Modulation of Human Memory by Deep Brain Stimulation of the Entorhinal-Hippocampal Circuitry

Emily A. Mankin[1] and Itzhak Fried[1,2,3]*
[1]Department of Neurosurgery, University of California, Los Angeles, United States, 90024;
[2]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, United States, 90024;
[3] Tel Aviv Medical Center and Tel Aviv University, Tel Aviv, Israel
*Corresponding author: ifried@mednet.ucla.edu; 310-825-8409

ABSTRACT

Neurological disorders affecting human memory present a major scientific, medical and societal challenge. Direct or indirect Deep Brain Stimulation (DBS) of the entorhinal-hippocampal system, the brain's major memory hub, has been studied in people with epilepsy or Alzheimer's Disease, intending to enhance memory performance or slow memory decline. Variability in the spatiotemporal parameters of stimulation employed to date notwithstanding, it is likely that future DBS for memory will employ closed-loop, nuanced approaches that are synergistic with native physiological processes. The potential for editing human memory—decoding, enhancing, incepting or deleting specific memories—suggests exciting therapeutic possibilities, but also raises considerable ethical concerns.

Keywords: Deep brain stimulation, neuromodulation, memory

BACKGROUND

The Challenge

One of the critical challenges facing society in the 21st century is the specter of a cognitive catastrophe affecting millions of people in our midst, who face gradual loss of memory. With an increase in the aging population and the prevalence of various dementias, such as Alzheimer's Disease (AD), there is an increasing need to find therapeutic measures; yet effective pharmacological agents have not been found to provide symptomatic relief that can restore quality of life. Preservation of human memory, and its enhancement when in decline, is therefore a major challenge for the human condition. Thus, we need to consider augmentation of human memory by introduction of neuroprosthetic devices that could interact with the

human brain via electrical or chemical signals. To achieve such a bionic future where brain and machine interface seamlessly, we need to consider specific brain networks where a direct causal role in memory processes has been established. Here we consider external modulation of the entorhinal-hippocampal circuit, the human brain's chief organ of declarative and episodic memory.

There are two major, parallel streams of discovery implicating the medial temporal lobe (MTL), with its hippocampal-entorhinal circuitry, as the hub of declarative memory (Buzsaki and Moser, 2013). First, the rodent literature has made major advances in locating the circuitry of spatial memory within the medial temporal lobe (Moser et al., 2008). Second, the medial temporal lobe is also the brain's chief circuit for transforming human and non-human primate experience into durable representations that can later be consciously retrieved. This is supported by a large body of basic science and medical discovery ranging from primate neurophysiology and lesion studies, to human electrophysiology and neuroimaging studies, as well as brain lesions resulting in specific memory deficits (Squire, 2004). Together these literatures support a unified model of the role of the entorhinal-hippocampal circuitry evolving across species to support both spatial and non-spatial memory, culminating in human semantic and episodic memory.

Electrical stimulation in the human brain

The main means of modifying brain function are chemical (pharmacological) and electrical. Electrical stimulation has thus been used to treat human brain dysfunction in disease. In particular, Deep Brain Stimulation (DBS) is an invasive form of electrical stimulation, in which stimulating electrodes are implanted directly into the brain and can apply electric current to the surrounding brain tissue.

This approach has been adopted to modulate neuronal circuits for therapeutic end. Its use has been particularly successful in Parkinson's Disease and other movement disorders (Gross and Lozano, 2000). The use of DBS is also being explored in various neurological and neuropsychiatric disorders such as depression, OCD, and others, with promising results (McLaughlin et al., 2016). More recently, several studies have addressed the challenge of applying DBS to the memory domain with the hope of ameliorating memory impairment that accompanies several disorders, such as Alzheimer's Disease, traumatic brain injury, and epilepsy.

Prior to therapeutic application of DBS, electrical stimulation was commonly employed to map cortical function. Pioneered by Wilder Penfield during operations on awake patients under local anesthesia, electrical stimulation in primary motor and sensory areas evoked discrete movements or sensations, but when applied elsewhere, such as Broca's and Wernicke's areas

or the angular gyrus, it disrupted performance on speech and language tasks (Penfield and Jasper, 1954, Penfield and Perot, 1963, Penfield and Roberts, 1959). Such disruption of complex cognitive functions indicated that the stimulated sites were involved in the function tested. In addition to elucidating the brain regions generally involved in various functions, this had immediate practical applications, allowing neurosurgeons to identify functional cortex that should be avoided during surgery (Szelényi et al., 2010, Ojemann et al., 1989).

Ojemann and colleagues used electrical stimulation (2-10 mA, bipolar at 50Hz) in the cortex during structured tasks to map memory processes. They found that stimulation of sites in temporal and frontal cortex, when applied at various stages of mnemonic processing, disrupted memory performance (recognition of verbal or visuospatial material or free recall) (Ojemann, 1978, Ojemann, 2003, Fried et al., 1982). The rationale of these studies was similar to language mapping: complex functions such as memory should be disrupted by gross stimulation of gray matter involved. The only site with stimulation-evoked improvement of memory was, in fact, in thalamus, where stimulation of the ventrolateral nucleus during encoding resulted in improved performance on subsequent retrieval (Ojemann, 1975).

Although cortical stimulation did not lead to memory improvement, upon stimulation of sites in the temporal lobe, patients occasionally reported real experiences, distinct memories or percepts. (Penfield and Perot, 1963). These experiences were characterized by vividness and authenticity ("more real than remembering"), yet two experiences were never activated concurrently, and the patients were aware that they were in the operating room. These experiences were felt to demonstrate durable representations in the temporal lobe that became accessible to human consciousness by the stimulating probe. Penfield then postulated: "There is a stream of consciousness within the brain… hidden in the interpretive areas of the temporal lobe there is a key mechanism that unlocks the past"(Penfield, 1958).

Experiential responses evoked by cortical electrical stimulation of the temporal lobe have been described in various publications since Penfield (reviewed in Lee et al. (2013b)), many of these giving the impression of recalled memories surfacing on the platform of consciousness. However, these responses were sporadic, and their relationship to specific neuronal circuitry difficult to dissect, especially since stimulation was presumed to affect a relatively large volume of tissue and neuropil. A recent report, however, demonstrated an ability to generate memory flashbacks in 48% of people with Alzheimer's Disease via strong (7-10 V) stimulation of the fornix and subcallosal area (Deeb et al., 2019). These experiences included both autobiographical, episodic memories and semantic memories in the form of concepts (e.g., patient "thinking about her daughter"). Some of these memories acquired more detail with increasing level of stimulation. These anecdotes of stimulation evoking strong memories have inspired new lines of research focused on intentionally modulating neural function to better

understand the neural processes involved in memory and to explore whether such modulation could be used therapeutically.

Spatiotemporal considerations of stimulation

Neuromodulation is a *spatiotemporal* intervention in brain function that introduces electrochemical changes with a distinct temporal profile at a particular brain circuit. A great strength of electrical, compared to pharmacological, neuromodulation is its relative precision in both the spatial and temporal domains. As the entorhinal-hippocampal system, with its complex afferent and efferent fibers, is critically implicated in episodic memory, much recent work has targeted stimulation within this circuit (Figure 1). Intervention can be limited to particular stages of information processing—including encoding, consolidation and retrieval. Alternatively, it can be delivered in a chronic manner, either continuously, cyclically, or at fixed intervals, without regard to external events. Furthermore, stimulation can be delivered independently of, or in response to, endogenous brain activity.

For each DBS study, then, it is important to consider the SITE, the spatial and temporal SCALE, the memory STAGE, brain STATE, and the SETTINGS of stimulation. Although we consider each of these separately below, it must be emphasized that these variables are not independent, and their interaction could dramatically affect the results of the study. Thus, two studies could both stimulate the same brain region and find different effects on memory if other factors differed.

There is a large literature on noninvasive neuromodulation in the form of transcranial magnetic or electrical stimulation. These methods are limited in their ability to focally target a specific brain structure. Except for occasional reference to these methods, we will limit the discussion here to invasive and direct application of electrical stimulation. Similarly, we reference some animal studies that have been illuminating regarding the mechanisms by which deep brain stimulation may act on memory circuits, but a thorough review of the animal literature is outside the scope of this review.

Clinical settings for intracranial stimulation

As with all studies involving intracranial electrodes in humans, ethical issues limit the subject population to those for whom there is a pressing medical need for electrodes to be placed. Thus, a large number of these studies have been conducted in subjects with pharmacologically-refractory epilepsy undergoing clinical seizure monitoring to identify the epileptogenic regions for possible surgical cure (e.g. Suthana and Fried, 2012). Because these patients frequently have electrodes placed in the medial temporal lobe, they are good candidates for stimulation studies. It should be noted that the hippocampal-entorhinal circuit may be impaired in some epilepsy patients, so some results may not generalize to the non-epileptic population. On the

other hand, many valuable insights into the function of the medial temporal lobe have been derived from studies in this population, and improving memory for people with epilepsy is, in itself, a therapeutic goal.

In addition, DBS has been explored as a potential treatment for a wide variety of neuropsychological diseases, including diseases characterized by cognitive impairment and memory loss—mainly AD (Lv et al., 2018, Posporelis et al., 2018), though a few trials have been conducted in Parkinson's Disease Dementia (Lv et al., 2018) and traumatic brain injury (TBI) (Kundu et al., 2018) as well. The DBS research in AD patients has focused largely on long-term (months to years), continuous stimulation with the hope that it could reverse or at least slow the progression of the disease (Table 1), whereas the research with patients with epilepsy has primarily studied whether brief stimulations within well-defined memory paradigms have an overall positive or negative effect on subsequent memory performance for that task (Table 2).

WHERE? SITE OF STIMULATION

Stimulation of hippocampus proper

Direct electrical stimulation of the hippocampus proper has generally been found to disrupt memory and thus confirmed the role of the hippocampus in memory function in the same manner that electrical stimulation of language areas demonstrated their role in language (Bickford et al., 1958, Chapman et al., 1967, Ommaya and Fedio, 1972, Halgren and Wilson, 1985, Halgren et al., 1985). The earliest of these studies used high stimulation amplitudes, often eliciting after-discharges, which were likely the source of the stimulation induced amnesia (Halgren and Wilson, 1985). Other early studies stimulated multiple sites at once, so the memory impairment cannot be directly attributed to hippocampal stimulation (Halgren et al., 1985).

More recent clinical opportunities to electrically stimulate in the hippocampus usually involve application of several milliamperes in a bipolar fashion through 2 mm contacts separated by a few mm. Such macrostimulation affects multiple neuronal layers and subregions of the hippocampus and it is difficult to see how it could interact physiologically in a positive capacity with the delicate hippocampal neuropil. Indeed, direct hippocampal stimulation has led to neutral (Suthana et al., 2012a, Coleshill et al., 2004, Lacruz et al., 2010, Fernandez et al., 1996, Kucewicz et al., 2018b) or negative (Jacobs et al., 2016, Coleshill et al., 2004, Lacruz et al., 2010) outcomes for memory when delivered during encoding and tested shortly afterward. Nevertheless, in one recent study, hippocampal stimulation did enhance recollection on a

word-pair association task following a longer delay to testing (10 minutes) (Jun et al., 2019). A small number of studies has also addressed the long-term consequences of continuous hippocampal stimulation in people who received chronic stimulation for a period of months to years. In general, when stimulation was applied continuously, around the clock, no long-term change in memory performance was observed (Velasco et al., 2007, McLachlan et al., 2010, Boex et al., 2011, Miatton et al., 2011).

A recent study used more physiological levels of stimulation, delivering microstimulation across many electrodes within the hippocampus in a closed loop fashion (Hampson et al., 2018). Recordings from hippocampal subfields CA3 and CA1 were used to model CA1 firing patterns based on CA3 activity. Later, during a delayed match to sample task, activity in CA3 was recorded and, based on the model, stimulation was applied in CA1 to mimic its expected output. This led to to significantly improved performance in 6 of 7 patients, compared to a non-stimulated condition or random stimulation condition, which in fact impaired memory in some subjects.

Stimulation of the entorhinal area

Suthana et al. (2012) found that stimulation applied in the entorhinal area during a spatial navigation task improved later memory performance, even when identical stimulation in the hippocampus provided no benefit. This marked the first demonstration that stimulating a brain region that directly projects to the hippocampus might be more effective for memory enhancement than stimulating the hippocampus proper. A subsequent study using a similar task, however, found primarily impairment in the five patients who received entorhinal stimulation (Jacobs et al., 2016). The same group also found a trend toward impairment in eight patients who received stimulation in the entorhinal cortex during a verbal memory task (Jacobs et al., 2016). Still a third group found enhancement of event-related potentials in hippocampus following entorhinal area stimulation during an item-color association memory task but no behavioral effect (Hansen et al., 2018). A possible difference among these studies is the site of stimulation *within* the entorhinal area, which could lead to different physiological effects on hippocampus. The spatial resolution of macrostimulation may be too large to determine the anatomical extent of the stimulation, or whether it involved white matter tracts, gray matter, or both (Figure 2). Additionally, extra-entorhinal regions were sometimes stimulated concurrently with entorhinal stimulation (e.g. hippocampus or parahippocampal gyrus (Jacobs et al., 2016) or perirhinal cortex (Suthana et al., 2012a)).

To mitigate these confounding factors, Titiz and colleagues applied microstimulation (150 μA) through single, small micro-wires (100 μm), rather than large bipolar contacts (Titiz et al., 2017), in an attempt to more precisely delineate the spatial extent of stimulation. Applying

205 microstimulation during the encoding phase of a person recognition task, they found memory
206 enhancement, but the effect was strongest when the stimulating electrode was positioned in
207 the white matter (angular bundle) of the entorhinal area. The angular bundle contains a dense
208 concentration of fibers of the perforant path (Yassa et al., 2010, Zeineh et al., 2017), which is
209 commonly the site of stimulation in studies of long-term potentiation (Bliss and Lomo, 1973).
210 The ability of the stimulating electrode to target this fiber tract may have been critical to the
211 success of stimulation.

212 To date, no studies of chronic stimulation in the entorhinal area have been conducted in
213 humans. In rodents, however, some chronic stimulation studies have shown promise. Rodents
214 with Alzheimer's pathology showed memory benefits from long-term entorhinal stimulation
215 (Mann et al., 2018, Zhang et al., 2015), likely due to effects of chronic stimulation on
216 neuroanatomic and molecular processes, such as an increase in neurogenesis and a decrease in
217 A-β and other molecular markers of Alzheimer's pathology (Mann et al., 2018).

218 ## Stimulation of fornix

219 The fornix is the main efferent pathway from the hippocampus, projecting back indirectly to the
220 hippocampus and entorhinal cortex via the various stations of the circuit of Papez (Papez, 1937)
221 (Figure 1). It is therefore a potential route for modulation of hippocampal activity.

222 Following a serendipitous observation of memory flashbacks with stimulation of the fornix
223 during a DBS procedure and subsequent improvement in memory scores several months later
224 (Hamani et al., 2008), a Phase I clinical trial was launched with one year of chronic bilateral
225 high frequency fornix stimulation in six participants with Alzheimer's Disease. The study
226 established safety with mixed clinical results (Laxton et al., 2010). Glucose metabolism was
227 increased after a year of DBS in some regions (Laxton et al., 2010), and hippocampal volume
228 either increased (2 of 6 subjects) or had a slowed rate of atrophy relative to matched controls
229 (Sankar et al., 2015). In a follow-up Phase II trial, 42 participants with mild AD were implanted
230 with bilateral fornix stimulators (Holroyd et al., 2015). After 12 months, no statistical
231 differences were found between patients who received active stimulation and those receiving
232 sham stimulation (i.e. stimulators were implanted but turned off) in the primary outcome
233 measure of cognitive decline, or in glucose metabolism (Lozano et al., 2016). Post-hoc analyses
234 suggested that while those under 65 experienced considerably greater exacerbation of
235 symptoms than their non-stimulated counterparts, those over 65 experienced moderate
236 slowing of disease progression compared to the non-stimulated group (Lozano et al., 2016).
237 Following up after a second year, during which all participants received active stimulation, the
238 delayed activation groups showed similar trends in the second year as the early activation

group in the first year, including the apparent worsening of symptoms for those under 65 (Leoutsakos et al., 2018).

Two small studies in participants with epilepsy have also tested fornix stimulation. In one, 4 hours of continuous low frequency stimulation led to moderate improvements on the delayed recall portion of the MMSE (Koubeissi et al., 2013). In the other, with too small a sample size for statistical analysis, 20+ minutes of theta-burst stimulation suggested enhanced performance on a complex figure memory test but decline in retention of word lists (Miller et al., 2015).

Animal studies have tested behavioral effects of fornix stimulation, along with molecular markers for neural activity or disease pathology. Chronic fornix stimulation enhanced memory performance in the Morris Water Maze under a variety of stimulation paradigms and in both healthy and impaired rodents (Zhang et al., 2015, Hao et al., 2015), as well as improved performance for novel object recognition memory (Zhang et al., 2015), contextual fear conditioning (Hao et al., 2015), and a delayed non-match to sample task (Sweet et al., 2014). These performance effects may be attributed to molecular changes induced by stimulation, such as increased neurogenesis and neuronal load and decreased pathological burden (Leplus et al., 2019, Hao et al., 2015). Shorter-term theta-burst stimulation of the fornix often rescued performance on memory tasks when tested in rodents with memory-impairing conditions, such as TBI, medial septal inactivation, or scopolamine injection (Hescham et al., 2013, Shirvalkar et al., 2010, Sweet et al., 2014).

Stimulation of other areas within the Limbic System and Forebrain

The Circuit of Papez is a set of brain regions forming an interconnected loop that was originally proposed as the anatomical basis of emotion (Papez, 1937). The circuit includes the hippocampus, mammillary bodies, anterior nucleus of the thalamus, cingulate gyrus, parahippocampal gyrus and entorhinal cortex, and the white matter tracts that connect them (Figure 1). Modulation of any component in this circuit, as well as related limbic structures such as the amygdala and the septal nuclei, may affect hippocampal activity, and thus may be considered for memory modulation.

Deep brain stimulation of the **Anterior Nucleus of the Thalamus** (ANT) has been primarily tested in rat models. Hescham and colleagues (2015) found no effect of short-term ANT stimulation on either behavior or cFos expression. On a longer-term scale, chronic ANT stimulation has shown more promise, likely due to ANT stimulation leading to an increase in neurogenesis (Toda et al., 2008, Hamani et al., 2011). In a rat model of AD, rats with ANT stimulation 4 weeks prior to testing showed improved performance on Morris Water Maze. This improvement, however, was less pronounced than in animals receiving stimulation in

either the entorhinal cortex or the fornix (Zhang et al., 2015). Chronic ANT stimulation has been recently approved as treatment for refractory epilepsy. Initial studies have shown minimal effect on human memory in implanted patients (Oh et al., 2012, Fisher et al., 2010), although with larger numbers of patients receiving ANT DBS there will be opportunity to test memory effects more extensively.

Amygdala stimulation in both rats (Bass and Manns, 2015) and humans (Inman et al., 2018) caused no memory difference on an immediate memory test but enhanced memory when tested after a 1-day delay. Stimulation also increased low gamma coherence between hippocampal regions CA1 and CA3 (Bass and Manns, 2015) or theta-gamma coupling between the amygdala and perirhinal cortex (Inman et al., 2018).

The **medial septum** is a primary source of cholinergic innervation to the hippocampus and plays an important role in pacing the hippocampal theta rhythm. In rodent studies, stimulation of the medial septum has had no effect on memory in healthy control animals, but in rodent models of epilepsy and TBI, stimulation of the medial septum at theta frequency improved memory, even rescuing it to levels equivalent to non-injured animals in those with TBI (Lee et al., 2013a, Izadi et al., 2019).

The **nucleus basalis of Meynert** in the basal forebrain is the primary source of cholinergic innervation throughout the cortex, including dense reciprocal projections with limbic and paralimbic cortices (Mesulam, 2013). Degeneration of this nucleus is implicated in symptoms of dementia, so it has been proposed as a potential target of DBS for AD (Gratwicke et al., 2013). While chronic stimulation of this area has not stopped the progression of AD in small pilot studies (2-6 subjects), it does seem to have slowed cognitive decline relative to matched controls (measured by ADAS-cog, ADAS memory, and MMSE scores), in both early- and late-stage AD (Kuhn et al., 2015a, Kuhn et al., 2015b).

Neocortical Stimulation

The entorhinal-hippocampal system has extensive connections with neocortex. There is major convergence of multisensory input from temporal neocortex into hippocampus through the entorhinal cortex, as well as frontal connections to the MTL (Von Der Heide et al., 2013). Therefore, electrical stimulation of temporal and frontal neocortex can utilize these highly functional connections to modulate hippocampal-entorhinal circuitry and affect memory function.

Several studies of epilepsy patients undergoing evaluation with neocortical electrodes have used direct cortical stimulation to probe or modulate memory function. Although early studies found that stimulation of the lateral cortex induced specific verbal or visuospatial memory

deficits (Penfield and Roberts, 1959, Fried et al., 1982, Ojemann, 1978), a recent study found that lateral temporal cortex was the only site, among several tested, where stimulation improved memory for lists of words (Kucewicz et al., 2018b). In another study, stimulation in the left superior frontal gyrus led to improved reaction times in a working memory task (Alagapan et al., 2019).

An approach that leveraged the wide coverage of electrodes in many patients with epilepsy used recorded data from multiple sites to build a classifier to predict subsequent memory success or failure based on neural activity during encoding. Ezzyat and colleagues (2017) set out to identify states where the brain could presumably benefit from stimulation. They first showed by retrospective analysis that if the brain was already in a state favorable for encoding, stimulation tended to impair subsequent encoding. On the other hand, if the brain was in a poor state for encoding, stimulation tended to increase later memory performance (Ezzyat et al., 2017). Applying this model and prospectively stimulating lateral temporal cortex selectively when the model predicted a poor encoding state led to improvement in memory performance for stimulated lists of words compared to performance on lists without stimulation (Ezzyat et al., 2018). This study is unique, in the sense that it utilized a closed-loop approach to prescribe stimulation based on brain signals recorded in real time.

Analyzing neural activity from multiple sites may also allow for identifying functionally connected brain regions that are modulated by memory demands. Kim and colleagues identified pairs of electrodes whose activity was correlated during spatial memory retrieval and then stimulated them conjointly, which led to selective impairment in spatial memory (Kim et al., 2018). Similarly, Fell and colleagues (2013) tested whether stimulating the hippocampus and rhinal cortex in phase with each other or in an anti-phase protocol might have differential effects. They found a trend toward in-phase stimulation resulting in better memory than no stimulation, which in turn was better than anti-phase stimulation. Together, these studies suggest that stimulation at multiple sites should be considered in devising protocols for modulation of broad memory networks.

WHEN? TEMPORAL PROFILE OF STIMULATION

Just as the site of stimulation has varied among different research methods, so has the temporal profile of stimulation. This relates to several considerations, including the memory stage at which stimulation is provided, the temporal profile of the stimulation waveform itself, the duration of stimulation, and the delay between stimulation and test. Recently, as closed-

loop methods have become more accessible, the relationship between stimulation timing and brain state has also been investigated.

Memory Stage

Although the traditional approach to memory research employs a division into stages of encoding, consolidation and retrieval, in continuous 'real life' behavior these stages are intermixed and cannot be easily separated into distinct time segments. The majority of research involving trial-based or item-based stimulation has provided stimulation during or just prior to encoding. These studies, which yielded variable results in memory performance, have been reviewed above.

Similar to encoding, stimulation of the hippocampus proper during retrieval had a detrimental or no effect on memory performance (Halgren et al., 1985, Lacruz et al., 2010, Merkow et al., 2017). Stimulation during both encoding and retrieval may have compounding effects, such that the memory changes to a greater degree than stimulating during only one or the other (Halgren et al., 1985, Lacruz et al., 2010). However, timing of stimulation may be a critical factor for retrieval. Norman et al. (2019) reported a content-specific transient increase in sharp wave ripples (SWR) in hippocampus prior to free recall. This could serve as a temporal biomarker for stimulation, similar to what has been reported in rodents during sleep (see below; Maingret et al., 2016).

Distractor tasks are often used between training and test in order to increase dependence of memory on the hippocampus, so neocortical stimulation during this period may impact the ability of the hippocampus to maintain the memory during the distraction. Indeed, direct hippocampal stimulation during a distractor task between encoding and retrieval led to greater impairment than during encoding or retrieval alone (Merkow et al., 2017).

Sleep is a major temporal window when consolidation of hippocampal dependent memory occurs, primarily during slow wave sleep (SWS). There is extensive rodent literature supporting a model in which hippocampal-cortical dialog during slow wave sleep promotes stabilization of labile memory traces for long-term storage (Buzsaki, 1989). These studies identified specific electrical signatures of consolidation, particularly sharp wave ripples, which are now considered a key mechanism for memory consolidation.

In rats, suppressing ripples by stimulating the ventral hippocampal commissure during sharp wave ripples disrupted the consolidation processes, resulting in poorer memory performance (Girardeau et al., 2009). Maingret and colleagues (2016) applied neocortical stimulation in the frontal lobe timed to the sharp-wave ripples, thus enhancing hippocampal-cortical coupling and resulting in enhanced performance on a spatial memory task in rodents. Fernandez-Ruiz et al

(2019) showed that prolongation of spontaneously occurring ripples by optogenetic stimulation increased memory in rodents during maze learning, which leads to the question of whether electrical stimulation in humans could also prolong ripples.

Interventions during SWS could modulate consolidation processes in humans. Several groups have used non-invasive stimulation (e.g. transcranial direct current stimulation or transcranial magnetic stimulation) during SWS. Providing rhythmic stimulation at the frequency of endogenous slow waves has led to increased slow wave activity in both open and closed-loop tests (Marshall et al., 2006, Massimini et al., 2007, Bellesi et al., 2014). Relatively few studies that tested the ability of non-invasive stimulation to evoke slow waves also examined the impact of this intervention on memory; nonetheless a meta-analysis of these studies suggests that on average there is a positive benefit for memory with this manipulation (Barham et al., 2016). Sensory stimulation, especially rhythmic bursts of noise delivered in the slow wave frequency range, has also led to increased slow wave activity (Bellesi et al., 2014), with at least one study reporting a concomitant memory enhancement (Ngo et al., 2013).

Together, these rodent and human non-invasive studies suggest that the memory consolidation stage is a potential target for enhancement of long-term memory. The ability to observe and respond in real time to local hippocampal features of sleep—which cannot be measured or targeted non-invasively—as well as to intervene directly at different points within the hippocampal-entorhinal-neocortical circuitry makes deep brain recording and stimulation during sleep an especially promising avenue for such enhancement.

Stimulation Parameters

The stimulation waveform is likely a factor in the success of stimulation to induce memory changes. Stimulation parameters may vary from continuous high frequency stimulation to even a single pulse. Modeled after the success of application of DBS in Parkinson's disease, many studies have applied continuous high-frequency stimulation at 130 Hz. The majority of these studies has either considered long-term effects of high-frequency stimulation in patients with AD or examined changes to the molecular markers of memory, disease, and neuronal activity in animal models. The animal model research often appears promising—with increased presence of cFos+ (Stone et al., 2011, Gondard et al., 2015, Hescham et al., 2016) and BrdU+ (Stone et al., 2011, Hao et al., 2015, Mann et al., 2018) cells, higher levels of Acetylcholine (Hescham et al., 2016), enhanced BOLD response (Ross et al., 2016), decreased markers of disease pathology (Mann et al., 2018, Leplus et al., 2019), and even some behavioral enhancement (Stone et al., 2011, Hao et al., 2015, Zhang et al., 2015, Mann et al., 2018). Unfortunately, corresponding behavioral changes have generally not been borne out in humans (Laxton et al., 2010, Oh et al., 2012, Boex et al., 2011, Lozano et al., 2016).

Efforts to enhance memory of specific items have generally targeted stimulation frequencies that reflect prominent endogenous rhythms in the hippocampus: 50 Hz stimulation is within the range of endogenous gamma rhythm, while 5-10 Hz stimulation is intended to mimic the theta frequency. Results have been varied among these protocols, with theta frequency stimulation more often showing enhancement (Koubeissi et al., 2013, Alagapan et al., 2019, Izadi et al., 2019, Lee et al., 2013a) and 50 Hz stimulation split between showing impairment (Coleshill et al., 2004, Jacobs et al., 2016, Merkow et al., 2017, Halgren and Wilson, 1985) and improvement (Inman et al., 2018, Suthana et al., 2012a, Bass and Manns, 2015, Fell et al., 2013). Combining these approaches by nesting a higher frequency stimulation pulse within a low frequency rhythm has been a promising approach in rodents (Boix-Trelis et al., 2006, Sweet et al., 2014), often yielding memory enhancement when low frequency or high frequency stimulation failed to do so (Sweet et al., 2014, Shirvalkar et al., 2010). In humans, theta burst stimulation is not yet well studied, but has shown promising initial results (Titiz et al., 2017, Miller et al., 2015).

Another important factor of the stimulation waveform is the amplitude of the stimulation current. Halgren demonstrated that stimulation strong enough to cause after discharges caused memory impairment (Halgren and Wilson, 1985). Many studies have, therefore, chosen stimulation amplitudes just below the after discharge threshold. Although the variability in other stimulation parameters precludes a meta-analysis of the effect of amplitude, it is notable that many of the studies in which stimulation caused memory impairment used this approach, applying amplitudes of stimulation in the milliampere rather than microampere range. One possible explanation for this effect may be that high amplitude stimulation is likelier to inhibit neuronal firing, even several centimeters from the stimulation site (Mohan et al., 2019, Herrington et al., 2016).

Timing Relative to Brain Activity

If stimulation is to enhance memory, it is likely to work by acting in concert with the brain's natural memory mechanisms. Closed-loop strategies taking into account on-going brain activity have been used effectively in animal studies, such as enhancing memory by temporally locking stimulation to sharp wave ripples (Fernandez-Ruiz et al., 2019, Maingret et al., 2016) or targeting a particular phase of endogenous rhythms (Siegle and Wilson, 2014). There has been a relatively small number of closed-loop stimulation studies in human memory. Initial studies include closed-loop methods that take into account spiking patterns (e.g. Hampson et al., 2018) or data-derived brain states (Ezzyat et al., 2017, 2018). So far, these closed loop methods look promising for memory enhancement, but more studies will be needed to confirm and refine these methods.

Memory formation involves mechanisms of synaptic plasticity which require coordination of action potentials across neuronal populations. In humans, Rutishauser and colleagues (2010) have shown that successful memory encoding in humans is predicted by a tight coordination of spike timing with the local theta oscillation Stimulation targeted at precise timing relative to ongoing brain rhythms is a strategy that has not yet been tested in human DBS. However, phase-amplitude coupling between frequency bands appears to be important in human memory (Mormann et al., 2005, Axmacher et al., 2010) and sleep (Staresina et al., 2015, Niknazar et al., 2015). Evidence from rodents indicates also that encoding and retrieval may be active at distinct phases of the theta cycle (Hasselmo et al., 2002) or frequency of gamma (Colgin et al., 2009), suggesting that targeting the appropriate phase or frequency could amplify the effects of stimulation. Targeting specific sleep rhythms via closed-loop systems has been shown to be the most effective for enhancing consolidation via auditory stimulation (Ngo et al., 2013, Batterink et al., 2016, Bellesi et al., 2014).

WHAT ARE WE MODULATING?

Memory is a multi-faceted phenomenon that exists in different forms (Squire, 2004) and on different time scales. Even within the domain of hippocampal-dependent memory, there are multiple variations that must be considered. Methods that modulate recognition memory, for example, may not have similar effects on free recall. Even within a single domain, the effects of the same stimulation paradigm may vary with the material to be recognized (such as faces vs words) (Lacruz et al., 2010). Tasks that lean primarily on verbal vs visual processing may be differentially lateralized in human processing (Smith and Milner, 1989, Fried et al., 1982, Ojemann, 1983, Haxby et al., 1996), such that the hemisphere of stimulation delivery matters (Titiz et al., 2017).

Forgetting is a process that occurs over time. If a memory benefit of stimulation were related to protection from forgetting, these benefits could be masked if the memory test is conducted too soon after learning. Stimulation of the amygdala, for example, showed no apparent change in memory performance for an immediate memory test but enhanced recognition memory after a one-day delay in both humans and rats (Inman et al., 2018, Bass and Manns, 2015). Similarly, if stimulation causes molecular changes that enhance memory, giving time for these changes to occur may also uncover effects that would not be obvious on an immediate test. For example, healthy mice receiving entorhinal stimulation six weeks prior to encoding had enhanced search strategies on the Morris water maze after a 4 week delay; these timescales are consistent with the timing required for a stimulation-induced increase in neurogenesis to affect memory of a

proximal event (Stone et al., 2011). Thus, future studies should follow patients for longer periods of time.

Several different pathological conditions can lead to impaired memory, including dementia, epilepsy, and traumatic brain injury. Each comes with its own underlying cause, and specifically targeting each condition's underlying neural changes may be critical to successful interventions. It is sometime difficult to separate the effect of stimulation on the disease process and its direct effect on memory function (e.g., in AD, enhancing memory processes vs slowing down the disease progression). In epilepsy patients one mechanism that appears to impact memory is when interictal discharges induce physiological events, such as sleep spindles, at inappropriate times (Gelinas et al., 2016). In such cases, a closed loop stimulation method targeted at suppressing interictal discharges could be effective.

A relatively recent advance in epilepsy treatment has been the advent of chronically-implantable devices that stimulate in a closed loop manner when certain electrographic signatures are detected (Figure 3A). A 2-year follow up study of temporal lobe epilepsy patients with such devices found a rather small (2%) increase in verbal memory scores (Loring et al., 2015).

FUTURE DIRECTIONS

Neuromodulation of human memory has focused primarily on the hippocampal-entorhinal system and its wide network of efferent and afferent targets. Studies to date have entailed substantial variability in the spatial and temporal characteristic of intervention. It is thus imperative that data be shared among investigators, criteria be established for monitoring the large number of relevant variables across research centers (Suthana et al., 2018), and studies be planned and interpreted in close association with basic neuroscience. The entorhinal-hippocampal circuitry is one of the most extensively studied of all brain networks, yielding some of the most striking correlations between neuronal mechanisms and behavior. Yet, there is still a substantial gap between the knowledge gained from basic science and the ability to apply it to modulate memory mechanisms in humans. Therefore, despite the overwhelming number of patients with neurological disorders affecting memory, we caution against premature launching of large DBS studies in this field, and advocate smaller adaptive studies where spatiotemporal variables of modulation can be changed more readily (Fried, 2015, Fried, 2016).

As we look toward the future of memory modulation, we must consider what are we trying to modulate. Most of the studies to date have been carried out in patients with neurological disorders, whether epilepsy or AD, where memory is impaired to varying degrees. Chronic studies that apply continuous stimulation, such as the fornix studies in AD, have primarily aimed to alter the disease process which causes the memory impairment, whereas acute studies have focused on transiently altering neural activity to promote a mnemonic brain state. These are not mutually exclusive approaches, however. For example, it might be useful to include acute studies of memory, where the momentary effects of stimulation on memory can be tested directly, in the patient population with AD.

Enhancing memory will likely require tapping into the brain's natural memory mechanisms in a manner more nuanced than most of what has been tried already. The amplitude of stimulation is likely critical to whether stimulation is acting as a lesion or a boost, with physiological level amplitudes less likely to induce widespread neuronal inhibition. Although DBS was introduced as a therapeutic approach for Parkinson's Disease with the thought that it might mimic a lesion, current thinking adopts a modulatory approach to the abnormal motor network underlying the symptoms of the disease. Modulation of cognition in general, and memory in particular, may prove more challenging since the assessment of modulated variables are much less obvious to both patient and physician compared to overt motor variables such as tremor or rigidity. Furthermore, in diseases such as PD and epilepsy, the goal of stimulation is to stop or dampen abnormal oscillatory brain rhythms that generate symptoms, whereas in the case of memory, the goal is to facilitate neuronal network activity that is conducive to memory. Achieving this will likely require tuning the stimulation parameters away from the high frequency stimulation protocols that have been customarily used for DBS, with a focus on identifying parameters that lead to physiological changes that are consistent with positive memory performance.

Substantial work remains to verify the physiological effects of the stimulation protocols reviewed here, as many studies report only behavioral effects. Among those that have reported physiological effects, a change in gamma power, arguably a reflection of action potentials, or theta-gamma coupling is common (Inman et al., 2018, Shirvalkar et al., 2010, Stypulkowski et al., 2017, Ezzyat et al., 2017, Kucewicz et al., 2018a). With respect to enhancing encoding by entorhinal stimulation, it has been proposed that the underlying mechanism involves resetting of the native rhythms of the human hippocampus (Suthana et al., 2012a) or the entrainment of neurons within the hippocampal subfields (Diamantaki et al., 2018). Future work should also elucidate circumstances under which stimulation directly influences neuronal spiking, modulates excitability of downstream structures, entrains neuronal firing toward coherence, or induces long-term potentiation (LTP). For instance, the use of theta burst stimulation of the perforant path (Titiz et al., 2017) may enhance encoding via LTP in the hippocampal subfields. The ability to record on micro-wires and reject stimulation artifact has allowed for following

546 spiking waveforms between stimulation and non-stimulation periods (O'Shea and Shenoy,
547 2018), which will provide valuable insights into the immediate and delayed effects of
548 stimulation on individual neuronal responses.

549 Just as early studies elucidated brain areas involved in particular cognitive functions, newer
550 studies may use stimulation to further our understanding of the neural mechanisms underlying
551 memory, as electrical stimulation can address causation rather than merely correlation. For
552 example, El-Kalliny and colleagues (2019) demonstrated a relationship between memory
553 performance and a gradual drift in low frequency spectral power in the temporal lobe, then
554 showed that using electrical stimulation to change this drift modulated memory performance
555 accordingly. Similarly, evaluating how hippocampal patterns of activity were modulated by
556 microstimulation that enhanced or failed to enhance memory specificity (Titiz et al., 2017)
557 could shed light on theories of human hippocampal pattern separation.

558 Such studies highlight the importance of the dialogue between the basic science of memory
559 and its modulation by electrical stimulation. Identifying the differing physiological effects of
560 stimulation when memory is enhanced or impeded will provide insight into mechanisms of
561 memory, while further understanding of the signatures of successful vs unsuccessful memory
562 will provide benchmarks against which to test the design of stimulation protocols. A recent
563 study showed that stimulation of the posterior cingulate cortex increased gamma power in
564 hippocamnpus, yet the behavioral result was impairment of memory, indicating that an
565 increase in hippocampal activity may not necessarily yield an improvement in memory (Natu et
566 al., 2019). Overall, then, converging evidence from multiple studies that report not only
567 behavioral but also physiological effects of stimulation may further our understanding of
568 memory processes and how to enhance them.

569 Using closed loop methods to compute and deliver appropriate neural codes directly to the
570 hippocampus may be more effective than fixed external stimulation but will require a much
571 clearer understanding of the native neural code of the human hippocampus (Hampson et al.,
572 2018). In the absence of such a model, targeting stimulation to white matter tracts may be a
573 more physiological approach to manipulating hippocampal activity and to reduce disruption to
574 the neuronal computations ongoing in the cell layers of the hippocampus (Titiz et al., 2017),
575 Using a constant train of high frequency stimulation ranging from 50 Hz to 200 Hz, as has been
576 used in several studies to date, may be based on the broad assumption that such frequencies
577 recruit single cells in target regions within the hippocampus-entorhinal circuitry. Selecting a
578 more physiological stimulation waveform, such as nested frequencies, could enhance theta-
579 gamma coupling, or other memory-relevant oscillatory patterns. In general, the more
580 stimulation mimics native physiological memory processes, the likelier it may prove effective in
581 enhancing memory.

A major challenge for the field will be translating the findings from short term experiments into effective chronic treatments of people who are suffering from memory impairment. A first step is to increase the cross-talk between the short-term memory studies with epilepsy patients and the longer-term studies of patients with chronic implants for AD or epilepsy. Epilepsy patients undergoing stimulation for memory should be followed for longer periods of time to allow for monitoring effects of stimulation, such as those induced by molecular changes, that may take time to emerge. Conversely, using naturalistic, closed-loop parameters in patients undergoing chronic stimulation, rather than focusing exclusively on the goal of slowing disease progression, may increase its efficacy for improving memory (Senova et al., 2018). Patients with temporal lobe epilepsy who have received chronically implanted neurostimulators, such as the responsive neurostimulator (RNS; Figure 3A), may be an ideal subject population for these crossover studies, as their physiological response to stimulation and memory tests can be recorded over the long term.

A further challenge for development of viable neuroprosthetic devices will be the transformation from tightly controlled memory experiments—where stimulation and tasks can be carefully coupled—to applying appropriate stimulation during the ongoing experiences of daily life. Using closed loop models for deriving timing of an intervention by analyzing states of the brain (e.g. Ezzyat et al., 2017, 2018) or assessing specific external demands and actuating electrical stimulation accordingly may prove useful strategies. It is currently difficult to envision a method for automatic detection of whether an individual is challenged with encoding or retrieval of information. Therefore, strategies that target encoding and retrieval differentially may be difficult to achieve. However, as research progresses, we may find neural markers of encoding or retrieval intention or need. In the meantime, one could envision giving control to users of a device themselves, allowing them to select a “learning” mode versus a “recall/testing” mode.

A major promising strategy for memory neuromodulation may involve the enhancement of consolidation during sleep based on measuring spontaneously occurring biomarkers of neural activity, such as slow waves, spindles and ripples. In general, sleep provides a relatively stable period of time with limited environmental input and decodable electrical activity, and thus may be ripe for neuromodulation to improve consolidation of memory traces.

Perhaps the final frontier for memory neuromodulation will be refining the specificity of modulation. Most of the human studies to date have involved interventions to improve general conditions for encoding new information. Specificity was limited to the types of memory or material tested (e.g., spatial memory, memory for faces or word lists etc.). But the question remains: can we enhance or even “incept” a specific select memory? Using optogenetic techniques in rodents, it has been possible to manipulate selected engrams, that is, the specific

subset of hippocampal cells that hold the key to a particular memory, and activate behavior that indicates memory has been induced (Ramirez et al., 2013). In another study, stimulation during NREM sleep in rodents triggered by the reactivation of a particular place cell, incepted a memory for positive emotion at a particular place, evidenced by the animal preferring this place in subsequent waking behavior (De Lavilléon et al., 2015). Similar approaches may offer not only the inception but also the deletion of specific memories.

Ethical Considerations: Opportunities and Risks

Several ethical issues arise in considering the use of deep brain stimulation for memory modification. Concerns can largely be divided into considerations regarding the invasive nature of DBS and issues pertaining to external intervention in the memory of an individual human being. As a surgical procedure, DBS carries relatively small risks, even in fragile patients such as elderly patients with Alzheimer's Disease (Laxton et al., 2010). These risks include mainly infection and bleeding, which may result in neurological deficit. Many studies with multiple intracranial depth electrodes (SEEG) implanted for diagnostic reasons in epilepsy patients where over 10 electrodes may be commonly implanted, show low (1-2%) intracranial bleeding or infection rates (Fenoy and Simpson, 2014).

However, as an invasive therapy that requires undergoing neurosurgery, DBS should be undertaken with caution. Indeed, we caution against efforts to apply DBS in healthy individuals. Although it has been found to be safe and well-tolerated, even for long-term use, there may be unforeseen risks to surgical interventions in brain parenchyma, including possible unknown neuropsychological side effects (Kubu and Ford, 2007). For instance depression has been found to be a possible side effect of the use of DBS in the ANT for epilepsy (Tröster et al., 2017). Additional ethical questions surrounding DBS generally include patient selection, informed consent, and equality of access to a high-cost intervention (Bell et al., 2009, Unterrainer and Oduncu, 2015). The question of informed consent is an especially relevant one for the case of expanding DBS for treatment of dementia or other cognitive impairment,

Memory modification, especially should it reach the level where specific memories can be manipulated, poses its own set of ethical challenges. Because our memories are strongly tied to our sense of self and identity, memory modification has significant implications for our autonomy as free human beings. Are we rushing an era where human memory can be edited?

Admittedly, one could hardly argue against providing a memory boost to a patient with early Alzheimer's Disease who wants to remain an active and productive member of his work and family environment. Is such a "memory aid" different from a hearing aid or cochlear implant? Should the "hard of remembering" be differently treated than the "hard of hearing"? Even

when it comes to manipulating specific memories, can one argue against deletion of a noxious memory in an individual with post-traumatic stress disorder (PTSD), where the ability to forget or diminish a specific traumatic experience may alleviate immense suffering?

On the other hand, who should decide under what circumstances a memory can be edited? Especially if such editing could involve not only the decoding and enhancing of human memories, but also the inception and deletion of specific wanted or unwanted memories? How would the modification of single memories interact with the entire memory network? Would it distort a person's sense of reality and identity? (Hui and Fisher, 2015, Liao and Sandberg, 2008). These questions may be of special concern in the vulnerable populations for which DBS is targeted, such as those with dementia, head injury or PTSD. If memory editing technologies advance significantly, it will be important to have safeguards to prevent potential misuse, such as requiring multiple levels of scrutiny with changes of stimulation protocols. One must also consider more sinister scenarios of misguided or abusive applications of memory manipulation or "hacking" of the human mind for nontherapeutic ends.

The present era entails the rapid development of several technologies (Figure 3). On the one hand, closed-loop implanted devices interacting with the human brain in daily life are already in clinical or advanced investigative use. These include the Responsive Neurostimulation device (RNS, NeuroPace), FDA-approved for use in epilepsy, and the RC+S (Medtronic), capable of streaming online neural signals in behaving individuals. At the same time, recording and stimulation devices with hundreds of electrodes and thousands of channels of single neuron and local field potential data are already in use in animal research and are on the threshold of being translated to human use. These include the Neuropixel probe (Jun et al., 2017) and the robotically-implanted probe of Neuralink (Musk, 2019). The large amount of data these technologies will produce, coupled with the incredible ascent of artificial intelligence, may translate into therapeutic use for memory manipulation, even without sufficient understanding of the underlying brain mechanisms.

As research and technology continue to push forward the prospect of memory enhancement and modification, we should actively engage in these discussions, encouraging ethicists, neuroscientists, neurologists, neurosurgeons, psychologists, engineers, caretakers, and other concerned citizens to join in conversation on the best ways to advance responsible intervention in one of the basic foundations of human individuality and autonomy, our memory.

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Declaration of Interests. *IF holds intellectual property in the field of deep brain stimulation assigned to the Regents of the University of California*.

FIGURES

Figure 1. Components of the limbic system have been targeted for deep brain stimulation for modulation of memory. The Circuit of Papez includes the hippocampus (a), which projects via the fimbria and fornix (b) to the mammillary bodies (c), which then project via the mammillothalamic tract (d) to the anterior nucleus of the thalamus (e). Thalamocortical fibers continue to the cingulate gyrus, from which the fibers of the cingulum (f) innervate the parahippocampal gyrus (g)—which includes the entorhinal cortex (h)—as well as many cortical areas. The circuit is completed as the entorhinal cortex projects to the hippocampus through several pathways, including the perforant path. Other components of the limbic system include the hypothalamus, amygdala (i), nucleus accumbens, and septal nuclei (j). Though not considered part of the limbic system, the Nucleus Basalis of Meynert (k) has also been targeted for chronic DBS for the treatment of AD, due to its large number of cholinergic projections throughout the brain. Regions that have been targeted for DBS and are reviewed here are shaded in color. Brain sketch by Natalie Cherry, inspired by the dissections in (Shah et al., 2012).

Figure 2. Large, widely spaced bipolar stimulating contacts may affect multiple brain regions and networks. Left: Coronal slice from a T1 weighted MRI of a participant with deep brain electrodes. Red circles: locations of adjacent macro electrodes (3.5 mm spacing); red crosshair: position of a 100-um diameter electrode that was used for microstimulation. Right: Enlargement of the medial temporal lobe. Top: white matter pathways between the entorhinal cortex and hippocampus. Bottom: distinct anatomical regions of the MTL. Adapted with permission from (Titiz et al., 2017).

Figure 3. Chronically Implantable DBS Systems of today and Tomorrow. A. Closed-loop Responsive Neurostimulation (RNS) system (*NeuroPace Inc*) used for treatment of epilepsy. The system includes a neurostimulator embedded in the skull and connected to two four-contact leads, a depth lead placed into deep brain structures and/or a subdural strip placed over the cortex. The system senses brain activity (intracranial EEG) and can apply stimulation at prescribed locations. When sensing epileptic activity, it can deliver stimulation to avert seizures (Courtesy of *Neuropace, Inc*). **B.** Proposed design for a closed-loop hippocampal neuroprosthesis for modulation of human memory. This unit includes depth leads placed in the entorhinal-hippocampal circuit providing both sensing and stimulation capabilities. The device extends the capabilities beyond current DBS and RNS by including: Recording of single units in addition to local field potentials, simultaneous **sensing** and **stimulation**, increased number of channels (32-64), wireless **data** and **power** transfer, and small size of implantable unit. The design additionally includes an external earpiece with modules for secure data handling, artifact rejection, closed-loop models, and a battery for power. Data transfer between intracranial and

724 extracranial parts is wireless by miniature RF coils. (Based on design for UCLA DARPA RAM
725 (Restoring Active Memory) project (I. Fried, PI); illustration courtesy of Dejan Markovic).

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Table 1

Reference	Patient population	Site	Duration (months)	Frequency (Hz)	Pulse Width (microsec)	Amplitude	Mono/Bipolar	Primary finding
(McLachlan et al., 2010)	Epilepsy	Bi Anterior Hipp	3	185	90	sub thresh for conscious appreciation	Bipolar	Some deterioration in patient 1 and no change in patient 2. (Hopkins verbal learning; brief visuospatial memory)
Boex et al. (2011)	Epilepsy	Am/Hipp	12-74	130	450	Variable	Bipolar or Quadripolar	No change in cognitive status for any of 5 subjects (Reversible impairment with quadripolar stim in one; and high amp in another)
(Oh et al., 2012)	Epilepsy	Bi ANT	12	100-185	90-150	1.5-3.1 V	Monopolar	Moderate improvement in delayed verbal recall and word fluency test. No impairment on any neuropsychological test
(Laxton et al., 2010)	AD	Bi FX	12	130	90	3-3.5 V	Monopolar	Inconclusive; 2 subjects were better than expected, 3 approximately the same, and 1 worse (ADAS-cog/MMSE). Glucose metabolism indicated increases in limbic/default network (typically impaired in AD)
(Leoutsakos et al., 2018)	AD	Bi FX	12 or 24	130	90	3-3.5 V	Monopolar	No differences between early onset vs delayed onset groups on a variety of neuropsychological tests
(Sankar et al., 2015)	AD	Bi FX	12	130	90	3-3.5 V	Monopolar	Increase in hippocampal volume and slowed atrophy in FX and MB in 2 of 6 subjects, who also had the least cognitive decline
(Fontaine et al., 2013)	AD	Bi FX	12	130	210	2.5 V	Bipolar	Some apparent slowing of disease progression on a variety of neuropsychological tests
Hamani et al. (2008)	Morbid obesity	Hypo-thalamus/FX	12	130	60	2.8 V	Monopolar	Spontaneous déjà vu (on first day); 3 weeks and 12 months after stim began, enhanced recall; Increased metabolic activity in ipsilateral Hipp and PHG
(Lozano et al., 2016)	AD	Bi FX	12	130	90	3-3.5 V	Monopolar	No difference between stimulated and sham group on behavioral measures (ADAS-cog/CDR_SB); possible benefit for only > 65 yrs; Increased glucose metabolism in several brain regions at 6 but not 12 months
(Kuhn et al., 2015a)	AD	NBM, Ch4	12	10-20	90-150	2.0-4.5 V	Monopolar	Slower disease progression than matched controls (ADAS-cog/MMSE)
Turnbull et al. (1985)	AD	NBM	2	50	210	3 V	Bipolar	Less decline in glucose metabolism in ipsilateral brain areas relative to contralateral; no improvement in memory/cognition (Stim delivered 30 sec on, 12 minutes off rather than continuous)
(Kuhn et al., 2015b)	AD; < 70 yrs	NBM	26-28	20	NR	NR	Monopolar	Stable memory results; moderate decline or improvement in overall cognitive (ADAS-cog/MMSE)

Table 1. Chronic stimulation for memory studies conducted in humans. All used continuous stim delivered through macroelectrode contacts. AD: Alzheimer's Disease; Bi: bilateral; Hipp: hippocampus; Am: amygdala; ANT: anterior nucleus of the thalamus; FX: fornix; NBM: nucleus basalis of Meynert; PHG: parahippocampal gyrus; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; MMSE: Mini Mental State Exam; CDR_SB: Clinical Dementia Rating Sum of Boxes; NR: Not Reported

Table 2

Reference	SITE	STAGE and STATE	Spatial SCALE	Temporal SCALE	SETTINGS (Frequency/Pulse Width/Amplitude)	Measure	Effect of STIM
Inman et al. (2018)	Am	Encoding	Macro, 5 mm	1 second;	50 Hz in 8 Hz/NR/ 0.5 mAmp	Object Recognition Memory; Theta-Gamma Coupling BLA to Perirhinal	Immediate test: no effect; 1-day test: improved memory and enhanced theta-gamma coupling for remembered stim objects relative to remembered non-stim objects
Miller et al. (2015)	FX	Entire task	Macro, 5 mm	Continuous; 20 mins before & whole task	200 Hz inside 5 Hz/ 100 µsec/7 mA	Complex Figures, Auditory-Verbal Learning; Naming	Complex figure test: improvement on immediate and delayed (sample size precluded statistical verification) Other tests: no change
Hansen et al. (2018)	ERA	Encoding	Macro, 3-4.5 mm	15 sec on/ 15 sec off	50 Hz/300 µsec/ 0.1 mAmp	Recognition Memory (Item/Color Association) ERPs at stimulus onset	Behavioral effect: none ERPs: larger amplitude in only the ipsilateral anterior hippocampus.
Titiz et al. (2017)	ERA	Encoding	Monopolar Micro	1 second stim;	100 Hz in 5 Hz/ 200 µsec/150 µAmp	Recognition Memory (Pictures of People)	Memory specificity enhanced with right angular bundle; no effect for right gray matter or left-sided stim
Suthana et al. (2012b)	Hipp & ERA	Encoding/ Practice,	Macro, 1.5 mm	5 sec on/ 5 sec off	50 Hz/300 µsec/ 0.5-1.5 mAmp	Spatial Learning Task; Theta-Phase Resetting	Memory: ERA enhanced; No effect of stim in Hipp. Theta-phase resetting: ERA increased in ipsilateral hippocampus
Hampson et al. (2018)	Hipp	Encoding/ delay; Closed loop "MIMO"	Multiple micro, 18 mm span	4 sec/trial	Model-driven pattern/ 1 msec/150 µAmp	Delayed match to sample (DMS); Delayed recognition (DR)	DMS & DR: significant improvements with MIMO vs no stimulation. DMS: "random" stim moderately worse than no stim.
Jun et al. (2019)	Hipp	Encoding	Macro, 6 mm	5 sec on/ 5 sec off	50 Hz/300 µsec/ 2 mAmp	Word-pair associations (Recognition) Theta power	Recollection: improved; Familiarity: no effect Theta power: enhanced in lateral middle temporal cortex during correctly remembered encoding trials.
Coleshill et al. (2004)	Hipp	Encoding	Macro, 1-2 mm	1.2 seconds	50 Hz/1 msec/10-20% below ADT	Recognition Memory (words or faces)	Words: impaired with left but not right Faces: impaired with right but not left
Lacruz et al. (2010)	Hipp and others	Encoding/ Recognition	Macro, 5 mm	1 ms every 5 sec	Single pulse/1 msec/ 5.1 +/- 0.9 mAmp	Recognition Memory (written words, objects, faces, geometric figures)	Unilateral stim: no effect Bilateral stim in Hipp: impaired for all; complete for faces; Stim outside of Hipp: no effect
Fell et al. (2013)	Hipp & Rhinal Cortex	Encoding/ distractor/re-call	Macro, widely spaced	Continuous	40 Hz/sine wave/ 0.01 mA	Number of words recalled;	in-phase vs anti-phase between Hipp and rhinal cortex: trend for in-phase better than sham better than anti-phase stimulation.
Jacobs et al. (2016)	Hipp, ERA, & others	Encoding	Macro, adjacent	4.6-5 sec on/, 4.6-5 sec off	50 Hz/300 µsec/ Max < ADT (0.5-1.5 mAmp)	Locations in open field; Verbal Free Recall	EC or Hippocampus: impaired memory in both tasks
Kucewicz et al, (2018a,b)	MTL	Encoding	Macro, adjacent	4.6 seconds	50 Hz/300 µsec/ 0.5-3.5 mA	Verbal Free recall; Stim-induced change in high gamma power	LTC stim: improved list-level (but not item level) memory; increases gamma power for subsequently forgotten words. Outside LTC: no effect
Merkow et al. (2017)	MTL	Encoding/ distractor/recall	Macro, 10 mm	5 seconds	50 Hz/300 µsec/1.9-5.0 mAmp (1 < ADT)	Free recall of short (3 word) word lists	impaired memory at all stages; Greatest impairment at beginning of distractor task
Ezzyat et al. (2017)	MTL & others [a]	Encoding	Macro, 5-10 mm	4.6 seconds	50 Hz/300 µsec/ < 3.5 mAmp	Classifier to predict likelihood of recall; Verbal Free recall	Enhanced for likely-to-forget items and hurt likely-to-remember.
Alagapan et al. (2019)	SFG	Entire trial	Macro, 10 mm	5 sec/trial	5, 9, or 10 /200 µsec/ 2 mAmp	working memory: lists of letters	No effect on accuracy (ceiling effect) but decreased reaction times
Ezzyat et al. (2018)	TC	Encoding, Closed loop	Macro, adjacent	500 ms/trial	variable/300 µsec/ 0.25-2.0 mAmp	Verbal Free Recall	Stim when in non-optimal state for encoding: Higher recall than expected
Kim et al. (2018)	Two non-MTL [b]	Retrieval	Macro, 3-3.75 mm	2 sec (inter trial interval)	50 Hz in 4 Hz/ 500 µsec (4 pulses)/ 4-5 mA (max < ADT)	Navigation task with spatial or temporal retrieval cue; Theta phase coherence	Impairment of spatial but not temporal retrieval Increased theta coupling immediately following stim offset that quickly changed to increased decoupling relative to baseline
Natu et al. (2019)	PCC	Encoding	Macro; adjacent	25 s (entire encoding)	100 Hz/200 µsec/NR	Verbal free recall; Oscillatory power in Hippocampus	Impairment of memory for first item of list; Decreased theta power and increased low and high gamma power in Hipp

Table 2. Selected short-term stimulation for memory studies conducted in humans. All were conducted in participants with refractory epilepsy undergoing seizure monitoring. Stimulation was delivered in an open loop manner unless noted in STAGE and STATE column. Hipp: hippocampus; Am: amygdala; FX: fornix; ERA: Entorhinal Area; MTL: (multiple sites with the) Medial Temporal Lobe; (L)TC: (Lateral) temporal cortex; ERP: event related potential; MIMO: multi-in, multi-out model for selecting stim pattern from neural activity (see text); [a] Electrode chosen with greatest "subsequent memory effect"; [b] Electrodes chosen to be functionally connected during spatial but not temporal task

Figure 1

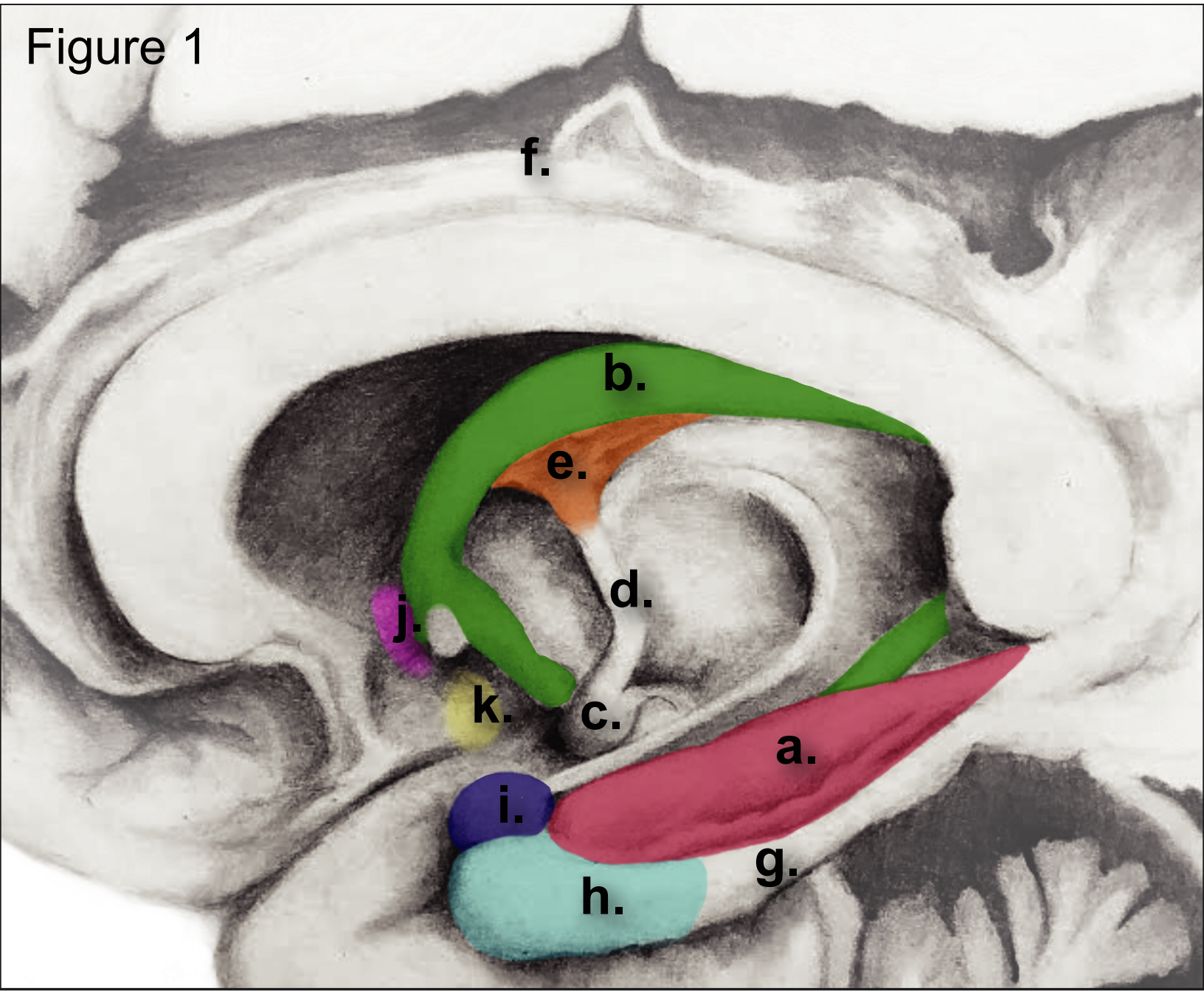


Figure 2

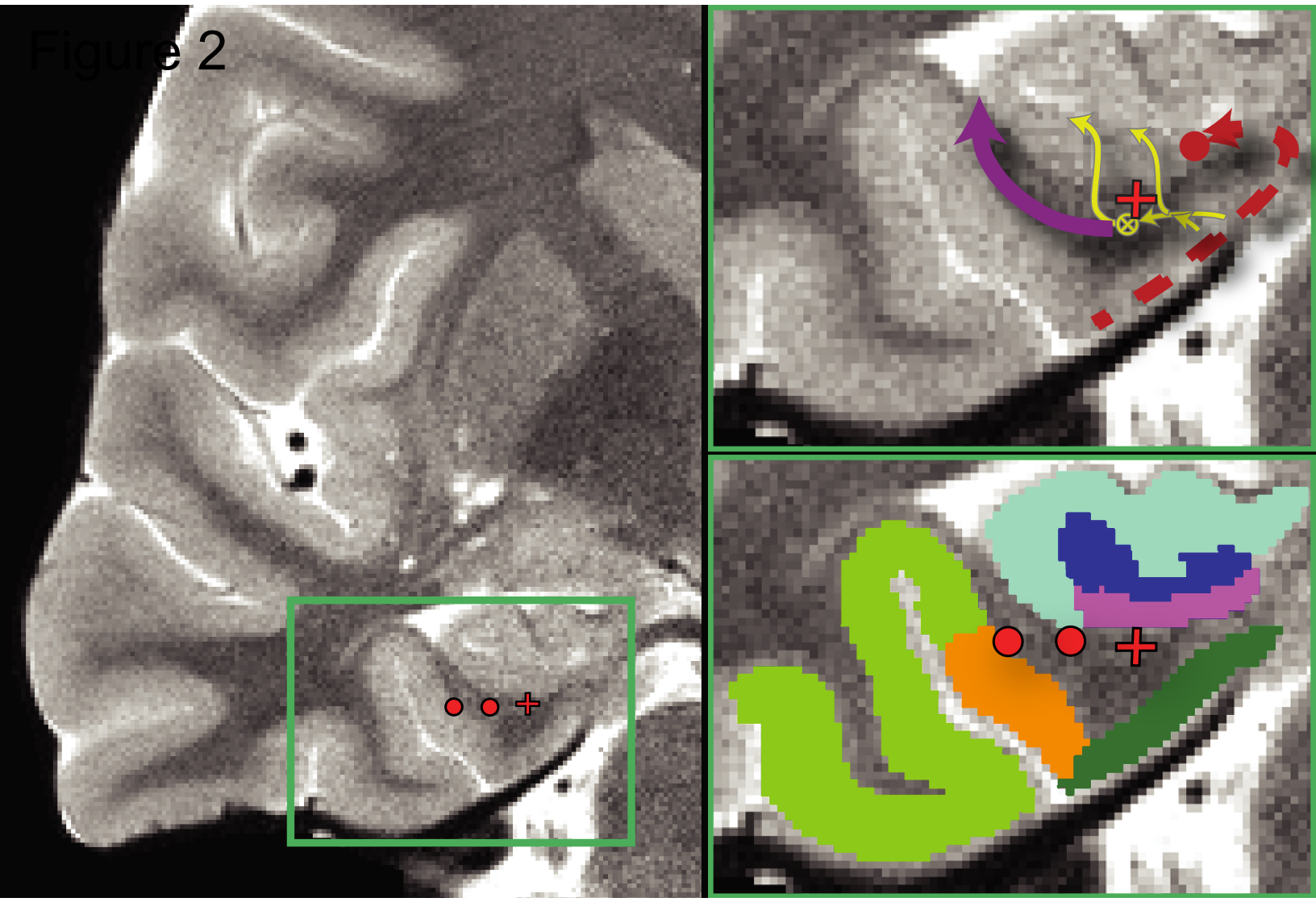
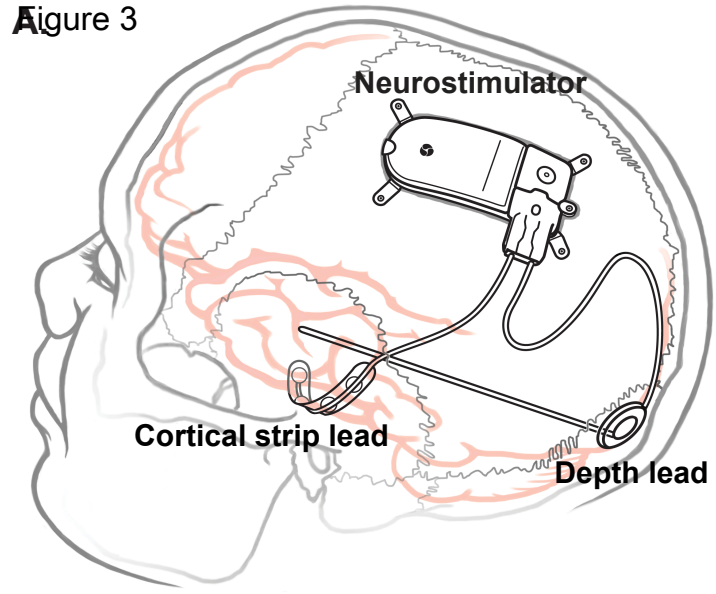
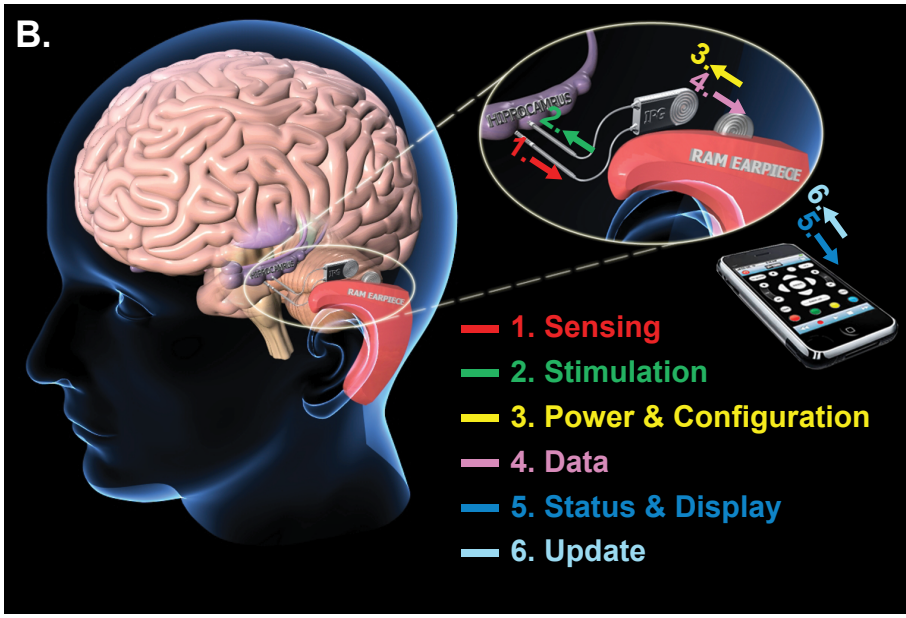

CA1
CA3-DG
Subiculum
Entorhinal Cortex
Perirhinal Cortex
Fusifom Gyrus
macroelectrode
100 μm microelectrode
Perforant Path
Alvear Path
Superficial Entorhinal Pathways

Figure 3


A.
Neurostimulator
Cortical strip lead
Depth lead


B.
HIPPOCAMPUS
RAM EARPIECE
1. Sensing
2. Stimulation
3. Power & Configuration
4. Data
5. Status & Display
6. Update