Current Neurology and Neuroscience Reports (2018) 18:30
https://doi.org/10.1007/s11910-018-0837-3

EPILEPSY (CW BAZIL, SECTION EDITOR)

Neurostimulation for Memory Enhancement in Epilepsy

Stephen Meisenhelter[1] · Barbara C. Jobst[1,2]

Abstract

Purpose of Review Memory is one of the top concerns of epilepsy patients, but there are no known treatments to directly alleviate the memory deficits associated with epilepsy. Neurostimulation may provide new therapeutic tools to enhance memory in epilepsy patients. Here, we critically review recent investigations of memory enhancement using transcranial electrical stimulation (tES), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), chronic intracranial stimulation, and acute intracranial stimulation.

Recent Findings Existing literature suggests that transcranial direct current stimulation (tDCS) produces a small enhancement in memory in neuropsychological patients, but transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) have not been found to have an effect on memory. Most studies of transcranial magnetic stimulation (TMS) have found that TMS has no positive effect on memory. Vagus nerve stimulation can acutely enhance memory, while chronic therapy does not appear to alter memory performance. We found that there is the most evidence for significant memory enhancement using intracranial stimulation techniques, especially chronic stimulation of the fornix and task-responsive stimulation of the lateral temporal lobe.

Summary Presently, there are no existing therapeutic options for directly treating epilepy-related memory deficits. While neurostimulation technologies for memory enhancement are largely still in the experimental phase, neurostimulation appears promising as a future technique for treating epilepsy-related memory deficits.

Keywords Neurostimulation · Accelerated forgetting · Memory enhancement · Memory in epilepsy · Responsive stimulation · Memory impairment

Introduction

Epilepsy patients rank memory problems as being one of their top three concerns, and memory problems are a concern for 42% of epilepsy patients [1]. In addition to difficulties with working and immediate memory, epilepsy patients often suffer from accelerated long-term forgetting (ALF), in which some defect of the slow consolidation process causes abnormally rapid degradation of memories over time [2]. It is not fully understood how epilepsy causes memory deficit, although there are many known contributory factors. Memory consolidation can be impaired by temporal lobe epilepsy (TLE) [3], which directly involves mesial temporal anatomical structures important for memory processing, or by idiopathic generalized epilepsy [4]. Hippocampal sclerosis in patients with TLE is known to alter the pattern of brain activations during memory encoding [5]. There is some evidence that the degree of ALF is correlated with seizure frequency, suggesting that seizures inhibit the consolidation process [3]. Even interictal epileptiform discharges (IEDs) are thought to cause temporary memory impairment [6]. Depression is often co-morbid with epilepsy and is known to contribute to memory impairment [7]. Tragically, anti-epilepsy drugs (AEDs) can also contribute to memory impairment [8–10].

There are no widely accepted methods for directly treating memory deficits associated with epilepsy. Practitioners can at best treat the epileptogenic activity or co-morbid mood

This article is part of the Topical Collection on *Epilepsy*

✉ Stephen Meisenhelter
stephen.meisenhelter.gr@dartmouth.edu

[1] Department of Neurology, Geisel School of Medicine at Dartmouth, Hanover, NH, USA

[2] Department of Neurology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

Published online: 19 April 2018

disorders that may induce memory deficits, providing indirect relief of memory symptoms. However, there is some emerging evidence that brain stimulation could more directly address epilepsy patients' memory concerns. Here, we review recent works investigating the effects of brain stimulation and vagal nerve stimulation on memory in epilepsy patients and provide recommendations for potential avenues of research into therapeutic interventions to treat epilepsy-related memory deficits.

Transcranial Electrical Stimulation

In transcranial electrical stimulation (tES), a small current is applied through electrodes positioned on distant parts of the scalp, resulting in the flow of current through the brain. Depending on the direction of the current flow (toward or away from a brain region), this is thought to cause subthreshold elevation or depression of the resting potential of neurons near the electrodes [11]. Current delivered with tES spreads throughout the brain and has effects in many distant regions [12], making it difficult to assign causality of effects elicited by this method of stimulation to individual brain areas. Due to the non-invasive nature of transcranial direct current stimulation (tDCS), studies of this technology that include analyses of memory effects are often conducted in healthy subjects [13]. Studies that include subjects with epilepsy are often designed to test the efficacy of tDCS as a means to reduce seizure frequency [14••, 15]. There are three subtypes of tES that differ in the types of waveforms that are applied to the brain: tDCS, transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS).

Transcranial Direct Current Stimulation

In tDCS, a direct current is applied through scalp electrodes for several seconds to several minutes. Many studies have examined the effects of tDCS on memory and learning, often with contradictory results [13]. Differences in effects in using tDCS are thought to be driven by electrode placement, polarity, amplitude, and duration of stimulation [11].

A 2005 study of 15 healthy participants found that anodal tDCS of the dorsolateral prefrontal cortex (DLPFC) elicited a 1.92% increase in performance on the three-back task [16], in which subjects were presented a series of letters and had to recognize if the current letter was the same letter that was presented three letters previously. The authors found that the effect was not present when other brain regions (such as M1) were stimulated. Additionally, a recent meta-analysis of tDCS memory enhancement studies [13] found a slight overall improvement in working memory during stimulation periods in neuropsychiatric patients (standardized mean difference = 0.77) and a trend toward significance in healthy participants when using anodal tDCS.

While the memory enhancement effects of tDCS are small in normal subjects, indications that tDCS may be useful for epilepsy patients are more favorable. A recent study found a 56.2% improvement in working memory and a decrease in seizure frequency following cathodal tDCS (in which the cathode is placed above the stimulation site) applied to the seizure onset zone of 10 epilepsy patients [14••]. A 32.4% improvement persisted until the subjects' next testing, 1 month after stimulation. However, this study did not have a control group, so it is unclear how much of this effect is attributable to the placebo effect. It is notable that cathodal stimulation, which is thought to decrease excitability [11], was associated with memory enhancement at the seizure onset zone while studies in healthy subjects have mostly reported findings with anodal (excitatory) tDCS. A 2015 meta-analysis of tDCS studies with epilepsy patients found that tDCS reliably reduces the frequency of IEDs and seizures [15]. Combined with the finding that IEDs can be detrimental to memory [6], these studies may point toward a mechanism through which tDCS can be used to decrease the excitability of the seizure onset zone, thereby reducing epileptiform activity and improving memory outcomes. tDCS has been shown to influence the concentration of glutamate and GABA [17].

Transcranial Alternating Current Stimulation

In tACS, an alternating current is applied through scalp electrodes. There are few studies of tACS for memory improvement, with most focusing on the technology as a potential treatment for depression. In [18], tACS was used to induce frontoparietal theta synchronization. tACS at 6 Hz applied simultaneously at the DLPFC and the posterior parietal cortex (PPC) was able to induce increases or decreases in response time in the delayed letter recognition task depending on the phase delay between the stimulators. The effect disappears when using 35 Hz tACS. Additional studies would help determine the extent to which tACS could be useful as a therapy for memory deficit in epilepsy patients.

Transcranial Random Noise Stimulation

In tRNS, random currents are applied through scalp electrodes. A study in which tRNS was applied to the DLPFC found no effect of tRNS on working memory in 30 healthy subjects [19]. A separate study of 12 healthy subjects found no improvement in a battery of working memory tasks with tRNS [20]. Although there are few studies on tRNS, the results consistently fail to find an effect on working memory.

Transcranial Magnetic Stimulation

In transcranial magnetic stimulation (TMS), an electromagnet is placed near the scalp and is activated in short pulses. The rapidly changing magnetic field generates a strong electrical field at intracranial targets [21]. Although the field generated by TMS is spatially diffuse [22], the brain area that is activated can be as small as several millimeters [23]. Effective blinding of the subject can be difficult when using TMS, as the coil produces a clicking sound during stimulation and the stimulation can cause skin sensations and scalp muscle contraction (discussed further in [24]).

TMS is thought to produce brief disruptions in the functioning of the targeted cortex, presumably by decreasing cortical excitability or inducing random electrical noise into the region [25]. Repetitive TMS (rTMS), in which TMS pulses are applied several times per second, is thought to produce longer lasting changes in cortical excitability, possibly by modulating long-term potentiation (LTP) and long-term depression (LTD) (see [26] for review). While TMS is considered to be safe in healthy people and people with epilepsy, the use of repetitive TMS (rTMS) in people with epilepsy is associated with a risk of inducing seizures [27], possibly due to increased activation of nociferous cortical regions.

The effect of TMS on memory has been extensively studied in healthy subjects. Two studies applied TMS to the DLPFC during various memory tasks and found that TMS impaired memory [28, 29]. However, while the previous studies used the 10–20 system to locate the stimulation target, two studies that positioned the stimulator using MRI guidance found that stimulating the dorsolateral cortex has positive effects on memory [30, 31]. While stimulation of the dorsolateral cortex produced positive effects, two studies agree that stimulation of the ventrolateral prefrontal cortex produces memory impairment [31, 32]. Stimulation of the precuneus had a slight positive effect on memory in one study [33]. Stimulation of the posterior parietal cortex had no effect on memory in two studies [33, 34].

In summary, TMS appears to have limited potential to enhance memory in epilepsy patients. However, the studies cited above have only tested for short-term improvements; we were unable to find studies that examined long-term changes in memory due to TMS. Clinicians must also consider that rTMS carries a safety risk for epilepsy patients [27], which negatively affects the risk-benefit balance of the technology's therapeutic use.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is typically prescribed as a therapy for treatment-resistant epilepsy. An implanted device delivers scheduled stimulation with an interval and frequency determined by the patient's neurologist. While the exact mechanism by which VNS reduces seizure frequency is unknown, it is hypothesized that VNS increases norepinephrine output by indirectly stimulating the locus coeruleus [35]. Studies of the memory enhancing effects of the VNS have been challenging partially because subjects can often detect when their neurostimulator is delivering stimulation [36].

Improved neurocognitive performance with VNS was first reported in 1999 [37], in which subjects with epilepsy and an implanted VNS received stimulation several minutes after the encoding phase of a memory task. The subjects' recognition memory was improved by 35.6% during trials in which they receive stimulation. However, the effect was only present when subjects received a low amplitude of stimulation (0.5 mA) and disappeared at higher amplitudes. In reply, another group reported results in 2001 in which VNS was delivered during the encoding and recall phases of a similar working memory task with a higher stimulation amplitude and found no effect. A 2006 study lent support to the findings of Clark et al. [37] that VNS should be delivered between encoding and recall, during the memory consolidation phase, in order to have a beneficial effect. In that study [38], 10 VNS subjects received stimulation immediately after the encoding phase of the Hopkins Verbal Learning Test (HVLT). Compared to trials with no stimulation, they had a 21% improvement in retention of words that they could recall immediately after the encoding period. However, there was no increase in the number of words that they initially encoded, consistent with the hypothesis that VNS enhanced memory consolidation but not encoding. A recent study [39••] of 20 epilepsy patients with VNS devices found that when subjects' VNS devices were active, they had decreased incorrect responses during a working memory task.

Several studies have examined the chronic effects of VNS on memory using clinical examinations. There does not appear to be any long-term memory enhancement effect after 6 months [40] nor after 13 to 19 months [41].

Overall, there is evidence that VNS during memory consolidation enhances memory in the short term. Strangely, there does not seem to be any long-term improvement in memory with VNS therapy.

Intracranial Electrical Stimulation

Working with subjects undergoing intracranial monitoring prior to epilepsy surgery provides an excellent opportunity to study the effects of epilepsy on memory. Macroelectrodes commonly used in electrocorticography (ECoG) studies sample from volumes of less than 4 mm in radius [42] and recordings can be recorded at sampling rates reaching several kilohertz, providing unmatched temporal and spatial precision. As the locations of the implanted electrodes are typically

determined based on clinical need, researchers are not able to record from the exact same location in multiple subjects, complicating data analysis. Furthermore, the effects of recent surgery can complicate efforts to obtain data from this patient population.

Chronic Intracranial Stimulation

There are a broad arrays of techniques used in scientific literature for stimulating the brain through intracranial electrodes. In this section, we consider techniques in which stimulation is not specifically time-locked to a memory task. We include studies ranging from long-term studies of patients with implanted neurostimulators to testing conducted during intracranial monitoring conducted prior to epilepsy surgery.

Several studies have examined the effects of various stimulation paradigms in the fornix. In these studies, it is generally hypothesized that stimulation of the fornix indirectly drives activity in the hippocampus and neighboring structures. A 2008 case report of an obesity patient with bilateral DBS (130 Hz) in the hypothalamus and fornix found increased performance on variants of paired associate learning tasks designed to test medium- and long-term memory (1 h and 1 week) with chronic stimulation [43]. Although the subject's electrodes were targeted at the hypothalamus, they were placed in contact with the fornix on both sides. Additionally, the subject reported that stimulation at higher voltages elicited vivid autobiographical memory experiences that became more vivid with more voltage, demonstrating that stimulation of the fornix can have some effect on memory. A study of six Alzheimer's disease patients [44] found that pulsed 130-Hz stimulation of the hypothalamus/fornix was associated with improved Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale Cognitive (ADAS-cog) memory scores over 12 months compared to AD population expectations. Using source localization, they found that stimulation activated the ipsilateral hippocampus and parahippocampal gyrus, later followed by the ipsilateral cingulate gyrus. As there was no control population in this study, comparisons were done to expectations of the AD population. It is unclear whether significance testing was conducted to assess for memory improvement. It is also unclear whether improvements seen during this study would be applicable to epilepsy patients, as pathophysiology differs between epilepsy and Alzheimer's disease. A later study in 11 patients with temporal lobe epilepsy who were undergoing intracranial monitoring found that low frequency (1 Hz) stimulation of the fornix beginning 1 h prior to testing improved subjects' performance in the delayed recall component of the MMSE and reduced interictal epileptiform discharge (IED) activity [45]. A study of four intracranial monitoring subjects with epilepsy found increased performance on the Medical College of Georgia Complex Figures (MCGCF) task but decreased performance on the Rey Auditory Verbal Learning Task (RAVLT) with continuous theta burst stimulation of the fornix applied throughout the test session [46]. However, due to the small sample size, the authors did not test for significance.

Many studies have also sought memory effects resulting from direct stimulation of mesial temporal structures. A small study found that chronic stimulation of seizure onset zones in the hippocampus improved memory over 18 months [47]. Stimulation was applied as a 1-min pulse of 130-Hz stimulation every 5 min. Due to the small number of subjects ($n = 9$), the authors did not test for significance but point out the trend toward improvement in the Rey Verbal Learning Test (RVLT), digit counting, logic memory, and the Bezarez Wind Mill Test. The subjects also experienced significant reductions in seizure frequency during this period, possibly explaining the improved cognitive results, as decreased seizure frequency is associated with improved cognitive outcomes [48]. Another study of two patients with bilateral hippocampal seizure onset zones found that continuous bihippocampal 185-Hz stimulation did not improve memory after 3 months [49]. However, this study was only conducted in two subjects, almost certainly making it underpowered. Two studies of epilepsy patients found that chronic pulsed 130-Hz amygdalar-hippocampal stimulation using implantable DBS devices did not improve memory over periods of several months to several years [50, 51].

The anterior nucleus of the thalamus has also been hypothesized to be involved in memory [52, 53]. A study of nine patients with a DBS device implanted to target the anterior nucleus of the thalamus showed significant improvement on the Rey-Kim Memory Test, a measure of verbal memory, when subjects received continuous pulsed 100–185-Hz stimulation [54]. These subjects also experienced a reduction in seizure frequency, which may have contributed to the memory improvement effect. In a longitudinal study of 67 subjects, 7 years of chronic stimulation in the anterior nucleus of the thalamus improved immediate visual recall scores on the Brief Visuospatial Memory Test Revised (BVMT-R), but did not affect verbal memory measures [55].

The NeuroPace RNS System is a neurostimulator designed to deliver stimulation in response to epileptogenic activity as detected by deep brain or cortical electrodes placed at the seizure onset zone. While we were unable to find any studies focused on memory outcomes in patients receiving responsive therapy, the RAVLT and Boston Naming Test (BNT) were included as an outcome measure in the system's pivotal trial [56]. The study found that subjects with mesial temporal onset seizures had significant improvement in AVLT learning scores, while subjects with neocortical onset seizures had significant improvement in BNT scores. Patient-specific device configurations make it difficult to determine which electrographic features triggered stimulation, or whether the

stimulation caused acute improvements or a more chronic neuromodulatory effect on memory. However, the flexibility of stimulation parameters available through the RNS System makes it an attractive method for future studies of chronic memory enhancement in epilepsy patients.

Acute Intracranial Stimulation

While chronic stimulation generally tries to enhance memory processes on a continuous basis, task-responsive acute stimulation aims to enhance memory of specific events or specific times during a task. It is generally assumed in these studies that the enhancement is short-lived, on the order of seconds to minutes long. The studies in this section use technologies that have not been largely deployed in a clinical setting, but still represent promising opportunities for novel future therapies.

A study of 12 epilepsy patients undergoing intracranial monitoring found that single 1-ms monophasic pulses to the hippocampus, time-locked to item presentation, impaired memory by 57% in an item recognition task when applied bilaterally but not unilaterally [57]. In five epilepsy patients undergoing intracranial monitoring, a study applied 5 s of 50-Hz pulsed stimulation to the hippocampus, entorhinal cortex, perirhinal cortex, or temporal polar cortex during the recall, distractor, or encoding phases of a free recall task. They found that stimulation at any point during the trial impaired recall, and stimulation during the distractor phase (between learning and recall) caused the most impairment [58].

An investigation into the effects of stimulation on spatial memory found that pulsed 50-Hz stimulation of the entorhinal cortex initially appeared promising. Subjects took more direct paths to their destinations in virtual navigation tasks when they received stimulation [59]. However, a separate study using very similar methods but with a larger number of subjects, and improved statistical methods demonstrated that direct stimulation of the entorhinal cortex impairs spatial memory significantly [60]. They also found that stimulation of the entorhinal cortex impaired verbal memory [60].

A study of 25 subjects undergoing intracranial monitoring prior to epilepsy surgery used closed-loop stimulation of temporal structures to enhance memory in a free recall paradigm (Figure 1) [61••]. In this study, subjects first participated in task sessions without stimulation. Data from these sessions was used to train a logistic regression classifier to detect when the subject's brain is in a "poor encoding state" and to locate the electrodes that most change between good and poor encoding states [61••, 62]. Subjects then received stimulation at these electrodes at a variety of frequencies between 10 and 200 Hz and several amplitudes (0.25 to 2 mA) for 500 ms to find the optimal stimulation settings to convert the brain state from a poor to a good encoding state [61••]. Finally, subjects completed more sessions of the free recall task, but with stimulation at the optimal electrode and parameters to convert from a poor brain state to a good brain state [61••, 63••]. A recent publication from this collaboration showed that in 25 subjects that received closed-loop stimulation, memory was improved by approximately 18% when stimulation was delivered to the left lateral temporal lobe during encoding when the brain was in a "poor encoding state" (unlikely to encode the presented word) [61••]. Stimulation of the left middle temporal gyrus was most effective at enhancing memory recall [61••]. Memory enhancement at this site was associated with an increase in gamma power during word presentation [64]. The group also found that in 22 subjects, stimulation in the lateral temporal lobe improved memory while stimulation in the parahippocampal regions, the hippocampus, and the prefrontal cortex did not [63••].

A study of 14 epilepsy patients undergoing intracranial monitoring found that 1 s of 50-Hz stimulation to the amygdala delivered at the offset of image presentation in an image recognition task improved memory of the images presented with stimulation after 1 day [65]. Stimulation was also associated with increased modulation of perirhinal gamma power by amygdala theta phase in successful recall trials.

While the other studies we reviewed have used macroelectrodes to record local field potentials, one group had used simultaneous recordings of tens of single units to develop a prototype hippocampal prosthetic algorithm that uses a multi-input, multi-output, non-linear dynamic model to attempt to replicate the functionality of the hippocampus [66]. While this technique has not yet been used to guide stimulation of the hippocampus in humans, a study in primates using this technique found that it significantly increases performance on a delayed match-to-sample task [67].

Mechanisms of Improvement

In many of the studies presented here that have demonstrated memory enhancement, it is unclear whether stimulation improved a fundamental process of memory or whether it enhanced memory by reducing epileptogenic activity. There is evidence that the latter may be true. First, patients who suffer from epilepsy-related accelerated forgetting tend to have better long-term memory after resective surgery [68, 69]. Additionally, studies which found that stimulation improves memory have also reported that the stimulation reduced the occurrence of IEDs [45]. Although there is controversy over the cognitive significance of IEDs (for review, see [70, 71]), these findings also lend support to the idea that IEDs impair memory [6, 72]. However, one study using task-responsive intracranial stimulation has reported finding memory enhancement effects on subjects with mild or no verbal memory deficit [63••], suggesting that it may be feasible to enhance memory separately from reduction of epileptiform activity.

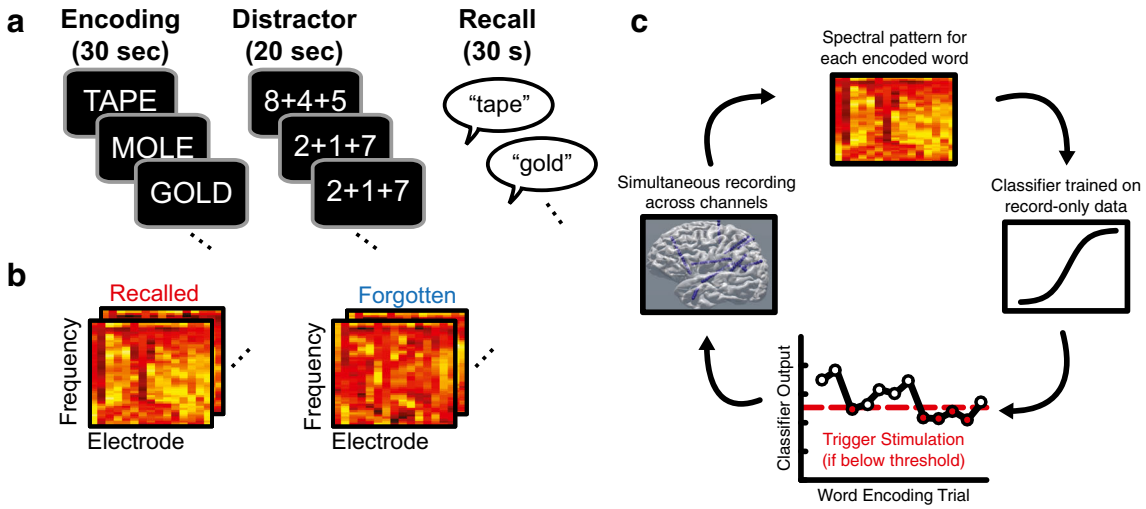

Fig. 1 A study of epilepsy patients undergoing intracranial monitoring. **a** Subjects participate in a free recall task in which a list of words is presented, subjects answer math questions for 30 s, and then subjects recall as many words as possible from the word list. **b** Power spectral analysis is used to compare brain activity during successful and unsuccessful encoding. **c** A logistic regression classifier uses this spectral analysis to predict whether the subject's brain is in a good or bad memory state immediately prior to word presentation. Stimulation is delivered if the predicted probability of recall is below a threshold. All panels reproduced from [61••]

Where and How to Stimulate

In the studies reviewed here, the focus has been on stimulation of the fornix, the anterior nucleus of the thalamus, the hippocampus, the entorhinal cortex, the middle temporal gyrus, the prefrontal cortex, and the vagus nerve. The largest and most consistent improvements in memory have been found in studies that stimulate the middle temporal gyrus and the mesial temporal structures. However, it is unclear that chronic direct stimulation of these areas is necessarily the most beneficial as a therapeutic intervention. Studies in which subjects received direct hippocampal or amygdalar stimulation generally found that stimulation had no effect or impaired memory [49–51]. The one study that found a beneficial effect of stimulation [47] stimulated electrodes in the hippocampus that were extremely close to the seizure onset zone, and it is likely that the memory improvement was due to the resulting reduction in seizures. The best evidence also suggests that stimulation of the entorhinal lobe does not improve spatial memory [60]. In contrast, studies in which the mesial temporal lobe is indirectly stimulated through the fornix have consistently found that stimulation enhances memory [43–45]. While chronic intracranial stimulation of the mesial temporal lobe does not appear to have a therapeutic effect, many studies have demonstrated that memory can be temporarily improved using temporal lobe stimulation synchronized to specific phases of a memory task or to specific brain states [57, 58, 61••, 63••, 65].

The consistent negative impact of TMS on memory suggests that temporary focal disruption of memory areas is generally not helpful for enhancing memory in healthy subjects. However, most TMS studies have been conducted in healthy subjects. If we believe that interrupting epileptogenic activity is likely beneficial to memory, responsive TMS may be able to induce at least momentary improvements in memory in subjects with epilepsy in a manner similar to acute intracranial stimulation. Furthermore, the beneficial effect of stimulation in the DLPFC seen by Blumenfeld, Lee, and D'Esposito [31] should be more thoroughly examined.

While the preponderance of studies using tES to investigate memory enhancement have found either no effect or a small effect size [13], one study found large improvements in memory [14••]. Until an explanation for this unusual result is uncovered, we cannot discount that some configurations of tES under some conditions could potentially improve memory.

Conclusions

The existing studies of neurostimulation for memory enhancement suggest that it may soon be feasible to treat the memory symptoms of epilepsy. The evidence suggests that non-invasive stimulation paradigms have smaller effects than invasive methods, indicating that it may be several years before an implantable device for memory enhancement is ready for clinical trials. However, both non-invasive and invasive methods show recently shown promising developments.

Acknowledgements We would like to thank the participants in the studies that contributed data to this work.

Funding Information This work was supported by the National Science Foundation (EPSCoR-1632738). NeuroPace, Inc. provided research equipment for use in other ongoing studies being conducted by SM and BCJ. BCJ receives other research support from Medtronic, Sunovion, and the Diamond Foundation.

Compliance with Ethical Standards

Conflict of Interest Stephen Meisenhelter reports equipment provided by NeuroPace, Inc.

Barbara C. Jobst reports research funding from Medtronic and Sunovion and equipment provided by NeuroPace, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. McAuley JW, Elliott JO, Patankar S, Hart S, Long L, Moore JL, et al. Comparing patients' and practitioners' views on epilepsy concerns: a call to address memory concerns. Epilepsy Behav. 2010;19:580–3.
2. Blake RV, Wroe SJ, Breen EK, McCarthy RA. Accelerated forgetting in patients with epilepsyEvidence for an impairment in memory consolidation. Brain. 2000;123:472–83.
3. Wilkinson H, Holdstock JS, Baker G, Herbert A, Clague F, Downes JJ. Long-term accelerated forgetting of verbal and non-verbal information in temporal lobe epilepsy. Cortex. 2012;48:317–32.
4. Davidson M, Dorris L, O'Regan M, Zuberi SM. Memory consolidation and accelerated forgetting in children with idiopathic generalized epilepsy. Epilepsy Behav. 2007;11:394–400.
5. Sidhu MK, Stretton J, Winston GP, Symms M, Thompson PJ, Koepp MJ, et al. Factors affecting reorganisation of memory encoding networks in temporal lobe epilepsy. Epilepsy Res. 2015;110:1–9.
6. Horak PC, Meisenhelter S, Song Y, Testorf ME, Kahana MJ, Viles WD, et al. Interictal epileptiform discharges impair word recall in multiple brain areas. Epilepsia. 2017;58:373–80.
7. Paradiso S, Hermann BP, Blumer D, Davies K, Robinson RG. Impact of depressed mood on neuropsychological status in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry. 2001;70:180–5.
8. Meador KJ, Loring DW, Moore E, Thompson WO, Nichols ME, Oberzan R, et al. Comparative cognitive effects of phenobarbital, phenytoin, and valproate in healthy adults. Neurology. 1995;45:1494–9.
9. Meador KJ, Loring DW, Abney OL, Allen ME, Moore EE, Zamrini EY, et al. Effects of carbamazepine and phenytoin on EEG and memory in healthy adults. Epilepsia. 1993;34:153–7.
10. Hermann B, Meador KJ, Gaillard WD, Cramer JA. Cognition across the lifespan: antiepileptic drugs, epilepsy, or both? Epilepsy Behav. 2010;17:1–5.
11. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527:633–9.
12. Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, et al. Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. J Neurosci. 2011;31:15284–93.
13. Hill AT, Fitzgerald PB, Hoy KE. Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. Brain Stimul. 2016;9:197–208.
14.•• Karvigh SA, Motamedi M, Arzani M, Roshan JHN. HD-tDCS in refractory lateral frontal lobe epilepsy patients. Seizure. 47:74–80. **The authors found in an uncontrolled study that tDCS could dramatically and chronically enhance memory in epilepsy patients. Further investigation of this method using a more controlled study design is needed.**
15. San-Juan D, Morales-Quezada L, Orozco Garduño AJ, Alonso-Vanegas M, González-Aragón MF, Espinoza López DA, et al. Transcranial direct current stimulation in epilepsy. Brain Stimul. 2015;8:455–64.
16. Fregni F, Boggio PS, Nitsche M, Bermpohl F, Antal A, Feredoes E, et al. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. Exp Brain Res. 2005;166:23–30.
17. Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. J Neurosci. 2009;29:5202–6.
18. Polanía R, Nitsche MA, Korman C, Batsikadze G, Paulus W. The importance of timing in segregated theta phase-coupling for cognitive performance. Curr Biol. 2012;22:1314–8.
19. Holmes J, Byrne EM, Gathercole SE, Ewbank MP. Transcranial random noise stimulation does not enhance the effects of working memory training. J Cogn Neurosci. 2016;28:1471–83.
20. Mulquiney PG, Hoy KE, Daskalakis ZJ, Fitzgerald PB. Improving working memory: exploring the effect of transcranial random noise stimulation and transcranial direct current stimulation on the dorsolateral prefrontal cortex. Clin Neurophysiol. 2011;122:2384–9.
21. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;325:1106–7.
22. Ueno S, Tashiro T, Harada K. Localized stimulation of neural tissues in the brain by means of a paired configuration of time-varying magnetic fields. J Appl Phys. 1988;64:5862–4.
23. Walsh V, Cowey A. Transcranial magnetic stimulation and cognitive neuroscience. Nat Rev Neurosci. 2000;1:73.
24. Davis NJ, Gold E, Pascual-Leone A, Bracewell RM. Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications. Eur J Neurosci. 38:2973–7.
25. Bolognini N, Ro T. Transcranial magnetic stimulation: disrupting neural activity to alter and assess brain function. J Neurosci. 2010;30:9647–50.
26. Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol. 2006;117:2584–96.
27. Bae EH, Schrader LM, Machii K, Alonso-Alonso M, Riviello JJ, Pascual-Leone A, et al. Safety and tolerability of repetitive transcranial magnetic stimulation in patients with epilepsy: a review of the literature. Epilepsy Behav. 2007;10:521–8.
28. Rossi S, Cappa SF, Babiloni C, Pasqualetti P, Miniussi C, Carducci F, et al. Prefontal cortex in long-term memory: an "interference" approach using magnetic stimulation. Nat Neurosci. 2001;4:948.
29. Gagnon G, Blanchet S, Grondin S, Schneider C. Paired-pulse transcranial magnetic stimulation over the dorsolateral prefrontal cortex interferes with episodic encoding and retrieval for both verbal and non-verbal materials. Brain Res. 1344:148–58.
30. Köhler S, Paus T, Buckner RL, Milner B. Effects of left inferior prefrontal stimulation on episodic memory formation: a two-stage fMRI. J Cogn Neurosci. 2004;16:178–88.

31. Blumenfeld RS, Lee TG, D'Esposito M. The effects of lateral prefrontal transcranial magnetic stimulation on item memory encoding. Neuropsychologia. 2014;53:197–202.
32. Kahn I, Pascual-Leone A, Theoret H, Fregni F, Clark D, Wagner AD. Transient disruption of ventrolateral prefrontal cortex during verbal encoding affects subsequent memory performance. J Neurophysiol. 2005;94:688–98.
33. Bonnì S, Veniero D, Mastropasqua C, Ponzo V, Caltagirone C, Bozzali M, et al. TMS evidence for a selective role of the precuneus in source memory retrieval. Behav Brain Res. 2015;282:70–5.
34. Sestieri C, Capotosto P, Tosoni A, Luca Romani G, Corbetta M. Interference with episodic memory retrieval following transcranial stimulation of the inferior but not the superior parietal lobule. Neuropsychologia. 2013;51:900–6.
35. Krahl SE, Clark KB, Smith DC, Browning RA. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. Epilepsia. 1998;39:709–14.
36. Morris GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. Neurology. 1999;53:1731–1.
37. Clark KB, Naritoku DK, Smith DC, Browning RA, Jensen RA. Enhanced recognition memory following vagus nerve stimulation in human subjects. Nat Neurosci. 1999;2:94–8.
38. Ghacibeh GA, Shenker JI, Shenal B, Uthman BM, Heilman KM. The influence of vagus nerve stimulation on memory. Cogn Behav Neurol: Off J Soc Behav Cogn Neurol. 2006;19:119–22.
39.•• Sun L, Peräkylä J, Holm K, Haapasalo J, Lehtimäki K, Ogawa KH, et al. Vagus nerve stimulation improves working memory performance. J Clin Exp Neuropsychol. 39:954–64. **The authors found that VNS stimulation acutely improved response accuracy in a working memory task.**
40. Hoppe C, Helmstaedter C, Scherrmann J, Elger CE. No evidence for cognitive side effects after 6 months of vagus nerve stimulation in epilepsy patients. Epilepsy Behav. 2001;2:351–6.
41. McGlone J, Valdivia I, Penner M, Williams J, Sadler RM, Clarke DB. Quality of life and memory after vagus nerve stimulator implantation for epilepsy. Can J Neurol Sci. 2008;35:287–96.
42. Muller L, Hamilton LS, Edwards E, Bouchard KE, Chang EF. Spatial resolution dependence on spectral frequency in human speech cortex electrocorticography. J Neural Eng. 2016;13:056013.
43. Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, et al. Memory enhancement induced by hypothalamic/fornix deep brain stimulation. Ann Neurol. 2008;63:119–23.
44. Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol. 2010;68:521–34.
45. Koubeissi MZ, Kahriman E, Syed TU, Miller J, Durand DM. Low-frequency electrical stimulation of a fiber tract in temporal lobe epilepsy. Ann Neurol. 74:223–31.
46. Miller JP, Sweet JA, Bailey CM, Munyon CN, Luders HO, Fastenau PS. Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation with four cases. Brain. 2015;138:1833–42.
47. Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia. 2007;48:1895–903.
48. Hermann BP, Seidenberg M, Bell B. The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. Progress Brain Res. Elsevier; pp. 429–38.
49. McLachlan RS, Pigott S, Tellez-Zenteno JF, Wiebe S, Parrent A. Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: impact on seizures and memory. Epilepsia. 2010;51:304–7.
50. Boëx C, Seeck M, Vulliémoz S, Rossetti AO, Staedler C, Spinelli L, et al. Chronic deep brain stimulation in mesial temporal lobe epilepsy. Seizure. 2011;20:485–90.
51. Miatton M, Roost DV, Thiery E, Carrette E, Dycke AV, Vonck K, et al. The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy. Epilepsy Behav. 2011;22:759–64.
52. Štillová K, Jurák P, Chládek J, Chrastina J, Halámek J, Bočková M, et al. The role of anterior nuclei of the thalamus: a subcortical gate in memory processing: an intracerebral recording study. PLoS One. 2015;10:e0140778.
53. Kopelman MD. What does a comparison of the alcoholic Korsakoff syndrome and thalamic infarction tell us about thalamic amnesia? Neurosci Biobehav Rev. 2015;54:46–56.
54. Oh Y-S, Kim HJ, Lee KJ, Kim YI, Lim S-C, Shon Y-M. Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. Seizure. 2012;21:183–7.
55. Tröster AI, Meador KJ, Irwin CP, Fisher RS. Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. Seizure. 2017;45:133–41.
56. Loring DW, Kapur R, Meador KJ, Morrell MJ. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. Epilepsia. 2015;56:1836–44.
57. Lacruz ME, Valentín A, Seoane JJG, Morris RG, Selway RP, Alarcón G. Single pulse electrical stimulation of the hippocampus is sufficient to impair human episodic memory. Neuroscience. 2010;170:623–32.
58. Merkow MB, Burke JF, Ramayya AG, Sharan AD, Sperling MR, Kahana MJ. Stimulation of the human medial temporal lobe between learning and recall selectively enhances forgetting. Brain Stimul. 2017;10:645–50.
59. Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, et al. Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med. 2012;366:502–10.
60. Jacobs J, Miller J, Lee SA, Coffey T, Watrous AJ, Sperling MR, et al. Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. Neuron. 2016;92:983–90.
61.•• Ezzyat Y, Wanda PA, Levy DF, Kadel A, Aka A, Pedisich I, et al. Closed-loop stimulation of temporal cortex rescues functional networks and improves memory. Nat Commun. 9:365. **The authors used closed-loop intracranial stimulation to acutely improve memory by 18% in a free recall task.**
62. Kragel JE, Ezzyat Y, Sperling MR, Gorniak R, Worrell GA, Berry BM, et al. Similar patterns of neural activity predict memory function during encoding and retrieval. NeuroImage. 2017;155:60–71.
63.•• Kucewicz MT, Berry BM, Miller LR, Khadjevand F, Ezzyat Y, Stein JM, et al. Evidence for verbal memory enhancement with electrical brain stimulation in the lateral temporal cortex. Brain. **The authors found that intracranial stimulation of the lateral temporal lobe could acutely improve memory, while stimulation of other temporal structures did not.**
64. Kucewicz MT, Berry BM, Kremen V, Miller LR, Khadjevand F, Ezzyat Y, et al. Electrical stimulation modulates high γ activity and human memory performance. eNeuro. 5:ENEURO0369–17.2018.
65. Inman CS, Manns JR, Bijanki KR, Bass DI, Hamann S, Drane DL, et al. Direct electrical stimulation of the amygdala enhances declarative memory in humans. Proc Natl Acad Sci. 2018;115:98–103.
66. Song D, Robinson BS, Hampson RE, Marmarelis VZ, Deadwyler SA, Berger TW. Sparse large-scale nonlinear dynamical modeling of human hippocampus for memory prostheses. IEEE Trans Neural Syst Rehabil Eng. 2018;26:272–80.

67. Hampson RE, Song D, Opris I, Santos LM, Shin DC, Gerhardt GA, et al. Facilitation of memory encoding in primate hippocampus by a neuroprosthesis that promotes task-specific neural firing. J Neural Eng. 2013;10:066013.
68. Evans SJ, Elliott G, Reynders H, Isaac CL. Can temporal lobe epilepsy surgery ameliorate accelerated long-term forgetting? Neuropsychologia. 2014;53:64–74.
69. Gallassi R, Sambati L, Poda R, Stanzani Maserati M, Oppi F, Giulioni M, et al. Accelerated long-term forgetting in temporal lobe epilepsy: evidence of improvement after left temporal pole lobectomy. Epilepsy Behav. 2011;22:793–5.
70. Lenck-Santini P-P, Scott RC. Mechanisms responsible for cognitive impairment in epilepsy. Cold Spring Harbor Perspect Med. 2015;5: a022772.
71. Drane DL, Ojemann JG, Kim MS, Gross RE, Miller JW, Faught RE, et al. Interictal epileptiform discharge effects on neuropsychological assessment and epilepsy surgical planning. Epilepsy Behav. 2016;56:131–8.
72. Ung H, Cazares C, Nanivadekar A, Kini L, Wagenaar J, Becker D, et al. Interictal epileptiform activity outside the seizure onset zone impacts cognition. Brain. 2017;140:2157–68.