (mA)				
STN stimulation in PD patients									
[79]	15 PD	–	130	3.1	0.04–0.08	Bilateral STN	No change	No change	Improved
[80]	6 PD	60	25	1.5–2	–	Bilateral STN	Improved	–	Improved
[81]	62 PD	60.5	137	2.4	–	Bilateral STN	Declined	No change	No change
[82]	6 PD	60–90	130–185	–	1–5	Bilateral STN	Declined	Improved	No change
[83]	19 PD	61.6	146.3	3.2	–	Bilateral STN	Declined	No change	No change
[84]	58 PD	60	130	0–7	–	Bilateral STN	Declined	No change	No change
[85]	20 PD	60	185	2.64–2.89	–	Bilateral STN	Declined	No change	Improved
[86]	26 PD	92.1	178.8	3	–	Bilateral STN	Declined	No change	No change
[87]	9 PD	–	–	–	–	Bilateral STN	Declined	No change	Declined
[88]	32 PD	60	130	–	–	Bilateral STN	Declined	Declined	No change
[89]	1 PD	60	130	3.5–4.2	–	Bilateral STN	Improved	No change	No change
[90]	77 PD	–	–	–	–	Bilateral STN	Declined	No change	No change
[91]	24 PD	500–1000	130	0.04–0.08	–	Bilateral STN	Declined	No change	No change
[92]	24 PD	72.5	144	3.2	–	Bilateral STN	Declined	Improved	No change
[93]	46 PD	–	–	–	–	Bilateral STN	Declined	No change	Declined
[94]	49 PD	66	184.8	3	–	Bilateral STN	–	Declined	–
[95]	18 PD	63.2	157.86	2.71	–	Bilateral STN	Declined	No change	–
[96]	24 PD	–	–	–	–	Bilateral STN	Declined	No change	No change
[97]	20 PD	60	144.1	2.9	–	Bilateral STN	No change	No change	No change
[98]	76 PD	60.5	137	2.4	–	Bilateral STN	Declined	–	Improved
[99]	42 PD	60	185	2.6	–	Bilateral STN	Declined	No change	No change
[100]	11 PD	–	–	–	–	Bilateral STN	Declined	Declined	–
[101]	34 PD	–	–	–	–	Bilateral STN	Declined	No change	Declined
[102]	135 PD	–	–	–	–	Bilateral STN	Declined	No change	No change
[103]	55 PD	50–100	100–200	>4	–	Bilateral STN	Declined	No change	Declined
[104]	37 PD	–	–	–	–	Bilateral STN	Declined	Declined	No change
[105]	123 PD	60	130	–	–	Bilateral STN	Declined	No change	Declined
[106]	44 PD	–	–	–	–	Bilateral STN	Declined	No change	Declined
[107]	17 PD	63.5–65.3	165–169.4	3.31–3.54	50.7–75.6	Bilateral STN	Declined	–	–
[108]	65 PD	–	–	–	–	Bilateral STN	Declined	No change	No change
MTL or fornix stimulation in TLE patients									
[54]	8 TLE	450	130	0.5–2	–	Bilateral AH	Declined	Declined	No change
[55]	9 TLE	250	2	3	–	Bilateral H	Decline	Declined	–
[53]	11 TLE	200	5	–	8	Fornix	–	–	–
[109]	2 TLE	90	185	≥0.5	–	Bilateral H	Improved	Improved	No change
[110]	10 TLE	450	130	1–2.5	–	L AH (5P), R AH (3P), bilateral AH (2P)	Improved	–	No change
[52]	9 TLE	450	130	<3	300	Bilateral H	Improved	Improved	No change

^aStudies were included if neuropsychological test results were compared before and after surgery. Abbreviations: –, data not available; P, patient; L, left; R, right; PD, Parkinson's disease; TLE, temporal lobe epilepsy; AH, amygdala-hippocampus; H, hippocampus. Verbal memory includes neuropsychological tests such as the Rey auditory verbal learning test, the California verbal learning test, the paired associate learning test, verbal fluency (semantic, phonological, or letter), digit symbol, and story-telling. Non-verbal memory includes the line orientation visuospatial test, the visuospatial memory test, the Rey-Osterrieth complex figure, the Benton visual retention test, facial recognition, and Raven's progressive matrices. Executive functions include neuropsychological tests such as Stroop tests, trail-making tests, a clock drawing test, the Tower of Hanoi, and the Wisconsin card sorting test.

and motor functions in the basal ganglia, it may simultaneously deteriorate memory processes in the MTL.

DBS of the MTL and fornix

A completely different picture emerges from studies on DBS of the MTL and fornix in TLE patients: stimulation of the hippocampus reduced the frequency and number of seizures, and did not impair memory functions (Table 2). Even after 18 months of electrical stimulation treatment, TLE patients did not show a further decline in different memory tests (Rey verbal learning, digit counting, logic memory and Wind Mill visual-spatial Bezarez test), and even a tendency to improve in these tests [52], suggesting

that DBS of the MTL may improve memory. Furthermore, a recent study demonstrated that low-frequency stimulation of the fornix might improve memory functions as measured by the Mini-Mental State Examination (MMSE), although practice effects might be the cause of the improvement in MMSE scores [53]. Despite this, other studies demonstrated that memory can be suppressed by MTL stimulation at higher amplitudes [54,55].

How does DBS affect memory? Using DBS to improve memory functions

The studies reported thus far suggest that DBS of the MTL and related brain regions may be used to improve memory

Table 3. Overview of DBS studies reporting stimulation of the MTL or fornix to improve memory^a

Refs	Patients	Stimulation parameters					Brain region stimulated	DBS phase	Memory tested
		Pulse type	Pulse width (μ s)	Frequency (Hz)	Voltage (V)	Current (mA)			
[58]	1 OB	Biphasic	60	130	3.0	–	Bilateral fornix	Encoding + retrieval	Recollection + familiarity
[3]	6 AD	Biphasic	90	130	3.0–3.5	–	Bilateral fornix	Encoding + retrieval	ADAS-Cog, MMSE
[4]	5 AD	Biphasic	90	130	3.0–3.5	–	Bilateral fornix	Encoding + retrieval	ADAS-Cog, MMSE
[2]	1 AD	Biphasic	210	130	2.5	–	Bilateral fornix	Encoding + retrieval	ADAS-Cog, MMSE
[6]	11 TLE	Sine wave	–	40	–	0.01	Bilateral rhinal + hippocampi	Encoding + retrieval	Word list learning task with free recall
[30]	7 TLE	Biphasic	300	50	–	0.5–1.5	Bilateral entorhinal cortices	Encoding	Navigation memory test
[61]	6 TLE	Biphasic	1000	50	–	10–20% below ADT	Unilateral hippocampus	Encoding	Recognition tests with words, objects and faces

^aAbbreviations: –, data not available; OB, obesity; AD, Alzheimer's disease; TLE, temporal lobe epilepsy; ADT, after-discharge threshold; ADAS-Cog, Alzheimer's Disease Assessment Scale, Cognitive Subscale; MMSE, Mini-Mental State Examination.

functions. Indeed, this hypothesis is supported by several recent studies, as reviewed below (Table 3).

DBS of the hypothalamus/fornix

The fornix is a large axonal bundle that connects the hypothalamus to the caudal part of the hippocampal formation [56]. Animal and human studies demonstrated that a lesion to the fornix disrupts LTM, but not working memory and general intelligence [56,57]. An incidental finding in a case study of a patient with bilateral hypothalamic DBS for treatment of morbid obesity demonstrated spontaneous reminiscences of past experiences as a result of stimulation [58], possibly due to activation of the MTL. This prompted the proposal that DBS of the hypothalamus/fornix may potentially be an important therapeutic approach for enhancing memory in AD patients. Notably, such reminiscences are dysfunctional phenomena, because they occur in an uncontrolled and involuntary manner that is not useful in guiding behavior. However, they may be due to a lower threshold for access to memories that can also be exploited for voluntary memory retrieval. Indeed, cumulative evidence from animal studies further supports this hypothesis. Specifically, it was demonstrated that electrical stimulation of the hypothalamus/fornix improved spatial memory and induced hippocampal neurogenesis [59,60]. More recent studies of fornix DBS in AD patients also supports the hypothesis that electrical stimulation of the hypothalamus/fornix may enhance memory: It was demonstrated that fornix DBS in AD patients increased neural activity within the MTL and within the default mode network (i.e., the network of brain regions that are activated during wakeful rest), and increased sustained glucose metabolism in temporal and parietal lobes [3]. Evaluation of cognitive functioning suggested possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients. Likewise, DBS of the fornix in five patients with mild AD led to increased glucose metabolism in widespread brain regions after 1 year of DBS, and this was associated with improved cognition, memory, and quality of life [4]. Another study found similar results when stimulating the hypothalamus/fornix in one AD patient: memory remained stable after 1 year of DBS treatment and glucose metabolism was

increased in the MTL [2]. These studies suggest that stimulation of the hypothalamus/fornix might induce synaptic plasticity, increase overall glucose metabolism in the human brain, and reverse the memory impairment observed in AD patients.

How does DBS affect neural oscillations?

It is an open question how DBS of the MTL modulates memory. One possibility is that it facilitates or even induces Hebbian long-term potentiation (LTP) as a neural correlate of learning and memory formation [16]. In this case, DBS would act by supporting physiological processes related to memory encoding. Alternatively, DBS may improve memory retrieval by supporting the reinstatement of previously learned information. This may, for example, be accomplished by an effect of DBS on the synchronization of neural assemblies (which represent the information that needs to be retrieved [17]). Thus, DBS may support retrieval by mimicking oscillatory activity patterns that have previously occurred during encoding, without necessarily affecting synaptic plasticity. Conversely, such an effect of DBS on reinstatement may also account for cases in which stimulation during encoding actually impairs subsequent retrieval [61]; this may occur if DBS is applied at a frequency or an artificially high amplitude that interferes with encoding processes, so that encoding-related activity cannot be successfully reproduced during subsequent retrieval. Finally, there could be a link between DBS and neurogenesis in the hippocampus, as suggested by animal studies [62,63].

Direct evidence of how DBS of the MTL enhances memory comes from recent DBS studies in TLE patients. Specifically, it was demonstrated that entorhinal stimulation during the learning phase of a virtual reality navigation task was associated with improved spatial memory performance (Figure 2A). Although direct hippocampal stimulation did not affect performance, four patients showed theta-phase resetting in the hippocampus during entorhinal stimulation [30], and previous studies have shown that hippocampal phase resetting is a good predictor of successful memory formation [13]. In addition, further subsequent analyses of cross-frequency coupling revealed increased theta–gamma coupling in the hippocampus following

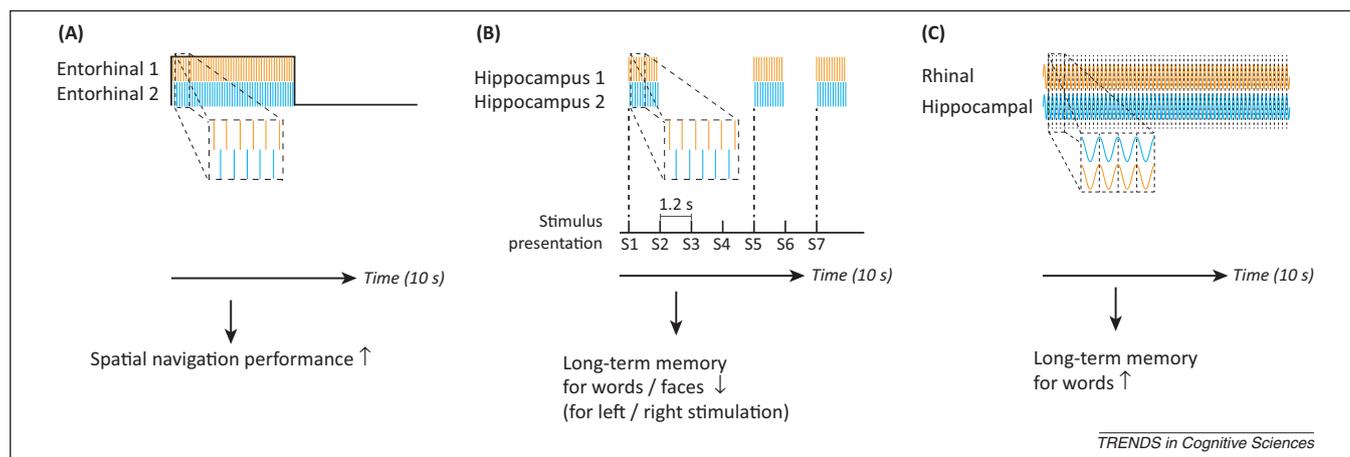


Figure 2. Effects of deep brain stimulation (DBS) of the MTL. **(A)** Block patterns (5 s on, 5 s off) at a frequency of 50 Hz with a pulse width of 300 μ s and a current amplitude of 0.5–1.5 mA were applied to the entorhinal cortex using a bipolar stimulation scheme. This stimulation scheme was delivered during learning in a spatial navigation paradigm and improved subsequent retrieval performance. **(B)** Biphasic stimulation patterns at a frequency of 50 Hz with a pulse width of 1000 μ s and an intensity of 10–20% below after-discharge threshold (ADT) were applied to the hippocampus during encoding. Stimulation of the left hippocampus specifically impaired subsequent recall of words, whereas stimulation of the right hippocampus deteriorated later retrieval of faces. **(C)** Continuous sine-wave patterns at a frequency of 40 Hz and a current amplitude of 0.01 mA were applied synchronously to rhinal and hippocampal contacts (in-phase, 0° phase lag) during both encoding and retrieval. Stimulation with a 0° phase lag improved memory for words in a word-list learning task.

entorhinal stimulation [64]. Results from a recent computer simulation study modeling the effect of electric stimulation in the hippocampus on theta–gamma cross-frequency coupling [65] shed light on the potential mechanisms underlying this effect and suggest that the frequency ratio of stimulation-induced cross-frequency coupling decreases with the stimulation strength if positive fields are applied. Conversely, it was found that direct DBS of the hippocampus did not yield consistent memory effects [30]. In fact, a previous study described that hippocampal stimulation during encoding, time-locked to stimulus presentation, significantly impaired subsequent recognition, and this effect depended on the laterality of electrical stimulation (left vs right) for different material (words vs objects vs faces) (Figure 2B) [61]. This is consistent with the deterioration of memory in neuropsychological tests reported in some earlier studies after hippocampal stimulation [54,55]. Furthermore, a recent pilot study by our own group demonstrated a moderate improvement in a verbal memory paradigm on stimulation of rhinal cortex and hippocampus synchronously in the gamma frequency range with zero-degree phase lag (Figure 2C) [6]. Stimulation was applied during both encoding and retrieval. In this study, our explicit aim was to mimic oscillatory patterns observed during normal memory formation, so we used a much lower stimulation amplitude than in typical DBS studies (0.01 mA vs \sim 1 mA).

Collectively, these studies raise the question of how DBS affects different memory processes (e.g., encoding vs retrieval, familiarity vs recollection) and whether DBS should target these processes separately. Alternatively to such a ‘tailored’ stimulation, DBS may target neural processes that support several memory functions. For example, DBS may support a neural process that occurs (with different strengths) during both familiarity-based and recollection-based recognition memory [66], or a process that occurs during both encoding and retrieval.

Concluding remarks

The results reviewed here allow for provisional answers to the three central questions raised at the beginning of this review, but also point to unresolved issues. Related to the question ‘How does DBS affect memory?’, it has been shown that whereas basal ganglia stimulation in the gamma frequency range impairs LTM (Table 2) – possibly by downregulating the MTL [51] – gamma-frequency stimulation of the MTL is less detrimental (Table 2 and Table 3) and can induce memory-related phenomena such as *déjà vu* and reminiscences (Table 1). Even though these phenomena are dysfunctional, they may be related to a facilitated access to memory traces and thus to retrieval processes. The effects of stimulation at lower frequencies still need to be investigated further.

Gamma-frequency DBS has been applied to two structures projecting to the hippocampus, the entorhinal cortex [30] and the fornix/hypothalamus [2–4,58]. These studies provided first evidence that DBS of the MTL itself, or of structures projecting to the MTL, may improve memory. Furthermore, results from two studies were related to the question ‘How does DBS affect neural oscillations?’ Entorhinal stimulation increased the phase stability of theta oscillations in the hippocampus [30], whereas perirhinal cortex stimulation specifically induced memory-related phenomena if the stimulation was followed by theta synchronization [28]. Although more studies are required to corroborate these findings, they suggest that gamma-frequency stimulation of input structures to the MTL typically affects EEG oscillations in downstream regions at lower (e.g., theta) frequencies rather than in the gamma band itself. These results are consistent with findings from other cortical networks [18,19] (but see [67]).

What is the functional relevance of such theta phase resetting and theta synchronization, or, more generally, how are oscillations related to long-term memory? Several studies point to the role of MTL theta synchronization [12,13] and MTL–neocortical theta coherence for memory

Box 3. Ethical considerations and alternative approaches

The question of whether DBS is ethically a suitable treatment for patients who do not react to conventional (pharmacological) treatments still remains controversial. Although DBS may help to mitigate the behavioral symptoms of the diseases, complications relating to the surgery, hardware, and stimulation may outweigh the possible benefits of DBS [111]. Furthermore, it is the responsibility of researchers to ensure that stringent regulations, regarding issues such as patient selection, informed consent, resource allocation, responsible publishing, and conflicts of interests, are upheld when conducting DBS studies [1]. Only then can the benefits and feasibility of DBS be accurately assessed as an alternative therapeutic approach to ameliorate memory dysfunction in patients in the longer term.

In parallel, other approaches for modulation of neural activity are being developed. A recent proof-of-concept study demonstrated that, compared to conventional chronic DBS, use of a brain-computer interface to control DBS required less stimulation time and energy consumption to reduce motor deficits in advanced PD [112]. In addition, it was shown that a custom-designed neural prosthesis (according to a specific nonlinear model) could be used to monitor hippocampal oscillations during memory encoding in rats. Then this information was used to predict oscillations associated with successful retrieval, and to deliver electrical stimulation pulses that mimic these retrieval-related activity patterns to improve memory [113]. Advances in optogenetics indicate that it can be used in combination with DBS to systematically activate or inhibit MTL circuitry to facilitate learning and memory in rodents [114–116]. Despite these advances, various safety and technical questions remain to be addressed before the approach can be applied in humans.

Box 4. Outstanding questions

- How exactly are memory-related phenomena such as *déjà vu* and *déjà vécu* related to veridical memory processes?
- Should DBS target specific memory processes (encoding vs retrieval, familiarity vs recollection) separately, for example by stimulating different subregions of the MTL? Should this depend on the specific memory dysfunctions in different patient populations?
- What is the functional role of gamma-band activity in *déjà vu* and *déjà vécu*? Does DBS of the MTL induce not only theta oscillations but also gamma band activity?
- Does DBS that uses low-amplitude stimulation parameters to mimic normal physiological activity achieve a better clinical outcome in the longer term compared to high-amplitude stimulation parameters?
- To what degree do electric currents induced by DBS spread to neighboring and remote brain regions, and what are the factors governing this current spread?

processes (Figure 1A) [27]. In principle, synchronization may occur if theta phase resetting is simultaneously induced in the hippocampus – which occurs after entorhinal stimulation (Figure 2A) [30] – and in connecting structures. Furthermore, MTL gamma-phase synchronization [12,13,16] and gamma coherence [14] support memory processes and may be mimicked by simultaneous rhinal-hippocampal stimulation (Figure 2C) [6]. Mechanistically, phase synchronization may improve memory by enhancing communication [68], by promoting synaptic plasticity [16], and/or by supporting binding of neural assemblies [17].

A very important although still largely unresolved question is to what degree the electrical current applied by DBS spreads to neighboring and related brain systems (Box 2). Computer simulations have been used to customize

stimulation parameters individually to mitigate motor dysfunction in PD patients while minimizing the impact on other cognitive functions [69]. With regard to MTL stimulation, although low-amplitude stimulation may result in more focal activation of specific brain regions [6], further studies are necessary to better estimate the volume of tissue activated via DBS to understand how current spreads to other subregions of the MTL beyond the one stimulated and how to dissociate DBS effects of specific MTL loci.

In conclusion, the present review suggests that DBS of the MTL and/or structures projecting to the MTL may be used to ameliorate memory dysfunction in AD patients. We propose that future DBS studies might attempt to mimic normal physiological conditions and patterns of extracellular electrical fields that support LTM operations. Furthermore, it is important to consider ethical constraints when conducting DBS studies, and alternative approaches are being developed to improve DBS technique (Box 3). Box 4 lists outstanding questions. A combination of animal and human experimental work, along with characterization of how DBS affects LTM encoding and retrieval, will be critical for the development of protocols for remediating memory deficits in AD and other diseases that involve memory dysfunction.

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