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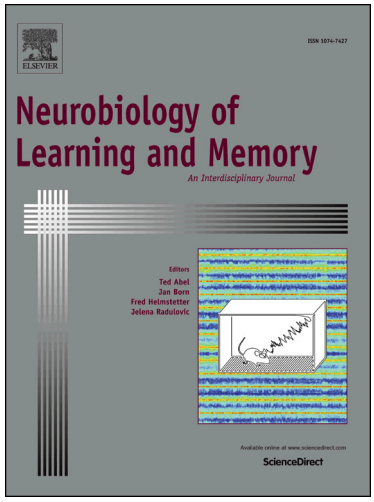

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Title: A network approach for modulating memory processes via direct and indirect brain stimulation: Toward a causal approach for the neural basis of memory

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Abstract

Electrical stimulation of the brain is a unique tool to perturb endogenous neural signals, allowing us to evaluate the necessity of given neural processes to cognitive processing. An important issue, gaining increasing interest in the literature, is whether and how stimulation can be employed to selectively improve or disrupt declarative memory processes. Here, we provide a comprehensive review of both invasive and non-invasive stimulation studies aimed at modulating memory performance. The majority of past studies suggest that invasive stimulation of the hippocampus impairs memory performance; similarly, most non-invasive studies show that disrupting frontal or parietal regions also impairs memory performance, suggesting that these regions also play necessary roles in declarative memory. On the other hand, a handful of both invasive and non-invasive studies have also suggested modest improvements in memory performance following stimulation. These studies typically target brain regions connected to the hippocampus or other memory "hubs," which may affect endogenous activity in connected areas like the hippocampus, suggesting that to augment declarative memory, altering the broader endogenous memory network activity is critical. Together, studies reporting memory improvements / impairments are consistent with the idea that a network of distinct brain "hubs" may be crucial for successful memory encoding and retrieval rather than a single primary hub such as the hippocampus. Thus, it is important to consider neurostimulation from the network perspective, rather than from a purely localizationalist viewpoint. We conclude by proposing a novel approach to neurostimulation for declarative memory modulation that aims to facilitate interactions between multiple brain "nodes" underlying memory rather than considering individual brain regions in isolation.

Keywords: brain stimulation, memory, network, tms, tdcs, dbs

Introduction

The use of electrical stimulation to modulate human memory has important implications for the basic understanding of the neural basis of memory and for therapeutic clinical applications. While neuroimaging studies in the past couple of decades have revealed important new information about the neural basis of human cognition, the types of inferences that can be made with these data are correlational in nature. Specifically, as has been pointed out in past work, neuroimaging is limited to inferences derived from observing brain activity related to a specific behavioral process (i.e., P(Activity | Behavior), Poldrack, 2006; Sarter, 1996). In contrast, stimulation methods allow us to make more powerful inferences regarding whether a given pattern of activity *causes* the behavioral process (i.e., P(Behavior | Activity); Sarter, 1996). In other words, stimulation that successfully up or down regulates neural activity, can establish necessity and/or sufficiency of brain regions for specific cognitive functions (Sarter, 1996).

Although there have been prior reviews on deep brain stimulation (Lee, Fell, & Axmacher, 2013; Sankar, Lipsman, & Lozano, 2014; Suthana & Fried, 2014), a comprehensive review that summarizes successful and unsuccessful invasive and non-invasive stimulation approaches to memory modulation is current lacking. A critical review of prior work may help design optimal strategies for determining both stimulation targets and patterns of stimulation that could successfully and reliably modulate human memory. Another important component missing from prior reviews is an explanation of the widely varied results of stimulation studies thus far - many resulting in disruption, some in enhancement, and others in no change in memory performance at all. One answer lies in methodological differences (e.g., stimulation parameters), but perhaps a more important issue is that these approaches have focused on modulating diverse, but single nodes in the memory network. With the growing theoretical consensus on memory as a network phenomenon rather than arising from a single or sparse number of memory “hubs” (McClelland, McNaughton, & O’Reilly, 1995; Nadel, Samsonovich, Ryan, & Moscovitch, 2000; Teyler &

DiScenna, 1986; Winocur & Moscovitch, 2011; Watrous et al. 2013), focal stimulation might be expected to produce inconsistent results. Our goal therefore is to review prior studies of stimulation-induced modulation of memory and discuss the strategies one might adopt in future studies.

In order to limit the scope of this review, we will restrict our discussion to specific long-term memory systems, study types, and populations. We focus on studies of declarative memory - the type of long-term memory involving access to recent experiences and general knowledge about the world (e.g., episodic memory, semantic memory; see Squire 2004 for review) and dependent on the cortico-hippocampal network (Buzsáki, 1996; Eichenbaum, 2000; Squire 2004). In contrast, other types of long-term memory (e.g., procedural memory, classical conditioning) do not depend on conscious retrieval, and are independent of the hippocampal system (rely on structures such as striatum, amygdala) - these will therefore not be considered here. We will also limit our review only to studies that report quantified measures of memory performance and exclude studies that present only subjective or descriptive results (autobiographical memory or déjà vu phenomena). Finally, studies where behavioral outcomes are reported as a byproduct of therapeutic stimulation in patients with neurodegenerative diseases (e.g., Alzheimer's Disease, Parkinson's Disease, Amyotrophic Lateral Sclerosis) or psychiatric disorders (e.g., depression, schizophrenia) will not be considered here so as not to deviate from our focus on the modulation of normal human memory function.

Types of stimulation

This review will discuss four different types of human brain stimulation techniques: acute and chronic direct electrical stimulation, transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS). Invasive methods (i.e., acute and chronic direct electrical stimulation) enable direct targeting of the limbic structures whereas application of non-invasive

stimulation is naturally biased to brain regions that are superficial (see Table 1). For example, TMS and tDCS studies that seek to modulate memory function target prefrontal and parietal constituents of the memory networks associated with encoding (Blumenfeld & Ranganath, 2007; Nyberg et al., 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994) and/or retrieval (Cabeza et al., 2004; Cabeza et al., 2003; Cabeza, Dolcos, Graham, & Nyberg, 2002; Donaldson, Petersen, & Buckner, 2001; Nyberg et al., 1996; Tulving et al., 1994; Vilberg & Rugg, 2008). Therefore, there are stark anatomical distinctions between the substrates of direct electrical stimulation and TMS/tDCS, but given that all methods can provide some insight into the modulation of memory processing, we will consider the results from all four methods.

We should state upfront that the current scientific understanding of the physiological effects of electrical stimulation of mammalian nervous tissue *in vivo* is primitive and is often based on several axiomatic assumptions and in many cases, unproven theoretical constructs. For example, studies using direct electrical stimulation generally aim at targeting a specific, focal region and the results are interpreted based on the presumption of focal excitatory effects. Past studies demonstrate, however, that direct electrical micro-stimulation can elicit current spread and signal propagation to broad cortical regions, and is likely to induce summated effects of excitation and inhibition on cell responses rather than purely excitatory effects (Borchers, Himmelbach, Logothetis, & Karnath, 2012). Nonetheless, we will review what is currently known about the mechanisms of both direct and indirect stimulation, i.e., the current theories of action of each of these modalities as they exist in the literature at the current time. We hope that by pointing out some of the gaps in our understanding of the mechanistic basis of neurostimulation, this review can provide an impetus to guide future studies aimed at more precisely understanding the neural consequences of electrical stimulation.

There are two fundamentally distinct approaches to *invasive* stimulation in humans. The first is stimulation using electrodes that are implanted acutely for the purpose of intracranial electrocorticography (ECoG) to localize epilepsy onset zones. Only acute or sub-acute periods of stimulation are feasible using this approach as the electrodes are explanted after the clinical goals are met. Therefore, we characterize these stimulation methods as acute direct electrical stimulation (aDES). aDES may be accomplished using either subdural grid electrodes (SDE) which target gyral cortical substrates (in the memory context this is usually entorhinal cortex in the temporal lobe) or depth electrodes that penetrate the brain and may be located within the medial temporal lobe structures (stereo-electroencephalography, SEEG).

We discuss six aDES studies on memory modulation which provide a useful framework for considering the varying effects of hippocampal stimulation on memory performance (Coleshill et al., 2004; Fell et al., 2013; Koubeissi, Kahriman, Syed, Miller, & Durand, 2013; Lacruz et al., 2010; Miller et al., 2015; Suthana et al., 2012). These studies all used depth electrodes targeting the hippocampus, parahippocampal cortex, or fornix. Most studies used high frequency pulses (40-200 Hz) with one exception (Koubeissi et al., 2013) in which low frequency pulses (5Hz) were used. Patients were tested with a recognition memory task, spatial navigation task, or standardized cognitive batteries that include measures of declarative memory. Stimulation or sham stimulation was typically the independent measure and changes in memory performance were the dependent measure.

The second method of direct human brain stimulation involves chronically implanted systems with internalized current generators. The effects of this approach stem from not just acute modulation but also chronic stimulation (i.e., potential plasticity induced by long-term stimulation). Deep brain stimulation (DBS) is a conventional term used for this type of stimulation, but since in many cases the targets are exactly the same as in aDES, there is no

relative difference in “depth.” Thus, for clarity, we define this method as the chronic direct electrical stimulation (cDES) in this review. DBS/cDES is currently widely used clinically to modulate neurological behavior in Parkinson’s Disease (PD) and dystonia, but targets in these cases are the basal ganglia and thalamus and any effects on declarative memory is inadvertent and generally not controlled for. We have therefore further restricted this review to cDES studies to those specifically targeting limbic or para-limbic structures.

In contrast to aDES stimulation, cDES allows assessment of the effects of continuous, long-term, stimulation, which can lead to long-term potentiation, and/or neurogenesis (Lee et al., 2013). cDES studies use patients with chronic neurological disease and typically test the effect of high-frequency stimulation (130-185Hz) of medial temporal structures using performance on standardized memory batteries – either verbal learning (e.g., California Verbal Learning, Rey Verbal Learning, Hopkins Verbal Learning) or visuo-spatial memory tasks (e.g., immediate and delayed recall of complex figures). These studies are informative because it is possible to hypothesize that DBS should have no direct effect on cognition (as it is not specifically designed to target cognitive function but rather to disrupt the underlying neurological process – seizures for example). Thus, any improvements in cognition are worth considering because of the implications these could have on understanding how direct stimulation could reorganize circuits important to learning and memory.

It is noteworthy though, that there are also inherent limitations in cDES studies because they are essentially opportunistic – performed to capitalize on the fact that patients receive stimulation over a long period, with no direct means of controlling stimulation with respect to cognitive questions in a rigorous fashion. This creates inherent limitations in the analysis of existing cDES studies: 1) effects being inherently associated with the network reorganization following clinical improvement, which are not well-understood, 2) variability in the study cohort

as a function of the disease, 3) continuous stimulation throughout and not restricted to specific components of memory processes (i.e., encoding or retrieval) – thus making the effects of stimulation harder to qualify, 4) practice effects, as testing is repeated over many different intervals spanning weeks and/or months. The five most relevant cDES studies are reviewed in this article.

The two non-invasive methods we review here, TMS and tDCS, induce very different types of neural perturbation. TMS induces electrical currents in the targeted brain region by creating brief high intensity magnetic fields around the stimulation coil, which is usually placed tangential to the scalp. The magnetic field created is perpendicular to the plane of the coil, and the electric field induced is perpendicular to this magnetic field; thus electric stimulation induced by TMS is parallel to the plane of the coil (Fox et al., 2004). TMS typically recruits a mixture of excitatory and inhibitory action potentials, which may vary by the specific area targeted and intervals between stimulation pulses (Hallett, 2000, 2007; Pascual-Leone, 2000; Siebner & Rothwell, 2003). Depending on the parameters used, TMS can have both disruptive and enhancing effects, though the relation between stimulation type and the underlying cortical physiology remains poorly understood.

TMS studies generally apply stimulation to disrupt brain regions previously revealed to be associated with memory functions (e.g., encoding, retrieval) by functional imaging studies. The 13 TMS studies in this review used controlled memory paradigms (item recognition, pair association, and source memory paradigms), and a variety of stimulation pulse types: single-pulses, paired-pulses, trains of pulses at a fixed frequency (repetitive TMS (rTMS), Hoogendam, Ramakers, & Di Lazzaro, 2010; Pascual-Leone, 1994), or short trains of pulses repeating at a low frequency (e.g., theta burst stimulation (TBS), Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

Unlike TMS, tDCS directly applies electrical currents through the scalp. tDCS delivers charge densities that do not directly lead to increases in neural spike rate but instead are thought to modulate population neuronal excitability (Coslett, Hamilton, Nitsche, & Paulus, 2011; Nitsche et al., 2008; Wagner, Valero-Cabre, & Pascual-Leone, 2007; Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). Regional excitability is increased by anodal (positive charge) stimulation and decreased by cathodal (negative charge) stimulation. Thus the technique carries promise in being able to evaluate the effects of up-/down-regulating the neuronal excitability of certain brain regions on cognitive functions. However, in general, it should be noted that the exact brain regions affected by tDCS cannot be precisely delineated (Bikson, Name, & Rahman, 2013; Polanía, Nitsche, & Paulus, 2011), and also that the effect sizes are often relatively small in these studies.

Similar to these TMS studies, tDCS studies also target frontal or parietal regions to modulate memory functions. We review 8 tDCS studies that tested the effects of increasing and decreasing the neuronal excitability in those regions on memory functions. Typically, anodal or cathodal stimulation is applied at a low current (1-1.5mA) for about 15-20 minutes during different phases of a memory task (e.g., encoding, retrieval). Tasks used in these studies varied considerably across studies, including item recognition, verbal learning, and paired associate learning. These studies often report improvements in memory by anodal stimulation, consistent with what one might expect from increased neuronal excitability of cortical memory nodes.

----- Table 1 goes here -----

Modulation of memory with deep brain stimulation

Invasive electrical stimulation methods allow direct targeting of deep structures in the medial temporal lobes, such as the hippocampus, a structure critical to human memory. While numerous studies have shown that hippocampal lesions impair episodic memory in particular (Vargha-Khadem et al., 1997; Yonelinas et al., 2002), inferences from human lesion studies are limited by the fact that 1) all comparisons are *between* patient and healthy control groups and 2) plasticity occurring post-lesion is difficult to control between patients. In contrast, direct stimulation of the human hippocampus is advantageous from the perspective that comparisons can be done within the same patient and plasticity effects can be better controlled (i.e., sham vs. real stimulation). Past stimulation studies have attempted modulating hippocampal and/or parahippocampal activity either by directly stimulating those targets or stimulating structures or fiber pathways that have direct connections with them, such as the fornix.

1. Hippocampal stimulation

Several studies have investigated the effects of direct stimulation of the hippocampus on memory encoding and retrieval with both acute and chronic stimulation schemes. Acute direct electrical stimulation (aDES) of hippocampus during memory *encoding* disrupts encoding of to-be-remembered stimuli. Specifically, Coleshill and colleagues (2004) tested how left and right hippocampal stimulation during encoding differentially affected later recognition for different types of items (e.g., word, face). In six patients, they applied high-frequency stimulation (biphasic constant-current pulses, 50 Hz) at the beginning of encoding item presentation (see Table 2). Stimulation of the left and right hippocampi impaired encoding for verbal and face items, respectively. Lacruz et al. (2010) also directly targeted hippocampus, but they compared the effects of bilateral vs. unilateral stimulation during both encoding and retrieval. In seven patients, single pulse (monophasic constant-current) stimulation was delivered every 5s, time-locked to memory item presentation onset. Similar to Coleshill et al, they also found that stimulation disrupted encoding. However, in contrast to Coleshill et al, they found that unilateral

hippocampal stimulation had no effect on memory performance compared to baseline, while bilateral stimulation impaired recognition memory across various item types (e.g., words, geometrical drawings, and faces). The discrepancy in the effects of unilateral hippocampal stimulation may be explained by the distinct stimulation design (high frequency train vs. single pulse), but despite such differences, the two studies consistently showed that direct hippocampal stimulation disrupts encoding.

In contrast, cDES studies typically report no effect of hippocampal stimulation on memory although this is likely explained by the fact that stimulation does not occur specifically during encoding (Boëx et al., 2011; McLachlan, Pigott, Tellez-Zenteno, Wiebe, & Parrent, 2010; Miatton et al., 2011; Velasco et al., 2007). In these studies, high frequency (130 – 450Hz) direct electrical stimulation was delivered chronically (3 to 18 months) to the hippocampal region, and patients were tested using standardized memory tasks in the baseline state (before stimulation or with stimulation off for a matched period of time) vs. after chronic stimulation. Behavioral changes in these studies varied across and within studies for both verbal and visuo-spatial memory. On verbal learning tasks, studies reported no effects (McLachlan et al., 2010, 3 months; Miatton et al., 2011, 6 months), a trend of improvement (Velasco et al., 2007, 18 months), or varying effects across subjects (Boëx et al., 2011, 3 months). Similarly, only one study reported some improvement in immediate recall in visuo-spatial memory (Miatton et al., 2011; 6 months) while others reported mixed results across subjects (McLachlan et al., 2010, 3 months) on visuo-spatial memory. Thus, in contrast to aDES studies, cDES studies provide conclusive evidence for neither memory disruption nor improvement. This likely arises, though, because aDES does not occur specifically during encoding. The lack of a direct effect on memory improvement, at least when considering across studies, is also important because these data suggest that direct stimulation of the hippocampus does not lead to (consistent) memory improvement.

----- Table 2 goes here -----

2. Forniceal stimulation

Another approach to performing invasive stimulation is to target structures or fiber pathways that have direct connections with memory structures like the hippocampus, such as the fornix. In contrast to studies that directly targeted hippocampus, these studies often report memory improvements. In one such aDES study, Koubeissi et al. (2013) reported that acute low-frequency stimulation of fornix (200~500 μs wide pulses delivered at 5 Hz continuously during 4-hour sessions) improved Mini-Mental Status Examination (MMSE) scores in eleven patients. The MMSE was administered before stimulation began and then hourly during stimulation. However, one potential issue with this study (also acknowledged by the authors) relates to the lack of control for practice effects involved in repeating the experiment (e.g., Postman & Rosenzwig, 1956). Thus, we cannot conclude that forniceal stimulation definitively improves episodic memory, although the findings do suggest that targeting the hippocampus indirectly through the fornix *may* result in some improvements.

A more recent aDES study using theta-burst (i.e., delivering a burst of high frequency pulses at a theta frequency) stimulation to the fornix reported improvement of visual memory retrieval (Miller et al., 2015). In this study, participants performed equally well on the initial complex figure task (copying a complicated line drawing) regardless of the stimulation condition, but performed numerically better at reproducing the figure immediately after, as well as after a 20-30 minutes long delay. However, these findings need careful interpretation for several reasons: 1) the effects were not statistically tested 2) the study sample was very small (n = 4), and 3) stimulation was not restricted to a specific phase of memory (see also comments in Fried, 2015). Again, though, this study points to some potential promise in improving memory by stimulating

the hippocampus indirectly through the fornix. Critically, though, while these studies support this intriguing possibility, alternative interpretations remain and thus convincing evidence is yet lacking.

3. Entorhinal cortex stimulation

Similar to targeting fornix, other studies aimed to modulate hippocampal function by stimulating the entorhinal cortex, to activate the hippocampus through direct connections via the perforant path. Suthana et al. (2012) showed improvements in navigation performance following acute stimulation of the entorhinal cortex, with their specific measure being the accuracy with which patients navigated to a goal location store (termed excess path length, i.e., Newman et al., 2007). Because navigation is often associated with integrity of the hippocampus (i.e., Astur, Taylor, Mamelak, Philpott, & Sutherland, 2002; Kolarik et al. 2016; Morris & Garrud, 1982) and not of the entorhinal cortex (e.g., Hales et al., 2014), the authors attributed the effects of stimulation to entorhinal cortex as occurring because it resulted in more endogenous, regularized input into the hippocampus than direct stimulation of the hippocampus (Suthana et al., 2012). In support of this argument, direct stimulation of the hippocampus had no effect on navigation yet stimulation of entorhinal cortex did reset on-going low frequency oscillations in the hippocampus. The effects size in this experiment was relatively modest, however, and it is not clear from the publication whether corrections were made for multiple comparisons – which might have adversely affected the statistical significance of the improvement in path to goals. Additionally, there may have been other factors influencing the directness of a path to a goal, including attention and motivational factors. Thus, it remains unclear whether the Suthana study improved memory performance. Jacobs et al. (2015) revisited this question using a spatial learning paradigm in which encoding period was controlled (i.e., fixed for each item) and concluded that entorhinal stimulation, as well as hippocampal stimulation, most often *impaired* memory. It is possible, though, that Jacobs et al. did not target the same area of entorhinal

cortex as Suthana et al. 2013 and reconciling the differences in findings between the two studies remains important.

4. Hypothalamic stimulation

A single case study showed significant improvement in verbal learning scores after 3-week long high-frequency stimulation (130 Hz) of hypothalamus (cDES), a procedure originally motivated to suppress appetite in a patient with morbid obesity (Hamani et al., 2008). The patient was tested using a standardized verbal learning task and an association memory task followed by remember/know judgment. The verbal learning score and recollection index significantly improved after 3 weeks of stimulation. The authors speculated that stimulation could be spreading throughout limbic structures (like the hippocampus), thus providing a possible explanation for how stimulation to the hypothalamus could improve memory. We must approach this study with caution though because it is not clear how hypothalamic stimulation would affect memory-related structures and the sample size (1 patient) limits generalizability. There are also alternative clinical interpretations that could underlie the reported memory improvements: general improvements in other clinical outcomes associated with appetitive changes could underlie the memory effects observed in this study. Again, though, this study does offer the intriguing implication that indirect targeting of the hippocampus could improve episodic memory.

To summarize, direct brain stimulation studies suggest that stimulating the hippocampus directly during encoding disrupts memory performance. In addition, inducing changes just in hippocampal neuronal activity is not sufficient to reliably induce improvements in memory performance. In cDES studies, direct stimulation of the hippocampus appears to produce little to no effect. The difference between aDES and cDES studies may possibly relate to the fact that aDES studies involve stimulation during specific phase of memory tasks (i.e., encoding or retrieval) while cDES involve stimulation independent of behavior. We might expect the former

to be more effective in terms of directly affecting particular memory processes while the latter's effects are more indirect and subject to variability across patients. It is also worth noting that most studies that have found memory improvements have done so via stimulation of structures *connecting* to the hippocampus. While this may be a promising means to provide a more endogenous form of modulation - as it must be conducted through afferent fibers to the hippocampus - the effects from these studies must be taken as preliminary due to low effect sizes (i.e., Button et al., 2013; Ioannidis, 2005), and potential alternative interpretations (e.g., general attentional/motivational effects and in the case of cDES studies, practice effects and clinical improvements over time).

Given the fact that hippocampal lesions typically result in profound amnesia (Squire et al. 2004; Vargha-Khadem et al. 1997; Yonelinas et al., 2002), one might expect that direct stimulation of the hippocampus would have profound effects on memory. The two studies that showed significant effects of the hippocampal stimulation on memory encoding (at least $p < .01$; Coleshill et al., 2004 and Lacruz et al., 2010) also did not show complete memory disruption (patients' performance were not consistently at chance levels across all stimulation trials). One explanation for these counterintuitive findings is that given that the hippocampus is a large structure, stimulation delivered to one part of it would not have striking effects on memory as hippocampal lesions do. Indeed, each hippocampal anatomical subfield (i.e., dentate gyrus, CA23, CA1, and subiculum) may have distinct subfunctions in memory Indeed, each hippocampal anatomical subfield (i.e., dentate gyrus, CA23, CA1, and subiculum) may have distinct subfunctions in memory (Amaral & Insausti, 1990; Stokes, Kyle, & Ekstrom, 2014; Hoge & Kesner, 2007). Thus, depending on which subfield (and indeed, which layer, or the anterior vs. posterior hippocampus) is stimulated, the observed effects may differ. Alternatively, it is possible, that during stimulation of the hippocampus, other nodes within the memory network may still be able to contribute to correct memory encoding and retrieval, therefore the observed functional

disruption being small. This argument essentially makes the point that other "hubs" within the cortex also critically contribute to declarative memory. Indeed, past neuroimaging studies have argued that lateral frontal and parietal regions are part of the core networks associated with memory encoding (Blumenfeld & Ranganath, 2007; Nyberg et al., 1996; Tulving et al., 1994) and/or retrieval (Cabeza et al., 2004; Cabeza et al., 2003, 2002; Donaldson et al., 2001; Nyberg et al., 1996; Tulving et al., 1994; Vilberg & Rugg, 2008). More recent theoretical and empirical studies have argued that these regions are part of a larger network of interacting brain regions subserving memory (King, de Chastelaine, Elward, Wang, & Rugg, 2015; Schedlbauer, Copara, Watrous, & Ekstrom, 2014; Watrous & Ekstrom, 2014; Watrous et al., 2013). Thus, a key prediction is that disruption of extra-hippocampal nodes should also produce impairments in memory function. Because these regions are uncommon targets for the depth electrode placement and are accessible using the non-invasive stimulation coils, many studies have investigated the role of these regions in memory processes using non-invasive stimulation such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).

Modulation of memory with frontal / parietal lobe stimulation

1. Left prefrontal cortex stimulation

Various non-invasive TMS studies have suggested that disrupting left prefrontal cortex (dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), or inferior frontal cortex (IFG)) during *encoding* impairs later retrieval of the memory items. This has been consistently demonstrated using various types of stimulation pulses (rTMS, single pulse, paired-pulses) and memory items (word, picture) (Blumenfeld, Lee, & D'Esposito, 2014; Gagnon, Blanchet, Grondin, & Schneider, 2010; Kahn et al., 2005; Machizawa, Kalla, Walsh, & Otten, 2010; Rossi et al., 2001; Sandrini, 2003; Skrdlantová, Horácek, Dockery, Lukavský, & al, 2005). Additional evidence suggests that the left prefrontal cortex is particularly important for verbal encoding. For example, disrupting this region 1) selectively impaired verbal learning but did not

affect encoding of face stimuli (Skrdlantová et al., 2005) or abstract stimuli (Epstein, Sekino, Yamaguchi, Kamiya, & Ueno, 2002) and 2) selectively impaired deep processing of words while memory for items encoded in the shallow processing condition was unaffected (Innocenti et al., 2010).

In contrast to the disruption typically observed with TMS stimulation of PFC (but see Köhler et al. 2004), several tDCS studies showed that increasing neuronal excitability in the left prefrontal region might improve memory. In two different studies, recognition accuracy and reaction time were improved by anodal and impaired by cathodal tDCS to the frontal lobes during memory encoding (Javadi, Cheng, & Walsh, 2012; Javadi & Walsh, 2012). Participants were tested in four separate sessions that used different stimulation regimes (e.g., anodal, cathodal, sham, or control stimulation). In each session, participants encoded a list of words across four blocks and tDCS was applied continuously in the latter two encoding blocks (Javadi & Walsh, 2012). Comparisons of the recognition accuracy across sessions (anodal, cathodal, sham, and control stimulation sessions) revealed that greater excitability of left DLPFC was associated with improved memory encoding while reduced excitability impaired encoding. This basic finding was conceptually replicated by the same group using briefer tDCS stimulation (Javadi et al., 2012). Instead of being applied continuously during encoding blocks, tDCS was applied briefly (1.6s) before or after the stimulus presentation (i.e., early or late in encoding trials) in each trial. Anodal stimulation early in trial improved encoding while cathodal stimulation late in trial impaired encoding. Together, these findings suggest that the excitability of frontal cortical neurons may modulate the encoding efficiency, and potentially improve memory performance.

A study by Kirov and colleagues similarly argued for encoding improvement during tDCS of the left prefrontal cortex although they took a slightly different approach (Kirov, Weiss, Siebner, Born, & Marshall, 2009). They used slow wave oscillations at 0.75 Hz with 0.33s-long rising and

dropping slopes to induce theta-activity in bilateral DLPFC either during encoding or retention. This induced significant increases in theta-activity in frontal regions and participants remembered more word pairs correctly when stimulation was applied during *encoding*. This study, though, did not correct properly for multiple comparisons and thus must be taken with caution.

In contrast to the reports of memory improvements using tDCS to left prefrontal cortex, one study reported that enhanced left DLPFC excitability during encoding was associated with blurred detail memory (Zwissler et al., 2014). In this study, participants performed a cued learning task with scene pictures followed by a forced choice recognition task, in which 'old' (previous learned) items were intermingled with lure items that were highly similar to old items. tDCS had no effects on recognition accuracy, but rather modulated the false alarm rate. Anodal stimulation increased and cathodal stimulation decreased the false recognition rate of the lure items, suggesting that higher excitability of left DLPFC may be detrimental to encoding of details. The reason for the difference in findings between these frontal tDCS studies is not clear. But to date, most tDCS studies targeting frontal areas have reported improved memory performance by increased neural excitability or theta-activity. Together with TMS findings, these findings suggest that left prefrontal regions play a critical role in the encoding and retention of of new information, particularly verbal information.

In addition, increased excitability of the left frontal lobes during *retention* period (between encoding and recall) was associated with reduced forgetting in healthy older adults (Sandrini et al., 2014). Thirty-six healthy older adults were divided into anodal left DLPFC tDCS and sham stimulation groups and participated over 4 sessions. They learned a list of 20 object words in the initial session, and tDCS was delivered for 15 minutes on the following day (session 2). Recall performance was tested twice after the stimulation session – 48 hours and 1 month after

the initial learning session – and in both the delayed recall sessions, correct recall rate was significantly higher in the anodal tDCS compared to sham stimulation group. This suggests that increased excitability of the left frontal regions may reduce the decay of previously learned information. To summarize, overall, left frontal stimulation with tDCS, when performed during memory encoding, may induce some memory improvements via general increases of cortical excitability (encoding, retention) or increased theta-activities (encoding). In contrast, stimulation of left PFC with TMS disrupts memory performance.

2. Right prefrontal cortex stimulation

Whereas stimulation studies targeting the left prefrontal cortex mainly focused on the encoding and retention of new information, right prefrontal cortex has been mainly studied in the context of *retrieval* of previously learned information. TMS studies consistently have shown that disrupting right DLPFC impairs retrieval of previously learned items (Gagnon et al., 2010; Rossi et al., 2001; Sandrini et al., 2003). For example in Sandrini et al. (2003), participants were presented with a pair of words in each trial and asked to judge whether the two words were semantically related or unrelated (encoding). Then, during the retrieval phase, one word from each pair was presented as a probe with two other words: the other word from the pair and a novel word. Participants were asked to respond which of the two words was paired with the probe word during encoding. rTMS was applied at the beginning of retrieval stimulus presentation to left DLPFC, right DLPFC, or sham sites. The retrieval error rates were significantly increased for semantically unrelated word pairs by right DLPFC stimulation compared to baseline, left DLPFC or sham stimulation. Similarly, using rTMS and paired-pulses stimulation respectively, both Rossi et al. (2001) and Gagnon et al. (2010) found that TMS to right DLPFC impairs retrieval compared to left DLPFC stimulation. Collectively, findings from TMS studies targeting prefrontal regions suggest that left and right lateral prefrontal regions play crucial roles in memory encoding and retrieval, respectively.

3. Parietal cortex stimulation

The findings from a couple of tDCS studies suggest that cortical excitability of parietal/ temporo-parietal regions during *encoding* may relate to the probability of decay of encoded memory (Flöel et al., 2012, Jones, Gözenman, & Berryhill, 2014). Two studies using parietal tDCS stimulation examined the effects of anodal tDCS on memory decay (i.e., immediate vs. delayed recall), but targeted quite disparate parietal regions (right temporo-parietal cortex and posterior parietal cortex, respectively). In the first study with 20 healthy older adults, participants learned the object-location association while either anodal tDCS or sham stimulation was applied over the right temporo-parietal cortex (Flöel et al., 2012). Anodal tDCS enhanced delayed recall (reduced decay after one week) but did not affect immediate recall. In contrast, stimulation of posterior parietal cortex (PPC) resulted in an opposite pattern. Anodal stimulation of left PPC during verbal encoding improved immediate free recall without affecting delayed recall (Jones et al., 2014). An important caveat in directly comparing the results from these two studies is that the two studies evaluated 'delayed recall' with a very different delay from the learning session (1 week vs. ~20 minutes), but it is interesting that the neural excitability of two disparate parietal regions during encoding seemed to nonetheless affect the durability of the encoded memory at differential temporal delays.

Augmenting neural excitability of the parietal regions with tDCS during *retrieval* was also associated with improved memory performance. Pisoni et al. (2015) tested the effects of anodal tDCS in bilateral temporal and parietal regions during recognition. Participants encoded a list of 96 words first and made old/new judgments in the recognition phase, where the studied items were intermixed with the same number of new items. Anodal stimulation to bilateral parietal regions significantly increased the discrimination sensitivity (d') compared to the sham stimulation condition. This study did not assess the effects of cathodal tDCS (decreasing the

cortical excitability), but several TMS studies investigated roles that parietal regions play in retrieval by disrupting it.

Interestingly, disrupting parietal regions during retrieval with TMS does not impact general memory performance, such as recognition accuracy, but specifically affects source memory retrieval (i.e. the ability to retrieve details under which a stimulus was encoded, such as its color or position on the screen). rTMS to inferior parietal lobule (IPL) during the stimulus presentation of a recognition task had little to no effect on item retrieval accuracy (%hits) but did affect source memory (Sestieri, Capotosto, Tosoni, Romani, & Corbetta, 2013). Specifically, stimulation produced a bias towards responding that an item was encoded as "pleasant or unpleasant" rather than "living or not living," although it did not alter overall memory performance between sham and stimulation groups. Similarly, in another study, TMS applied over precuneus during retention (between encoding and retrieval) significantly reduced source memory errors without affecting general memory performance as measured by recognition accuracy (Hit, CR, FA rates; Bonnì et al., 2015). In contrast, superior parietal lobule (SPL) stimulation did not affect memory performance (Bonni et al., 2015; Sestieri et al., 2013). Thus, these studies suggest that the inferior parietal lobule specifically may be more critically involved in correctly retrieving contextual details than correctly recognizing previous learned items.

In contrast, one TMS study reported *improvements* in recall of previously learned items following stimulation of parietal cortex (Wang et al., 2014). Resting state fMRI was used to target putative connections from parietal cortex to the hippocampus, and memory improvements due to stimulation were attributed to activating long-term potentiation in cortical-hippocampal synapses. However, memory improvement, as measured by number of words correctly recalled that were previously associated with a face in this study, were not statistically significant. Specifically, when the same subjects received sham stimulation, the number of words recalled

was on par with that following real TMS (Table S2 in Wang et al., 2014, see also Wang & Voss, 2015). Because this study did not find a statistically significant improvement in raw memory scores compared to sham stimulation and most past studies have shown a disruption of memory performance following parietal stimulation, it is parsimonious to conclude that focal parietal stimulation alone is generally disruptive to memory performance. It is also unclear how stimulation of the hippocampus would be possible via polysynaptic connections from parietal cortex in the absence of stimulation of any other polysynaptically connected areas (e.g., visual and motor cortex). The innovative use of resting state fMRI to target the hippocampus in this study, though, leaves open the possibility for interesting effects to be obtained by indirectly targeting the hippocampus with TMS.

Synthesis: Network based effects of neurostimulation on memory processes

Converging evidence from the four different methodologies discussed above suggests that memory modulation may be possible if multiple memory nodes are stimulated. Specifically in the case of DES studies, some degree of memory modulation was observed when structures are indirectly targeted through structures or fiber pathways highly connected with the intended site of modulation (as previously have been suggested also in a TMS/PET study, Narayana et al., 2012). Indirectly targeting the hippocampus via projecting fibers such as those contained in the fornix may direct currents to a broader network and thus be more effective than directly targeting hippocampus in isolation. In addition, studies using tDCS - which has the least anatomical specificity for targeting a stimulation site amongst the methods reviewed here - suggest some memory improvements following anodal stimulation. Together, these findings tentatively suggest that stimulating multiple memory nodes in concert could enhance cognitive processes supporting memory.

Thus, the stimulation studies published so far make the point that for effective modulation of memory performance to be achieved, a network perspective rather than a purely focal stimulation approach should be considered. Declarative memory relies on a distributed network of multiple neocortical and medial temporal regions that serve cohesive roles in memory processes (Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011; Buzsáki, 1996; Eichenbaum, 2000; McClelland et al., 1995; Norman & O'Reilly, 2003; Preston & Eichenbaum, 2013; Watrous et al. 2013). For example, functional connectivity, characterized by phase synchronization of oscillatory activity, between the medial temporal, frontal, and parietal regions is critical for successful memory retrieval (Watrous et al., 2013). Thus, it seems reasonable to suggest that stimulation will likely be more effective when it targets multiple brain areas in the functional networks rather than a single area in isolation. Yet, not all the nodes in the "memory network" are inter-connected via direct synaptic projections. For example, the hippocampus has direct projections with parahippocampal regions (Eichenbaum, 2000; Suzuki, 1996), and most of its connections with neocortical areas are indirect through entorhinal and parahippocampal cortex (Figure 1; Bird & Burgess, 2008; Eichenbaum, 2000; Lavenex & Amaral, 2000).

----- Figure 1 approximately here -----

How then do indirectly connected brain areas, such as the hippocampus and neocortical areas, exchange information? One possibility is that coherent (i.e., phase synchronized) oscillations between different brain regions reflect the coordinated activity of disparate ensembles of neurons, indicating their cohesive involvement as a network (Buzsaki & Draguhn 2004; Fries 2005). The evidence for this comes primarily from studies showing that even remotely connected brain areas often show increased coherence within specific neural oscillation frequencies (Backus, Schoffelen, Szebényi, Hanslmayr, & Doeller, 2015; Benchenane et al., 2010; Buschman & Miller, 2007; Varela, Lachaux, Rodriguez, & Martinerie, 2001; Watrous et al.,

2013; Womelsdorf et al., 2007). Moreover, increased coherence between brain regions, particularly hippocampus and prefrontal cortex, relates to better memory performance (Benchenane et al. 2010; Fell, Ludowig, Rosburg, Axmacher, & Elger, 2008; Watrous et al. 2013). Thus, coherent activity within specific frequency bands, reflected via the local field potential (LFP), may be an important way in which disparate brain areas exchange information.

How exactly might this work at the physiological level of neuronal populations? The exact underpinning of the LFP remains debated, although rhythmic fluctuations in membrane potentials of thousands of neurons, via excitatory and inhibitory post-synaptic potentials, are a core component (Bédard, Kröger, & Destexhe, 2004; Ekstrom, 2010; Logothetis, 2003; Mitzdorf, 1985). At a physiological level, neural oscillations are often associated with modulation of spike rate; many neurons exhibit increased firing rate at one phase of a specific rhythm, resulting in time-locked patterns with the neural oscillations in local field potential (LFP) signals (e.g., Fox, Wolfson, & Ranck, 1986; Jacobs, Kahana, Ekstrom, & Fried, 2007; Mukamel et al., 2005; O'Keefe & Recce, 1993). A direct correlation between the LFP and spike rate of two interacting neurons, though, is not necessary for a meaningful interaction between two ensembles, as long as both ensembles experience co-synchronous modulation. Consistent with this, several reports have suggested that spike rate and the LFP may often be weakly coupled or not coupled at all (Ekstrom et al., 2007; Ekstrom, Suthana, Millett, Fried, & Bookheimer, 2009; Schridde et al., 2008). How then can coherent oscillations be meaningful if they don't result directly in changes in spike rate?

One of the suggested mechanisms is that coherent oscillations influence different neuronal groups into synchronized rhythms of neural excitability, which can facilitate communication between regions or neuronal groups by providing windows for optimal information flow (Fell & Axmacher 2011; Watrous, Fell, Ekstrom, & Axmacher, 2015 for review). This could occur by

increasing the possibility of long-term potentiation/depotentitation within the ensemble. For example, frequency-specific increases in oscillatory activity provide optimal windows for plasticity, with low-frequency oscillations linked to increases in long-term potentiation (LTP) at the peak of an oscillation (Holscher, Anwyl, & Rowan, 1997; Huerta & Lisman, 1993; Huerta & Lisman, 1995; Pavlides, Greenstein, Grudman, & Winson, 1988; Watrous & Ekstrom, 2014). In this way, synchronous modulations of the LFP between different brain regions could be responsible for co-modulations of plastic states between disparate ensembles.

Recent evidence and theoretical models further suggest that these same frequencies may be necessary for inducing activity once plasticity has occurred (Narayanan & Johnston, 2007; Watrous & Ekstrom, 2014). In addition to the relationship between increased coherence within specific frequency bands and better memory performance reported in some studies (Benchenane et al. 2010; Fell et al., 2008; Watrous et al. 2013), animal studies also have shown that direct electrical stimulation can entrain action potentials (i.e., spikes) and oscillatory activity (Anastassiou, Perin, Markram, & Koch, 2011; Fröhlich & McCormick, 2010). Thus, while the exact mechanisms whereby coordinated low-frequency oscillations between indirectly connected brain areas facilitate network function and behavior more broadly remain to be fully elucidated, macrostimulation that modulates synaptic and/or spiking activity in the targeted neuronal populations may be a promising approach to modulating oscillatory dynamics and function of a network.

Modulating the phase coherence between low-frequency oscillations in the cortico-hippocampal network may be particularly effective, given the importance of coordinated low frequency activity to memory (Anderson, Rajagovindan, Ghacibeh, Meador, & Ding, 2010; Fell & Axmacher, 2011; Foster, Kaveh, Dastjerdi, Miller, & Parvizi, 2013; Watrous et al., 2013). Coherent oscillations of cortical networks often manifest within narrow frequency bands, which may reflect different

types of cognitive computations (i.e., spectral fingerprinting, Siegel et al., 2012). This in turn may allow multiple processes to share a common neural substrate, or network. Thus, coherent oscillations, either via synchronized spiking or coherent membrane potential fluctuations, within specific frequency bands in subgroups of neural ensembles may be an important way in which a limited number of nodes can participate in different cognitive operations.

Indeed, a recent study using electrocorticography (ECoG) recording data from intractable epilepsy patients provided evidence that memory retrieval may involve spectral fingerprinting (Watrous et al., 2013). Specifically, patients were first asked to navigate in a virtual city and learn the spatial layout of the city (where 5 different stores were located) and the order in which they visited different stores. Later they reported the spatial and temporal relationships of all possible pairs of the stores. Successful memory retrieval was associated with greater global connectivity in a network comprised of parahippocampal and multiple frontal and parietal regions. Critically, the correct retrieval network recruited highly similar nodes for spatial and temporal condition, but the connectivity relied on distinct frequency bands for the two types of information (i.e., spatial and temporal information, Figure 2; Watrous et al., 2013; see also comments in Knight & Eichenbaum, 2013). These findings suggest that oscillatory synchronization at specific frequencies between brain regions may underlie retrieval of highly complex episodic memories (i.e., episodic memories comprised of multiple types of information) in the human brain (Watrous & Ekstrom, 2014).

----- Figure 2 approximately here -----

Given that successful memory processing relies on coherent oscillations of multiple medial temporal and neocortical regions at particular frequencies, it follows that stimulation targeting multiple nodes in a network, rather than a single node as is often done in stimulation studies,

will be more effective in modulating memory performance. Stimulating just one node, and at arbitrary times relative to ongoing processes, is more likely to disturb endogenous network communication and result in network 'un-coordination'. Consistent with this, past studies targeting just the hippocampus in isolation with aDES typically show memory disruption. In contrast, stimulation of fiber pathways (e.g., the fornix) that are highly connected with hippocampus and other limbic structures has shown some improvements in memory. Similarly, tDCS, which broadly modulates excitability across the cortex, often results in improvements in memory while TMS, which provides relatively focal targeting, often disrupts memory.

Figure 3 reiterates the idea that an effective memory modulation may require setting multiple nodes in the memory network in coordination - with an example of a simplified network with the parahippocampal (PHG), hippocampal (HPC), and prefrontal (PFC) nodes (Figure 3a: note that the hippocampal node is directly connected with the parahippocampal, but not PFC node). Successful retrieval of memory requires these nodes to be phase-synchronized at a particular frequency band as shown for 'successful retrieval' (Figure 3b, first column). At any random point that the network is not involved in successful retrieval, these nodes are likely to be oscillating out-of-phase (Figure 3b, second column, 'endogenous phase'). If electrical stimulation is delivered to hippocampus at this stage, it may reset the oscillatory phases of hippocampus and the directly connected, parahippocampal node (Figure 3b, third column, 'stimulation on HPC'), but not the PFC node. This in fact would result in 'un-coordination' in the network. We speculate that it would require stimulating multiple nodes, particularly the ones that are not directly connected, to induce coherent oscillations in the whole network (Figure 3b, fourth column, 'stimulation on HPC and PFC').

----- Figure 3 approximately here -----

Indeed, evidence suggests that modulating inter-regional oscillatory coherence is more efficient at inducing behavioral changes. Fell et al. (2013) compared participants' performance on a verbal learning task while electrical pulses were delivered to the rhinal cortex and hippocampus either in-phase or out-of-phase. Compared to sham stimulation condition, patients remembered more items correctly in the in-phase condition and fewer items in the out-of-phase condition. As the authors concede, the findings are preliminary due to a low effects size. Their findings, however, may nonetheless explain why many studies with direct hippocampal stimulation impair memory performance - stimulating one site in the hippocampus may cause the hippocampus to be out-of-phase with the ongoing endogenous oscillation in the neighboring regions that need to communicate with hippocampus.

Another study by Lee et al. (2012) showed that theta band stimulation of the medial septal nucleus (MSN) in rats with traumatic brain injury (TBI) significantly increased theta power in hippocampus and improved spatial working memory. These findings may be explained by the fact that MSN has broad connections with other cortical as well as hippocampal regions, thus stimulation of MSN may have an effect of stimulating multiple nodes in the network. Importantly, because this study used a between-subjects design in rodents, and the connections of the septal nucleus are well-established (Bland, Oddie, Colom, & Vertes, 1994; Vertes & Kocsis, 1997), it was able to better control for practice effects, stimulation targeting, and clinical improvements that otherwise make such studies with cDES difficult in humans. Together, these findings support the idea that a stimulation model that considers network communication is more likely to be successful in either enhancing or disrupting memory.

So far in this review, we have discussed findings from prior neurostimulation studies and based on these, proposed a network-based approach of neuro-modulation. The logic is that given the significance of low frequency phase coherence between multiple regions in successful memory

retrieval, a stimulation regime that mimics such dynamics could potentially enhance memory performance. Another important consideration could be the use of regimes with much higher spatial and temporal specificity. As discussed earlier, stimulation using non-invasive methods inherently impacts broad regions, whereas direct electrical stimulation via depth electrodes (aDES, cDES) allows targeting relatively specific, focal neuronal population. However, direct stimulation studies still had limited stimulation selectivity in the sense that stimulation was typically delivered using macroelectrodes for sustained period of time (for seconds, throughout the entire experiment session, or even longer). Lacruz et al. (2010) employed relatively selective targets both spatially and temporally using a single pulse at the time of visual stimulus onset. However, they used relatively high current strength (4-6mA) to bluntly inactivate the target regions rather than to modulate an oscillatory rhythm. Highly selective stimulation, in time, space and the current strength, perhaps using optogenetic approaches (Gerits, & Vanduffel 2013; Yizhar et al., 2011) that target ultra-scale networks, should be considered in future neuromodulation studies, although this approach is unlikely to be viable in humans due to the need for viral transfections.

The road ahead: Additional considerations regarding direct vs. indirect cortical connections and underlying mechanisms.

Current induced by stimulation is likely to spread through direct connections, as illustrated by numerous cortico-cortical evoked potential studies (Conner et al., 2011; Keller, Honey, Entz, et al., 2014; Keller et al., 2014; Matsumoto et al., 2004). This does not cause a major problem if the network of interest is based on direct connections, in which case the current spread is likely to be intended for network stimulation. However, in the case of memory network, some of the inter-node connections are only indirect (Figure 1). The challenge then becomes how to stimulate 'the network' (i.e., multiple nodes) while keeping induced current within the nodes of interest. A potential solution is to stimulate multiple sites (the nodes) of the network

simultaneously at a low amplitude to minimize the current spread outside the nodes (Fell et al., 2013; Lee et al., 2013; Suthana et al., 2012).

Another important challenge remains in our limited understanding of the specific mechanisms by which stimulation causes its effects, or in other words, what neurophysiological changes occur between the stimulation and the behavioral changes. For example, does applying direct electrical current with short pulses at a low frequency induce a low-frequency oscillation, particularly at the stimulation frequency? Studies sometimes make such implicit assumptions, but the field is lacking a fundamental insight to accept or modify such assumptions. Encouraging advances have been made on this end for TMS (Thut & Miniussi, 2009; Thut & Pascual-Leone, 2009; Vernet et al., 2013), transcranial alternating current stimulation (tACS; Fröhlich & McCormick, 2010; Herrmann, Rach, Neuling, & Strüber, 2013), and direct brain stimulation (Logothetis et al., 2010; Tolias et al., 2005). For example, Vernet et al.(2013) used a combined TMS-EEG approach to evaluate the cortical effects of continuous theta-burst stimulation (cTBS). They found that cTBS over the primary motor cortex increased the power of theta-band oscillations in this region. Yet, such mechanistic studies are rare and it is possible that oscillatory patterns induced by rhythmic stimulation could vary by brain regions based on patterns of connectivity and cell types (e.g., Schridde et al., 2008, Ekstrom 2009). A better understanding of the neurophysiological outcome of stimulation may also help interpreting some of the previous findings (e.g., why hippocampal stimulation sometimes impairs memory function and other times does not affect it).

Similarly, we can speculate about the potential ways in which stimulation may alter neuronal activity although as of yet there are no definitive answers and different stimulation regimes may have different effects on memory networks. One possibility is that stimulation induces certain oscillatory activity that may improve or disrupt the encoding and reinstatement of encoded

information (Watrous et al., 2013). Alternatively, it may facilitate physiological processes involved in long-term potentiation (Canals, Beyerlein, Merkle, & Logothetis, 2009; Lee et al., 2013). Stimulation may also affect memory via neurobiological changes, for example by enhancing hippocampal neurogenesis. Specifically, a rodent study has shown that high-frequency stimulation of the anterior nucleus of the thalamus significantly increased the number of dentate gyrus cells (Toda, Hamani, Fawcett, Hutchison, & Lozano, 2008). Additionally, behavioral improvements induced by DBS may also be confounded by clinical improvement unrelated to the stimulation or practice effects. Thus, depending on the parameters used, different mechanisms may be at play, leading to different effects on memory. While there is a suggestion that indirect hippocampal stimulation sometimes results in memory enhancement, a better mechanistic understanding of the effects of direct stimulation would greatly enhance our ability to reconcile the mixed results across studies.

Conclusion

The field of neuroscience has long sought to define the neural substrates of memory function and to modulate memory function. Stimulation techniques allow us to draw causal relationships between the neural substrates and cognitive functions. Invasive and non-invasive approaches together have established that the hippocampal, frontal and parietal regions comprise crucial parts of memory network. However, efforts to enhance memory function by stimulating individual nodes in this memory network have shown decidedly mixed results, and the varied stimulation-induced improvements reported in the literature seem to result from spread of current to directly connected brain regions, or in the case of tDCS, weak modulatory activity that spreads throughout the cortex. Thus, we suggest that for stimulation approaches to reliably enhance or disrupt memory, a network-level modulation of coherence is likely to be most effective.

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Figure Captions:

Figure1. The anatomy of hippocampal-cortical memory network in human brains. upper panel: parahippocampal (blue) and medial parietal (dark green) regions. lower panel: hippocampus (dark red, depicted through the lateral temporal lobe), lateral parietal (green) and frontal (MFG, purple; VLPFC, dark purple) regions. Hippocampus has direct connections with the parahippocampal regions (the orange arrow), but not with neocortical regions. Parahippocampal gyrus, on the other hand, has rich projections to and from neocortical regions (light blue arrows) as well as with the hippocampus, thus serves to mediate the information between hippocampus and neocortical regions.

Figure 2. Spectral fingerprinting and multiplexing in memory retrieval. (a) The network exhibits stronger phase synchronizations at a lower frequency band (1-4Hz) for the retrieval of spatial information and at a higher frequency band (7-10Hz) for retrieval of temporal information. Figure reproduced from Watrous et al., 2013 (b) The same network is involved in the retrieval of spatial and temporal memory, but its nodes communicate via selective frequency bands for these distinct types of information. Figure reproduced from Knight & Eichenbaum, 2013.

Figure 3. Stimulation of single and multiple nodes in the network. (a) a simplified network with three nodes: hippocampus (HPC), parahippocampal regions (PHG), prefrontal cortex (PFC). HPC has direct projections with PHG, but not with PFC. (b) hypothetical phase vectors and their coherence among these regions. ‘Successful retrieval’ requires coherent oscillation in the nodes of the network. ‘Endogenous phase’ depicts that these regions are less likely to be in-phase with one another when the network is not involved in retrieval process. ‘Stimulation of HPC’ can reset the oscillatory phase of HPC as well as the nodes directly connected with it, i.e., PHG. Dotted lines depict the endogenous oscillatory phase before stimulation and solid line depicts

the new phase induced by stimulation. ‘Stimulation of HPC and PFC’ may indeed bring all the nodes in coherent phase.

Table 1. Summary of Stimulation Methods.

	Invasive Stimulation Methods		Non-invasive Stimulation Methods	
	acute direct electrical stimulation (aDES)	**chronic direct electrical stimulation(cDES)**	**transcranial magnetic stimulation (TMS)**	**transcranial direct current stimulation (tDCS)**
advantages	• capable of targeting deep structures (e.g., hippocampus) • broader coverage than cDES as the electrodes are implanted for epilepsy monitoring • allows stimulation during specific functional phase (e.g., encoding or retrieval of memory)	• capable of targeting deep structures (e.g., hippocampus)	• allows testing in healthy population • greater specificity in targeting specific neocortical brain areas than tDCS	• allows testing in healthy population • allows evaluating the effects of up-/down- regulating the neuronal excitability (via anodal and cathodal stimulation) • provides a direct means of altering currents within the brain
limitations	• limited to a patient population (i.e., intractable epilepsy) • targets limited by the clinical relevance/need	• stimulation effects harder to qualify due to continuous stimulation throughout the entire memory testing (not restricted to specific epochs of memory process) • difficulty in dissociating specific cognitive improvements from clinical improvements • variability in the study cohort as a function of the disease • practice effects – testing (using the same battery) is often repeated over stimulation periods • targets limited by the clinical relevance/need	• target regions are limited to cortical surface • the exact effects on neural currents remain unclear and difficult to predict • generally limited to between-subject, or within-subject blocked design	• target regions are limited to cortical surface • generally limited to between-subject, or within-subject blocked design • less anatomical specificity than can be provided by a TMS coil

Table 2. Summary of studies with stimulation parameters, paradigm, and behavioral results.
N = sample size, reflects only the number of patients that were included for memory tasks, RAVLT = Rey audiovisual learning task, RVDLT = Rey visual design learning test, CVLT = California Verbal Learning Test, CSRT = Coetsier story recall test, MMSE = mini-mental state examination, MT: motor threshold, OB = obesity patients, ITLE = patients with intractable temporal lobe epilepsy, HOA = healthy older adults, HPC = hippocampus, LH = left hippocampus, RH = right hippocampus, BH = bilateral hippocampus, ERC = entorhinal cortex, DLPFC = dorsolateral prefrontal cortex, pVLPFC = posterior ventrolateral prefrontal cortex, PPC = posterior parietal cortex, SPL = superior parietal lobule, IPL = inferior parietal lobule, l / r prefix denotes left / right side of the brain. '-' in stimulation phase: not relevant for chronic stimulation with DBS, * no change from control condition, Experiments listed below used within-subjects designs unless indicated otherwise (in the protocol column).

Type	Authors	Sample Size	Target / Control	Parameters	Protocol	Stimulation Phase	Memory Task	Memory Performance Change
aDES	Coleshill et al., 2004	6 ITLE	LH, RH / no stimulation	biphasic, 1ms train at 50Hz	intermixed trials	encoding stimulus presentation	item recognition (face, object, word)	LH, word recognition, impairment RH, face recognition, impairment
	Fell et al., 2013	11 ITLE	BH, rhinal cortex / sham	bipolar continuous sine wave, 40Hz, 0.01mA	in-phase vs. out-of-phase stimulation between target regions, blocked trials	entire session	verbal learning (German version of RAVLT)	in-phase, improvement anti-phase, impairment
	Koubeissi et al., 2013	11 ITLE	Fornix / no stimulation	bipolar square waves, 200 µs pulse width, 5Hz, 8mA	before vs. during stimulation (4 hour long) blocked across-session	entire session	MMSE	improvement
	Lacruz et al., 2010	6 ITLE	LH, RH, BH / no stimulation	monophasic, 1ms pulse width, 4-6mA, single pulse	blocked across-session	encoding, recognition stimulus onset	item recognition (verbal and non-verbal items)	BH, during encoding and encoding+recognition, recognition for words, geometric drawings, faces, impairment
	Miller et al., 2015	4 ITLE	Fornix / no stimulation	100ms train at 200Hz, 5 trains per second, 7 mA	On vs. off for 50% of trials blocked trials	not specified	RAVLT complex figure learning	complex figure learning, improvement
	Suthana et al., 2012	7 ITLE	ERC, HPC / no stimulation	biphasic square, 300 µs pulse width, 50Hz, 1-2mA, 5s long trains (5s off)	on vs. off intermixed trials	encoding entire phase	spatial learning task	ERC, learning pace, improvement
cDES	Boex et al., 2011	5 ITLE	amygdalo–hippocampal complex / no stimulation	450 µs pulse width, 130Hz, <2V	on vs. off period (3 months each)	-	RAVLT RVDT	visual delayed recall, impairment (2/5 patients) verbal memory, impairment (1/5 patients)

	Hamani et al., 2008	1 OB	bilateral ventral hypothalamus / no stimulation	60 µs pulse width, 130Hz, 2.8V	baseline vs. after 3 weeks cDES	-	CVLT Wechsler Memory Behavioral Evaluation of Memory Spatial Associative Learning	CVLT scores, improvement
					on vs. off (1 week or 1 hour apart)	-	association memory + remember/know	recollection, improvement
	McLachlan et al, 2010	2 ITLE	BH / no stimulation	continuous, monopolar, cathodal, 90 µs pulse width, 185 Hz, max amplitude without patients' realization	on vs. off period (3 months each)	-	Hopkins Verbal Learning Brief Visuospatial Memory Test	inconsistent across 2 patients
	Miatton et al., 2011	10 ITLE	HPC (ipsi- or bilateral, anterior) / no stimulation	450 µs pulse width, 130 Hz, 1 V / 2.5 V	baseline vs. after 6 months cDES	-	RAVLT RVDLT CSRT Complex Figure Test	Complex Figure Test, improvement
	Velasco et al., 2007	9 ITLE	BH (anterior) / no stimulation	450 µs pulse width, 130 Hz, 300 µA, 1min on 4mins off	baseline vs. after 18 months cDES	-	RAVLT digit counting logic memory Bezare Wind Mill Test	improvement
TMS	Blumenfeld et al., 2014	29	lVLPFC lDLPFC / sham	TBS 3-pulse 50Hz trains, every 200ms, at 80% active MT	between-subject	encoding before task (for 30s)	word recognition	lVLPFC, impairment lDLPFC, improvement
	Bonni et al., 2014	30	precuneus lPPC / sham	continuous TBS 3-pulse 50Hz trains, every 200ms, at 100% MT	between-subject	retention	picture recognition + source memory task	precuneus, source retrieval, improvement
	Epstein et al., 2002	10	lDLPFC rDLPFC vertex / sham	paired pulses at 120% MT	between-subject (DLPFC vs. sham stimulation) blocked trials (stimulation sites)	retention	association learning	rDLPFC, impairment
	Gagnon et al., 2010	18	lDLPFC rDLPFC / sham	paired-pulses, 3ms inter-pulse interval, 0.5 Hz at 90% MT	blocked across-session	encoding, retrieval stimulus presentation	item recognition (words and random shapes)	lDLPFC TMS during encoding, impairment rDLPFC TMS during retrieval, impairment than lDLPFC TMS* No difference between verbal and non-verbal items

	Innocenti et al, 2010	18	lDLPFC rDLPFC / sham and no stimulaion	rTMS 500ms trains of 10Hz at 50% MT	blocked trials	encoding stimulus presentation	deep vs. shallow encoding followed by a recognition task	lDLPFC, deep processing benefits eliminated
	Kahn et al,, 2005	14	lpVLPFC rpVLPFC / none	single pulse at 70% maximum	intermixed trials	encoding stimulus presentation	word recognition	left pVLPFC, impairment for familiar words right pVLPFC, improvement for familiar words
	Kohler et al., 2004	12	lIFG / rIFG left parietal	rTMS 750ms trains of 7Hz at 100% MT	blocked trials	encoding stimulus presentation	word recognition	lIFG, improvement
	Machizawa et al., 2010	15	lIFG rIFG / sham	paired-pulses 40ms inter-pulse interval 1 pair per trial 120% MT	blocked trials	encoding stimulus presentation	word recognition	lIFG/rIFG, impairment
	Rossi et al., 2001	13	lDLPFC rDLPFC / none	rTMS 500ms trains of 20Hz at 50% MT	blocked trials	encoding, retrieval stimulus presentation	picture recognition	lDLPFC TMS during encoding, impairment rDLPFC TMS during retrieval, impairment
	Sandrini et al., 2003	12	lDLPFC rDLPFC / sham	rTMS 500ms trains of 20Hz at 10% subthreshold	blocked trials	encoding, retrieval, stimulus presentation	word pair association	lDLPFC, rDLPFC TMS during encoding, impairment rDLPFC TMS during retrieval, impairment
	Sestieri et al., 2013	16	IPL SPL / sham	rTMS 15ms trains of 20Hz at 100% MT	blocked trials	retrieval stimulus presentation	item recognition + source memory	IPL, recognition, impairment compared to SPL TMS*
	Skrdlantová et al., 2005	10	lDLPFC / sham	rTMS 0.9Hz at 110% MT	blocked across-session	encoding entire phase	verbal recall face recognition	verbal recall, impairment
	Wang et al., 2014	16	Parietal / sham	rTMS 20Hz at 100% MT, 20minutes	blocked across-session	independent of task, across 5 consecutive days	pair association (face-cued word recall)	improvement
tDCS	Floel et al., 2012	20 HOA	right temporoparietal cortex / sham	1mA, 20 minutes	anodal blocked across-session	encoding entire phase	associative learning + free recall (immediate and delayed)	less decay at delayed recall
	Javadi and Walsh, 2012	32	lDLPFC / sham & control (M1) stimulation	1mA, 20minutes	anodal, cathodal blocked across-session	encoding entire phase (exp1) recognition	word recognition	anodal, improvement cathodal, impairment

					entire phase (exp2)		
Javadi et al., 2012	13	lDLPFC / none	1.5mA, 1.6s in each stimulation trial	anodal, cathodal blocked trials	encoding before / after stimulus presentation	word recognition	anodal tDCS early in trials, improvement cathodal tDCS late in trials, impairment
Jones et al., 2014	20*4	lPPC rPPC / sham	1.5mA, 15mins	anodal blocked across-session	encoding, retention	CVLT	lPPC tDCS during encoding, learning pace / immediate free recall, improvement
Kirov et al., 2009	28	bilateral DLPFC / sham	tSOS (slow wave oscillation, 0.75Hz) current 0-260 μA, 0.33s-on/0.33 s-off 0.33s slopes	anodal blocked trials	encoding, retention	paired associate learning (verbal and non-verbal)	tSOS during encoding, improvement (verbal pairs)
Pisoni et al., 2015	44	bilateral parietal & temporal / sham	1.5mA, 15minutes	anodal between-subject	recognition entire phase	verbal learning (balanced old-new decision)	improvement
Sandrini et al., 2014	36 HOA	lDLPFC / sham	1.5mA, 15minutes	anodal between-subject	retention (the day after encoding)	word list learning + free recall (on day 3 and day30)	less decay at delayed recall
Zwissler et al., 2014	96	lDLPFC / sham	1mA, 15minuntes	anodal, cathodal between-subject	encoding entire phase	picture recognition with cued learning	anodal, increased false alarms cathodal, decreased false alarms

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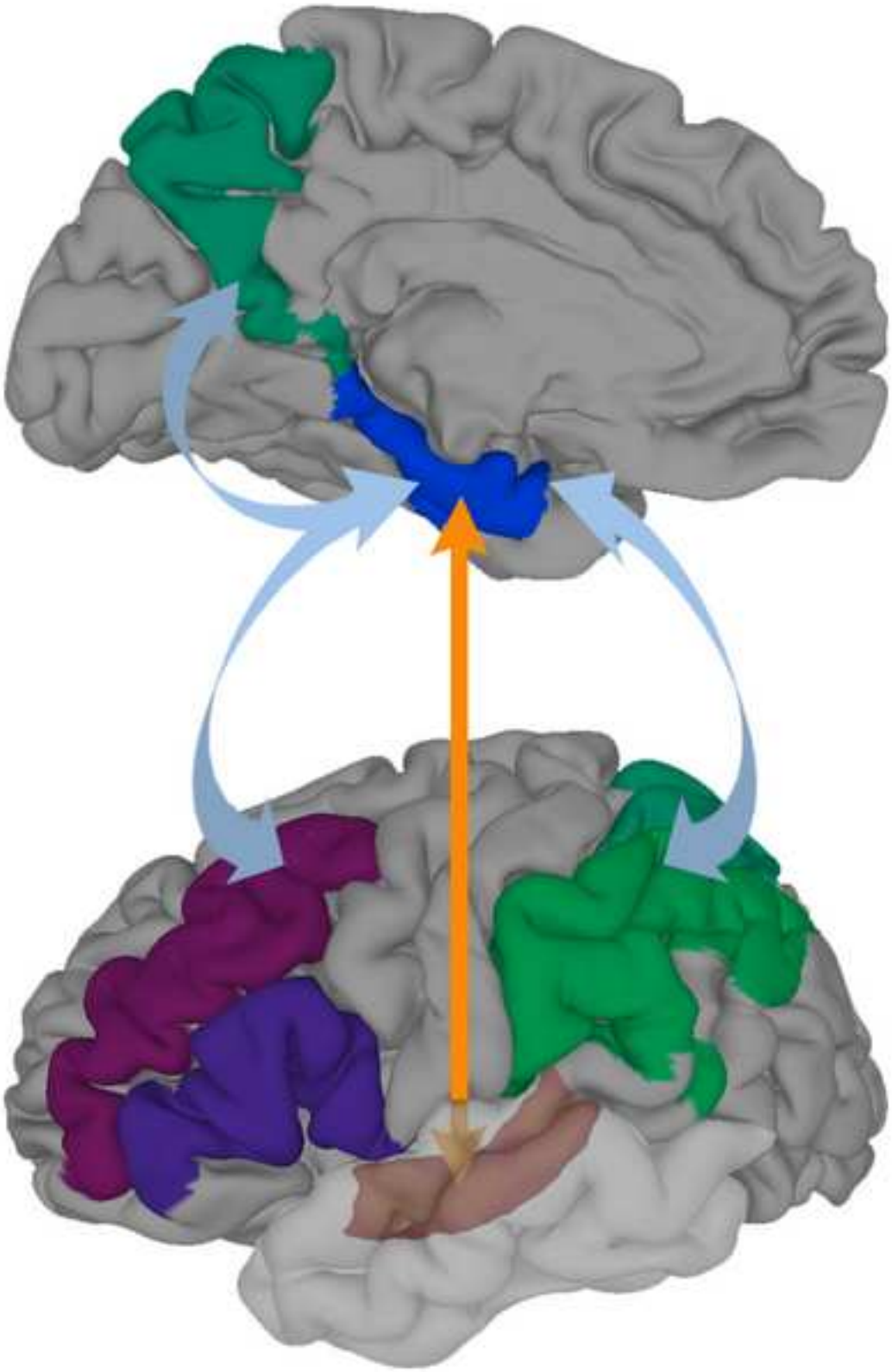

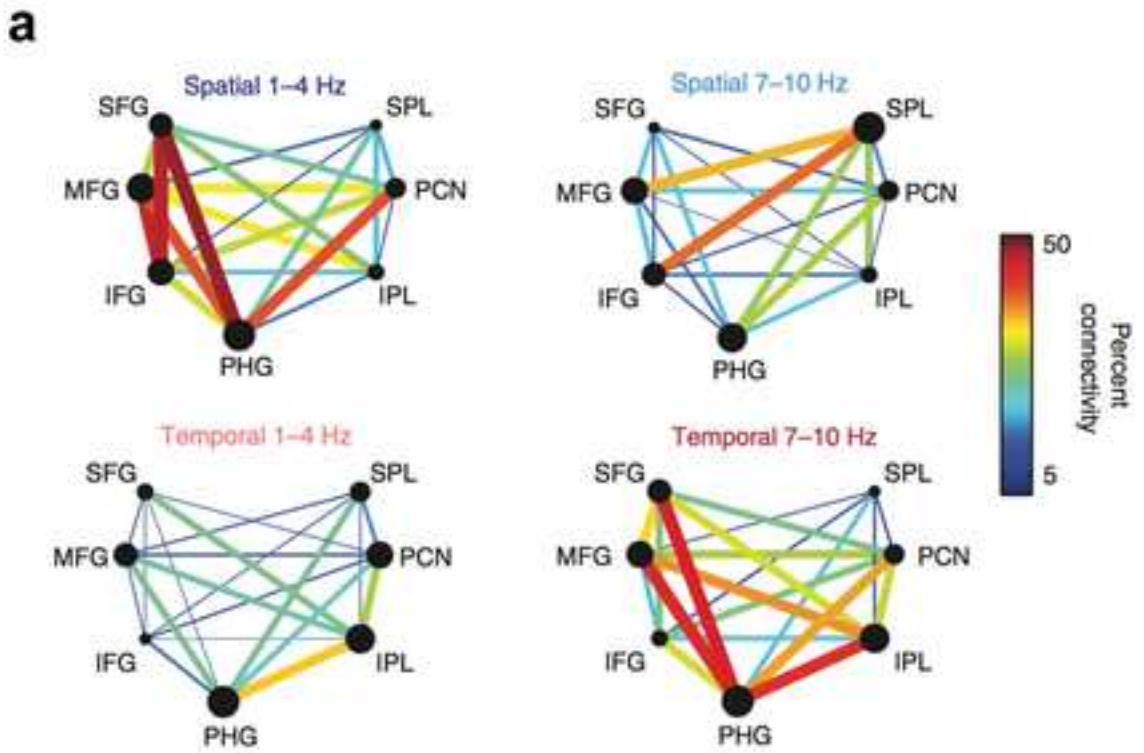

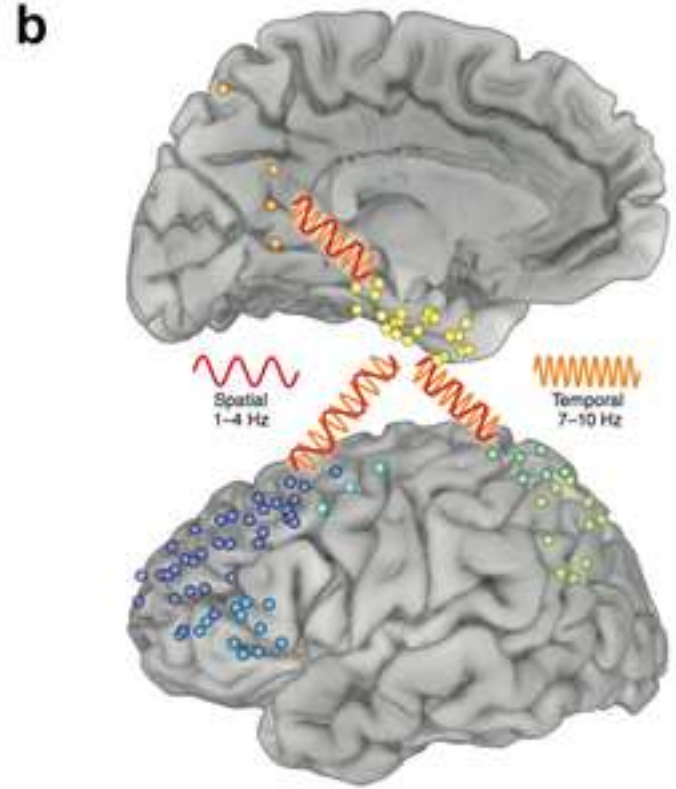

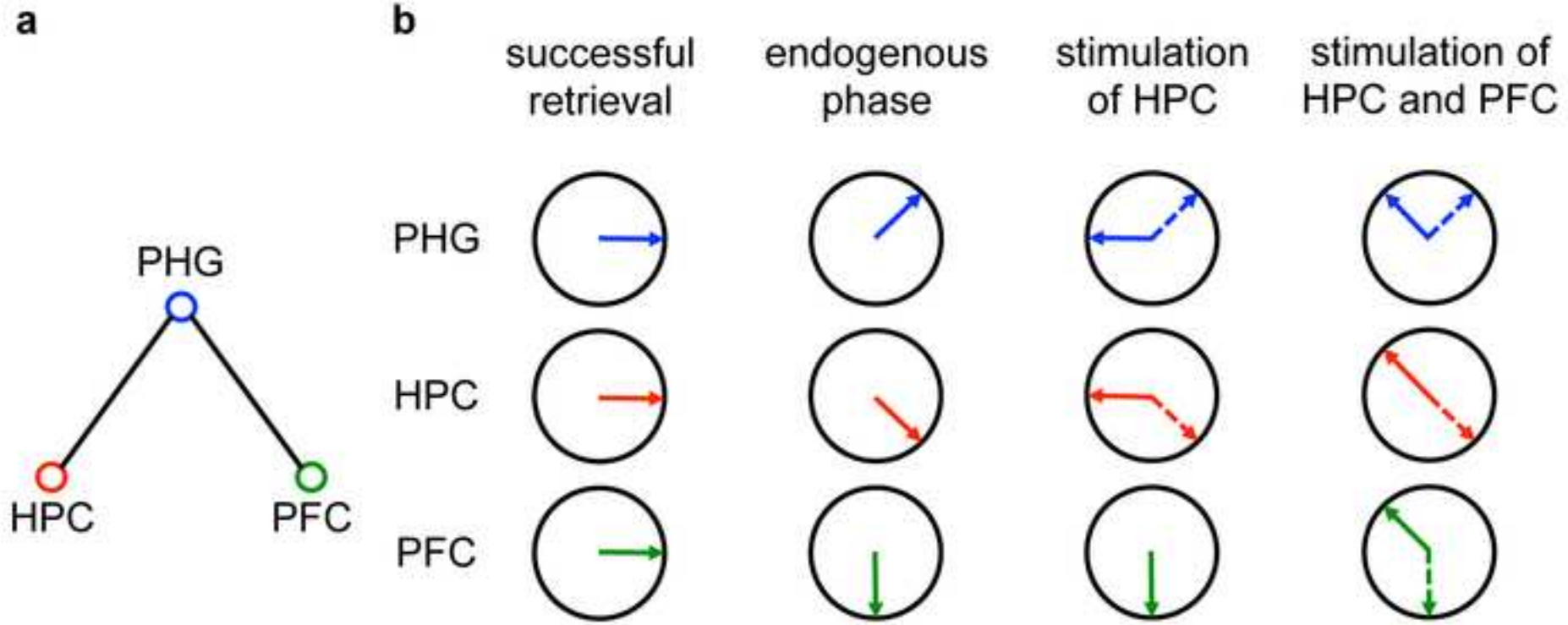

Highlights

1. This review provides a comprehensive summary of both invasive and non-invasive neurostimulation methods seeking to modulate memory.
2. We discuss studies that have shown both disruption and augmentation of memory and offer proposals for inconsistent findings.
3. We propose a novel approach of neurostimulation for effective memory enhancement based on the idea of modulating networks of interconnected brain hubs.