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Review

Deep brain stimulation for enhancement of learning and memory

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ABSTRACT

Deep brain stimulation (DBS) has emerged as a powerful technique to treat a host of neurological and neuropsychiatric disorders from Parkinson's disease and dystonia, to depression, and obsessive compulsive disorder (Benabid et al., 1987; Lang and Lozano, 1998; Davis et al., 1997; Vidailhet et al., 2005; Mayberg et al., 2005; Nuttin et al., 1999). More recently, results suggest that DBS can enhance memory for facts and events that are dependent on the medial temporal lobe (MTL), thus raising the possibility for DBS to be used as a treatment for MTL- related neurological disorders (e.g. Alzheimer's disease, temporal lobe epilepsy, and MTL injuries). In the following review, we summarize key results that show the ability of DBS or cortical surface stimulation to enhance memory. We also discuss current knowledge regarding the temporal specificity, underlying neurophysiological mechanisms of action, and generalization of stimulation's effects on memory. Throughout our discussion, we also propose several future directions that will provide the necessary insight into if and how DBS could be used as a therapeutic treatment for memory disorders.

Contents

Introduction

Episodic memory, or the ability to remember personal experienced events, is severely compromised in various neurological disorders affecting the medial temporal lobe (MTL) including Alzheimer's disease, temporal lobe epilepsy, traumatic brain injury and other MTL injuries such as those occurring during stroke, cardiac arrest, or encephalitis. While deep brain stimulation (DBS) has been used to successfully treat movement disorders such as Parkinson's disease and dystonia, an exciting new frontier of DBS is the enhancement of cognitive function, and memory in particular. The implications of such enhancement to patients affected with disorders of memory may be of great significance. In the current review, we summarize several studies illustrating the potential for DBS or cortical surface stimulation to enhance episodic learning and memory. We also discuss and propose several future directions that would provide necessary insight as to whether DBS could be useful for treating memory disorders.

DBS of the MTL circuit enhances memory

In achieving potential enhancement of memory function by stimulation, understanding MTL circuitry is of critical importance since the ability to form episodic memories critically depends on this structure (Eichenbaum, 2000; for review see Squire et al., 2004). The human MTL consists of several functionally and structurally distinct areas including the hippocampus, amygdala, and adjacent parahippocampal,

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entorhinal, and perirhinal cortices. The hippocampus is comprised of even smaller sub-structures known as CA fields 1–4, dentate gyrus, and subiculum. Anatomical studies in non-human primates have characterized MTL circuitry, which is largely conserved across mammalian species (Manns and Eichenbaum, 2006). Overall, sensory information from widespread cortical areas enters the hippocampus through initial synaptic connections via the perirhinal and parahippocampal cortices (Amaral and Witter, 1995; Duvernoy and Bourgouin, 1998; Suzuki and Amaral, 1994). Parallel pathways from the perirhinal cortex and parahippocampal cortex then converge onto neurons within the entorhinal cortex (ERC). From the ERC, information is then projected onto hippocampal subregions dentate gyrus and CA3 (via the perforant path), and CA1 (via the direct path, Amaral and Insausti, 1990). Hippocampal neurons have both incoming afferent and outgoing efferent connections with the ERC and other non-MTL areas such as the hypothalamus, septal nuclei, anterior nucleus of the thalamus, and the nucleus basalis of Meynert via branches of the fornix white matter pathway. Thus the perforant and fornix pathways constitute major sources of ingoing and outgoing information to and from the hippocampus.

The effects of brain stimulation on behavior are highly dependent on the precise location of delivery. For example, DBS for treatment of Parkinson's disease is most effective when delivered to highly specific regions within the basal ganglia, such as the subthalamic nucleus and the globus pallidus, while DBS for depression is useful when delivered to the subcallosal cingulate gyrus (Davis et al., 1997; Lang and Lozano, 1998; Lozano, 2012; Obeso et al., 2001). Activation of previous experiences or memories has been shown to result from DBS of memory related brain circuits such as those within the temporal lobe. The pioneering early studies of Wilder Penfield have shown that electrical stimulation of areas in the temporal lobe can cause a small percentage of patients to report feelings of familiarity (déjà vu) and the re-experiencing of old memories (Penfield and Perot, 1963). More recent studies have replicated Penfield's findings and shown that electrical stimulation of similar sites in the ventral temporal lobe results in the reporting of past experiences and sometimes the vague experiences of déjà vu (Jacobs et al., 2012; Selimbeyoglu and Parvizi, 2010). In addition, extra-temporal stimulation of the hypothalamus has also been shown to create experiences of déjà vu and enhance verbal memory in a single patient (Hamani et al., 2008). It has been suggested that a potential mechanism of this hypothalamic enhancement of memory may be related to close proximity of the DBS electrode to the fornix, which may be indirectly stimulating activity within the MTL (Hamani et al., 2008).

The MTL is a brain region, which is clearly related to declarative memory function. Direct manipulation of this circuitry, in particular of the hippocampal–entorhinal cortex network offers a unique opportunity to influence learning and memory performance. Interestingly electrical stimulation of the hippocampus proper has been found to interfere with retrieval of information (Halgren and Wilson, 1985; Halgren et al., 1985; Lacruz et al., 2010). However DBS of the entorhinal area has been recently shown to enhance spatial memory in humans when DBS is provided during the learning phase (Suthana et al., 2012). It is likely that stimulation of the entorhinal area may enhance hippocampal dependent memory because of close proximity of electrodes to the perforant pathway. Future studies will need better depiction of MTL related white matter pathways perhaps through the use of advanced methods of high-resolution diffusion tensor imaging (DTI; e.g. Yassa et al., 2010), which can elucidate the exact area of entorhinal DBS placement within humans to determine proximity to the perforant pathway.

DBS of various other regions outside the MTL (e.g. anterior nucleus of the thalamus, hypothalamus, and septal nucleus, or even the vagus nerve) that have efferent and afferent connections to the hippocampus have been shown to enhance memory (Clark et al., 1999; Hamani et al., 2008, 2011; Lee et al., 2013; Oh et al., 2012). Whether the nature of memory enhancement from DBS of these areas is due to overall increases in attention, arousal, or perceptuomotor function, however, is still unclear. Although results show that entorhinal DBS-induced memory enhancement is not due to enhancement of perceptuo-motor functions (Suthana et al., 2012), other stimulated regions (e.g. vagus nerve) may affect memory through these or other alternative cognitive functions (Clark et al., 1999). For a simplified summary of recent studies that have reported DBS related enhancement of memory see Table 1.

Direct DBS of the hippocampus generally shows disruptions in memory (Halgren and Wilson, 1985; Halgren et al., 1985; Lacruz et al., 2010). It is possible that stimulation of a large population of hippocampal neurons especially when given above the threshold to elicit afterdischarges may disrupt local neuronal circuitry necessary for successful learning (Halgren and Wilson, 1985; Halgren et al., 1985). Future studies would need to determine how large the population of stimulated hippocampal neurons would actually need to be in order to reach threshold for behavioral changes. Alternatively, it may not be the actual number of neurons stimulated but the nature of the stimulation that would most strongly affect memory. In fact, recent studies in rodents show that when hippocampal electrical stimulation matches hippocampal input activity with respect to both spatial and temporal firing patterns, memory enhancement can in fact result (Berger et al., 2011; Hampson et al., 2012). Furthermore, optogenetic reactivation of hippocampal neurons that are activated during learning leads to enhanced memory expression (Liu et al., 2012). Thus, stimulation of the hippocampus directly can lead to both disruption and enhancement of memory, depending on the precise effect stimulation has on underlying neuronal activity. The use of specific and physiologically meaningful hippocampal stimulation may thus enhance memory.

It is important to note that the nature of tasks used to measure memory performance differs widely across DBS studies (see Table 1). For example, studies have used both verbal (Clark et al., 1999; Fell et al., 2012; Hamani et al., 2008) and spatial (Lee et al., 2013; Stone et al., 2011; Suthana et al., 2012) memory tasks, but not both within the same study. Neuroanatomical studies suggest that the posterior rather than the anterior portion of the hippocampus may receive and send more spatially relevant information (Colombo et al., 1998; Maguire et al., 2000). Thus, characterization of the precise effects of DBS at anterior versus posterior MTL structures during a variety of memory tasks will be an important area for future research. Another issue that remains involves whether DBS application should be provided unilaterally or bilaterally. While some studies show that bilateral stimulation can modulate memory (Hamani et al., 2008; Stone et al., 2011) others have found that unilateral stimulation may be sufficient (Suthana et al., 2012). Specifically how bilateral versus unilateral DBS results in memory enhancement should directly be investigated in future DBS-memory studies.

Temporal specificity of effects

Overall, an important aspect of memory enhancing DBS would be its application at a specific phase of information processing, namely during the learning, recall, or consolidation phase. Evidence from neurorehabilitation studies (Murphy and Corbett, 2009) suggests that therapeutic intervention would be ideal if used in an as-needed basis such as during learning or recall. Perhaps similarly, DBS may have larger effects depending on whether it is applied during learning (encoding), recall (retrieval), or memory consolidation. Neuroimaging studies suggest functional and structural dissociations within the brain and even the hippocampus during encoding compared to retrieval (Lepage et al., 1998; Schacter and Wagner, 1999; Zeineh et al., 2003). For instance, the CA3 and dentate gyrus regions of the hippocampus may be preferentially involved during encoding compared to retrieval (Suthana et al., 2009; Zeineh et al., 2003). Since the ERC projects to hippocampal subregions along different spatial trajectories, it would be of interest to know how DBS of these diverging projections during encoding versus retrieval would thereby differentially affect memory behavior. Results in rodents (Lee et al., 2013) and in humans (Clark et al., 1999; Fell et al., 2012; Suthana et al., 2012) suggest that DBS before, during or immediately after learning may be sufficient to enhance

Table 1
Summarized are recent publications that have utilized DBS as a method to enhance memory. Included is whether the study was carried out in humans or rodents, what brain areas were stimulated, and whether the stimulation was bilateral and in white or gray matter. Included are the specific DBS parameters used such as current amplitude, frequency of stimulation, pulse width (pw), train duration, and charge density ($\mu C/cm^2$) if reported. The type of memory task used, during what phase of learning DBS was given, and what behavioral effects were found is also shown. Lastly, neuronal changes, if investigated, are summarized in addition.

Study	Group	Brain region stimulated	Electrode location	DBS parameters	Memory task	DBS phase	Behavioral improvements	Neuronal changes
Soriano-Mas et al. (2005)	Rodents	Hypothalamus	Gray matter	10–250 μA, 50 Hz, 0.3 s trains	Spatial	Immediately after encoding	Spatial memory	N/A
McNaughton et al. (2006)	Rodents with hippocampal theta activity blocked	Septohippocampal fibers	White matter	7.7 Hz, 0.5 ms pulse, 2–10 V, per cycle (theta from supramammillary)	Spatial	Encoding + Retrieval	Spatial memory	Hippocampal theta partially restored
Berger et al. (2011)	Rodents	Hippocampal CA1 region (bilateral)	Gray matter	0.1–15 V, 20–100 μA, 1 ms pw, 1.5–3 s trains	Spatial	Encoding	Spatial memory	N/A
Hamani et al. (2011)	Rodents, corticosterone treated	Anterior nucleus of thalamus (bilateral)	Gray matter	2.5 V, 90 μs pw, 130 Hz, 1 h continuous (60–90 $\mu C/cm^2$)	Spatial	33 days before encoding	Spatial memory	Increased hippocampal neurogenesis
Stone et al. (2011)	Rodents	Entorhinal (bilateral)	Gray matter	50 μA, 130 Hz, 90 μs pw (<30 $\mu C/cm^2$)	Spatial	Encoding	Spatial memory	Increased hippocampal neurogenesis
Lee et al. (2013)	Rodents with TBI	Medial septal nucleus	Gray matter	80 μA, 7.7 Hz, 1.0 ms pw, 1 min continuous	Spatial	1 min before encoding	Spatial working memory	Increased hippocampal theta power
Clark et al. (1999)	Epilepsy patients	Vagus nerve	Gray matter	0.75–1.5 mA, 30 Hz, 0.5 ms pw, 30 s train	Verbal	Immediately after encoding	Verbal recognition	N/A
Jacobs et al. (2012)	Human case study (epilepsy)	Ventral temporal (unilateral)	Gray matter	5–8 mA, 50 Hz, 300–600 μs pw, 1–2.8 s train	Verbal	Retrieval	Autobiographical memory	Decreased activity
Laxton et al. (2010)	Alzheimer's patients	Hypothalamus (bilateral)	White matter	3.0–3.5 V, 130 Hz, 90 μs pw, continuous	Verbal	Encoding + Retrieval	ADAS-cog and MMSE in 3/6 patients	Increased MTL metabolic activity
Suthana et al. (2012)	Epilepsy patients	Entorhinal (unilateral)	White matter	0.5–1.0 mA, 50 Hz, 300 μs pw, 5 s trains (2.5–7.6 $\mu C/cm^{2)}$	Spatial	Encoding	Spatial memory in 6/6 patients	Hippocampal theta phase resetting
Fell et al. (2012)	Epilepsy patients	Entorhinal, Perirhinal + Hippocampus (unilateral)	Gray matter	0.01 mA, 40 Hz zero lag in-phase, continuous (<1.25 $\mu C/cm^2$)	Verbal	Encoding + Retrieval	Verbal recall (trend)	Rhinal–hippocampal gamma phase synchrony
Oh et al. (2012)	Epilepsy patients	Anterior nucleus of thalamus (bilateral)	Gray matter	1.5–3.1 V, 90–150 μs pw, 100–185 Hz, continuous	Verbal	1 year prior to encoding	Verbal memory	N/A
Koubeissi et al. (2013)	Epilepsy patients	Fornix	White matter	8 mA, 0.2 ms pw, 5 Hz train, 4 h continuous (20 $\mu C/cm^2$)	Verbal	Prior to encoding	Verbal recall	Increased hippocampus & posterior cingulate evoked responses

subsequent memory. Other studies have shown that stimulation can have effects on memory during retrieval (Hamani et al., 2008; Jacobs et al., 2012). It thus seems possible that neuroprosthetic devices aimed at cognitive enhancement may not need to apply stimulation continuously but in an on-demand timed regimen, during specified time intervals of information processing. However, further studies are required to determine the stage of mnemonic processing when DBS is most effective, which will ultimately be informative as to its mechanism of action.

Underlying neurophysiological mechanism of action

How does memory enhancing DBS affect neuronal activity at the site of delivery? Most clinical DBS studies, such as those for Parkinson's disease, stimulate nuclei or areas of gray matter. While some studies suggest that DBS of gray matter suppresses the activity of nearby neurons, others suggest that it excites afferent and/or efferent axonal projections (for review see McIntyre et al., 2004). Studies using simultaneous electrical stimulation, electrophysiology and fMRI have shown that stimulation can cause increases or decreases in activity of downstream brain areas depending on the stimulation site and frequency (Logothetis et al., 2010). Therefore, while DBS can have local effects through modulation of the activity of thousands of neurons within a given area (Tehovnik, 1996) it can also have upstream or downstream effects through modulation of the activity of projecting axons to other directly connected brain areas. Thus, DBS of a given area may actually have profound effects on afferent or efferent projections rather than the actual site of stimulation (Rattay, 1999). Reactivation of hippocampal neurons using optogenetic and electrical stimulation that mimics input activity supports the idea that modulation of afferent projections could indeed result in enhancement of memory (Berger et al., 2011; Liu et al., 2012). Additionally, direct stimulation of white matter axonal projections may show even larger increases in neuronal or metabolic activity of downstream areas, while stimulation of gray matter may show more suppression of local neuronal activity (Jacobs et al., 2012; Laxton et al., 2010). A recent study in humans with 6 patients diagnosed with mild Alzheimer's disease showed that DBS of the fornix/hypothalamus while showing only moderate improvements in memory in some of the few patients studied, resulted in increased glucose metabolism of the MTL and other structures as measured by PET (Laxton et al., 2010). Further support for DBS of white matter areas being more useful for memory enhancement comes from studies showing direct electrical stimulation of the fornix and perforant pathways in rodents, which increases hippocampal neurogenesis, long-term potentiation, and acetylcholine release, all of which are hypothesized to contribute to improvements in learning and memory (Blaise and Hartman, 2013; Toda et al., 2008; Vertes, 2005). Strong direct electrical stimulation of the rodent perforant white matter pathway however at only certain frequencies (4- and 50-Hz trains) resulted in significant increases in the fMRI BOLD signal within the ipsilateral hippocampus (Canals et al., 2008). Transient stimulation of the rodent perforant path has also been shown to induce persistent firing of dentate gyrus granule cells, leading to up-states of mossy fibers and subsequent hilar neurons. It is thought that persistent activity in assemblies of hilar neurons may help generate short-term memory representations of stimulus features, such as during stimulus novelty (Larimer and Strowbridge, 2009). The combination of high-resolution DTI of white matter pathways and novel techniques of electrode visualization combined with simultaneous DBS, imaging and electrophysiological recordings will aid in determining the precise location of DBS electrodes that will produce the largest neuroenhancing of effects on hippocampal-dependent memory.

The effects of stimulation as we currently understand them are quite complex since the electrode size, electrode position with respect to the orientation of neurons, stimulation frequency, pulse width, current amplitude, and polarity can all have varying effects on underlying neural activity and consequent behavior. A recent study in anesthetized monkeys demonstrates the complexity of stimulation's effects on neural activity whereby changes in the frequency and site of stimulation resulted in opposite outcomes (Logothetis et al., 2010). In DBS studies of Parkinson's disease, pulse widths between 60 and 90 μs and frequencies above 50 Hz are necessary for successful clinical outcomes (Volkmann et al., 2002). However, stimulation pulse width and polarity of the electrode can have different preferred settings depending on the precise brain area given stimulation (Albert et al., 2009). Importantly though, stimulation parameters that are most successful in cortical or basal ganglia areas may or may not apply to DBS of MTL circuitry for memory. Therefore, future DBS of memory studies will need to make within study comparisons of differing stimulation parameters in order to understand the precise impact that DBS parameters can have on memory. Currently, effects on memory have been shown using 40–50 and 130 Hz frequencies, and pulse widths ranging from 60 to 300 μs (Table 1). Comparison of effects of stimulation frequencies, pulse widths, current amplitudes, electrode size and precise site of delivery that would yield the strongest improvements in memory remains to be determined.

Traditionally DBS effects on neuronal tissue have been thought to be either inhibitory or excitatory of local or connected areas. However, there is an increasing awareness that what may be altered is in fact the oscillatory patterns of neuronal activity. Specifically, studies have shown that DBS can alter ongoing oscillatory activity that may contribute to learning and memory (Fell et al., 2012; Jacobs et al., 2012; Suthana et al., 2012). Although the exact role of oscillatory activity in memory still remains unknown, it is thought to represent rhythmic changes in cortical excitability (Fries, 2005) that may result in either minimal or maximal neuronal processing and communication. Intracranial recording of local field potentials (LFPs) in humans have yielded important insights. Theta LFP oscillations (3–8 Hz) have been widely implicated to play a role in episodic memory (Buzsaki, 2005; Kahana et al., 2001; Landfield et al., 1972) and the strength of their amplitude measured in the human MTL has been shown to predict the success of episodic encoding (Guderian et al., 2009; Lega et al., 2011). DBS of the medial septal nucleus given at the frequency of theta increases the power of recorded hippocampal theta oscillations and consequent spatial working memory (Lee et al., 2013). Furthermore, rats treated with tetracaine hydrochloride to block hippocampal theta activity, showed partial rescue of spatial memory and hippocampal theta activity when given electrical stimulation to the septahippocampal pathway that mimicked supramammillary recorded theta activity (McNaughton et al., 2006). Perforant pathway stimulation given during specific phases of the ongoing theta oscillation can induce optimal conditions for long-term potentiation that are important for learning and memory (McCartney et al., 2004). Theta resetting, or the phase locking of the theta rhythm with incoming sensory stimuli, has been proposed as one mechanism by which the hippocampus may enhance the encoding of new incoming sensory information and thus enhance memory (Vinogradova et al., 1996). Theta resetting has been shown in both rodents and humans during cognitive tasks (McCartney et al., 2004; Mormann et al., 2005; Rizzuto et al., 2003; Tesche and Karhu, 2000). Interestingly, electrical stimulation of both the fornix and perforant pathways induces resetting of the theta wave in the rodent hippocampus (Williams and Givens, 2003). DBS of the entorhinal area in humans also results in phase resetting of the ipsilateral hippocampal theta oscillation (Suthana et al., 2012). Additionally, theta activity that predicts recall success is strongly linked to the gamma oscillation (30–100 Hz; Lega et al., 2011). The phase of theta oscillations and their relationship to the amplitude of gamma oscillations in monkeys and humans have been related to memory performance (Canolty and Knight, 2010; Mormann et al., 2005). This has been termed a type of phase-amplitude cross frequency coupling (CFC) and is thought to assist with entrainment of internal cognitive processes with external stimuli or events, a process crucial for successful memory formation. Whether or not DBS enhancement of human memory increases hippocampal

CFC will be an important question to investigate in future studies. Overall, DBS effects on theta and/or gamma oscillatory activity within and across brain regions may provide an important tool for determining the underlying mechanism, optimal location and parameters needed to maximize behavioral improvements.

There is also considerable interest in the relationship between the phase of theta oscillations and the timing of single neuronal spiking both in rodents (O'Keefe and Reece, 1993) and humans (Jacobs et al., 2007). Human intracranial studies have shown that the spiking rate of single hippocampal neurons predicts whether a recently learned item will be remembered (Cameron et al., 2001; Fried et al., 1997). It has been hypothesized that the theta-spiking relationship may reflect the cued recall of an upcoming item stored in memory (Jensen and Lisman, 1996; Tsodyks et al., 1996). A recent study in humans showed that the relationship between spiking and theta during encoding predicted memory success (Rutishauser et al., 2010). A tighter coordination between hippocampal single neuron spiking and the simultaneously recorded theta LFP oscillation during initial viewing of the image predicted the success of the formed memory for that image (Rutishauser et al., 2010). These results implicate a direct role for theta-linked spiking activity in episodic memory. Altogether, intracranial studies in humans affording simultaneous LFP and single neuron recordings have begun to link potential mechanisms by which the theta and gamma oscillations together with single neuron activity may support successful episodic memory. Insight into how external stimulation, single neurons, and oscillatory activity work together to support the successful encoding and recall of individual memories will be an important area for further investigation.

Generalization of effects

Thus far, studies showing DBS-related enhancement of human memory have mostly been carried out in epilepsy patients who need implantation of intracranial depth electrodes for clinical reasons. Therefore, the question remains as to whether DBS effects on memory can in fact be generalizable and extend to other patient populations (e.g. traumatic brain injury and Alzheimer's disease). Theta-frequency DBS administered to the medial septal nucleus increased hippocampal theta and improved spatial memory in traumatically brain-injured rodents (Lee et al., 2013). One study investigated the effects of DBS of the fornix/hypothalamus in a phase 1 clinical trial in 6 patients diagnosed with Alzheimer's disease (Laxton et al., 2010) with some evidence of enhancement of glucose metabolism within the MTL and other areas across the entire group. Stimulation of the nucleus basalis of Meynert has been proposed as another site for DBS related memory enhancement in Alzheimer's disease (Hardenacke et al., in press) based on DBS related cognitive enhancements resulting in one patient with Parkinson's disease (Barnikol et al., 2010). Future larger and/or double-blinded clinical trials investigating DBS at various brain sites in patients with neurological disorders, some related to the MTL, will provide more specific information as to how useful DBS may be for treating MTL related memory disorders.

Future directions in neuroenhancement of memory

DBS technology has the potential for significant improvement in the future. For example, a DBS system that incorporates feedback from simultaneous recording electrodes such as those recording oscillatory patterns or single neuron activity will provide more sophisticated stimulation protocols (e.g. Berger et al., 2011). Controllable DBS systems that do not utilize continuous stimulation but instead provide on-demand stimulation during periods of critical information processing may also be of great use.

Future advancements in current methodologies for non-invasive electrical stimulation of the brain including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), may provide substantial improvements for focal delivery of stimulation to the temporal lobe for memory. Currently both TMS and tDCS are limited to the stimulation of large surface cortical structures; stimulation of hippocampal and MTL structures is currently not feasible with these techniques. Therefore TMS and tDCS studies have mostly investigated the effects of stimulation on cortical areas such as the dorsolateral prefrontal and parietal cortex during perception and working memory tasks. Within these studies, depending on the type of TMS (e.g. rTMS) or tDCS stimulation (e.g. anodal vs. cathodal) and specific parameters (e.g. frequency) both behavioral disruption and facilitation of working and episodic memory have been shown (for review see Manenti et al., 2012). Recent studies have also explored unilateral and bilateral tDCS of the anterior temporal lobe in which they have generally found improvements in verbal and visual memory tasks (Boggio et al., 2009, 2012; Chi et al., 2010). Still, due to the large area of the temporal lobe that is likely being stimulated during tDCS (Nitsche et al., 2008) it is unclear what neural effects underlie this enhancement of memory. It will also be necessary to characterize the differential effects of stimulation on cortical versus subcortical areas of the temporal lobe on hippocampal-dependent memory. Future improvements in non-invasive techniques may progress to more focal treatment modalities. Thus it will be important to keep a dialogue between non-invasive and invasive technological and clinical research in order to advance optimal therapies.

Future improvements in multi-modal non-invasive technologies, such as fMRI or MEG, may be able to detect neural signatures reflective of DBS related neurophysiological changes within the hippocampus that result in memory enhancement (e.g. theta phase resetting or theta gamma CFC). Through the combined use of DBS, single-unit and LFP recordings, used in conjunction with non-invasive measurements such as EEG, TMS, tDCS, and fMRI, studies may be able to optimize detection and determine the precise neuronal correlates of DBS related behavioral changes. Training using techniques such as neurofeedback may also afford patients the ability to modulate DBS related oscillatory activity and/or coupling changes in order to achieve similar albeit perhaps smaller improvements in memory as those afforded by external DBS methods.

Summary and conclusions

Overall, it is necessary that future studies build upon and elucidate the mechanism of action used in DBS enhancement of memory. Clearly, the location, parameters, and phase of delivery of DBS are quite variable across studies. Thus, systematic comparisons and consistent methodologies across future studies will contribute to the understanding of DBS and its effects on learning and memory and whether it will be a useful therapeutic treatment for patients with memory disorders.

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