Deep Brain Stimulation for Memory Deficits

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Here: a review of the neurobiology and circuitry behind memory as well as current studies involving neuromodulation for memory disorders.

Memory impairment is a disabling condition and one of the most common complaints affecting patients with neurological deficits. Neurological disorders, such as Alzheimer disease (AD), Parkinson disease (PD), traumatic brain injury (TBI), and epilepsy, as well as normal aging, can lead to problems in declarative, working, and episodic memory. These impairments often place significant psychological, social, and financial stresses on patients and their families.

Medical treatments for cognitive deficits are limited and suggest a need for new and innovative therapy. Deep brain stimulation (DBS) is a successful and prevalent treatment for movement disorders, such as PD, tremor, and dystonia; however, its use in treating neuropsychiatric disorders has come to the forefront only in recent years.

In this article, we review the neurobiology and circuitry behind memory as well as current studies involving neuromodulation for memory disorders.

Neuromodulation for memory disorders

DBS is a surgical technique that delivers pulsed electrical impulses to the brain. In addition to its use in treating movement disorders, DBS has been used to manage chronic pain, obsessive-compulsive disorder, and depression. However, the application of DBS for cognitive dysfunction has not been well established.

The Papez circuit is a neural network that is thought to be involved in emotion and episodic memory (Figure). There is evidence that parts of this circuitry may be altered in neurocognitive disorders such as AD, PD, and epilepsy, which suggests potential targets for neuromodulation. The frontal-striatal circuitry has also been implicated in memory processes and cognitive dysfunction. Specifically, deficits in working memory and retrieval often reflect dysfunction in the frontal-striatal systems.

In addition to neural circuitry, specific firing patterns of different brain regions have been associated with mechanisms of learning. For instance, intracranial recordings have demonstrated that high-frequency activity within the prefrontal area, medial temporal lobe, and inferior parietal cortices has been associated with encoding and retrieval states. In contrast, increased hippocampal low-frequency (theta) activity may be important before memory tasks. Preclinical and clinical DBS trials have begun to target these circuits for memory deficits.

Neurodegenerative disorders and memory

Neurodegenerative diseases, such as AD and PD, are characterized by significant deficits in working memory, episodic memory, and semantic memory. MRI findings have demonstrated a reduction in hippocampal and entorhinal cortex volume in the early stages of AD, and decreased metabolism in the frontal lobe, medial temporal lobe, and parietal regions. As episodic memory is thought to be mediated by the hippocampus, these findings correlate with deficits in episodic memory and precede widespread cognitive deterioration. In contrast, patients with subcortical dementia often have deficits in working memory as opposed to episodic memory.

DBS for Alzheimer disease

There are 2 primary DBS targets for AD: the fornix (an axonal output tract of the Papez circuit that connects the hippocampus to the mammillary bodies) and the nucleus basalis of Meynert (cholinergic neurons within the basal forebrain projecting to the neocortex).

During a case study at our institution, in which DBS of the hypothalamus and fornix was applied for morbid obesity, there was an incidental finding of improved verbal recall (Table). In another case study, bilateral fornical stimulation stabilized memory scores and increased mesial temporal lobe activity in a patient with AD. Our group pursued phase 1 and subsequent phase 2 trials for the surgical DBS treatment of learning and memory deficits in patients with advanced AD. This trial demonstrated that fornical (130 Hz) stimulation increases cerebral glucose metabolism and may
slow cognitive decline in patients older than 65 years, but may worsen cognition in those younger than 65 years.

In both AD and Parkinson dementia, there is basal forebrain degeneration. The basal forebrain consists of the medial septal nucleus, diagonal band nucleus, and the nucleus basalis of Meynert. Degeneration of the basal forebrain, and more specifically the nucleus of Meynert, results in decreased cholinergic projections to the neocortex and a reduction in long-term potentiation. Turnbull and colleagues\(^1\) initially postulated that nucleus of Meynert stimulation might improve cognition in patients with Alzheimer senile dementia. However, in this case report, long-term nucleus of Meynert stimulation increased cortical glucose metabolic activity but did not have a beneficial clinical effect. More recently, a pilot study of nucleus of Meynert stimulation in 8 patients with AD has shown promising memory results in a subpopulation.\(^2\)

**DBS for Parkinson disease**
The rigidity, tremor, and bradykinesia that characterize PD may be accompanied by cognitive dysfunction and depression in the absence of dementia. Affected patients often suffer from episodic and semantic memory deficits. In addition, they may experience working memory deficits secondary to disruption of the frontal-striatal neuronal circuits, including the prefrontal cortex.

Current DBS targets for PD are typically the subthalamic nucleus and globus pallidus pars interna. Both targets are equally beneficial for motor symptoms in PD; however, the globus pallidus pars interna appears to be a better target for patients with depression. There is some evidence that subthalamic nucleus DBS may be beneficial for some cognitive tasks, while other findings suggest that subthalamic nucleus DBS leads to worse working memory performance.\(^3,4\)

In an attempt to address the cognitive dysfunction associated with PD, concomitant nucleus of Meynert and subthalamic nucleus stimulation improved neuropsychiatric function in one patient. Interestingly, there was a rapid decline in neuropsychiatric function when the stimulation was turned off, but once again improved when stimulation was turned back on.\(^5\)

The frontal-striatal circuitry is also thought to play a role in cognitive processing. The pedunculopontine nucleus is thought to modulate this circuitry. Evidence suggests that low-frequency stimulation of the pedunculopontine nucleus decreases reaction times without affecting motor reaction times in patients with PD, but does not affect accuracy during working memory tasks.\(^6\) These results suggest that stimulation of the pedunculopontine nucleus may improve working memory efficiency. Results from another study suggest that low-frequency pedunculopontine nucleus stimulation improves verbal long-term memory.\(^7\) This has been associated with increased metabolism in the dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, superior frontal gyrus, inferior frontal gyrus, inferior parietal lobule, and supramarginal gyrus.

**DBS for epilepsy**
Epilepsy leads to structural changes in the hippocampus and surrounding tissue. Scoville and Milner\(^8\) initially described a correlation between hippocampal structural damage and episodic and semantic memory deficits. More recent diffusion tensor imaging, positron emission tomography, and quantitative MRI studies suggest that patients with frontal and prefrontal lobe damage suffer from working memory deficits.\(^9-11\) It is interesting to note that patients with mesial temporal lobe epilepsy have greater memory impairment than those with extratemporal or generalized seizures.\(^12\)

DBS has been explored as a promising new treatment for medically refractory epilepsy. Specifically, anterior nucleus of the thalamus stimulation has been used to surgically treat drug-resistant epilepsy with significant improvement in seizure reduction (SANTE trial).\(^13\) With anterior nucleus of the thalamus stimulation, there is also improvement in verbal fluency tasks and delayed verbal memory.\(^14\) Other stereotactic targets that have been researched are the subthalamic nucleus, central-medial thalamic nucleus, hippocampus, amygdala, and cerebellum.

The Papez circuit is thought to be involved with episodic memory. The anterior thalamic nucleus is one node of the Papez circuit and has connections with a number of areas involved in memory, such as the superior frontal and temporal cortices, the dentate gyrus, cingulum, anterior cingulate cortex, and entorhinal cortex. It also has projections from the subiculum via the fornix.

While DBS is being pursued for antiepileptic effects, evidence suggests that it may be beneficial in epileptic patients with memory deficits. Although direct hippocampal stimulation has not been shown to be beneficial for memory — and may even impair verbal memory — a case series by Suthana and colleagues\(^15\) in which the entorhinal cortex was targeted with high-frequency stimulation (50 Hz) in 7 patients with epilepsy demonstrated improvement in spatial working memory deficits and resetting of the hippocampal theta rhythm. However, more recently, Jacobs and colleagues\(^16\) conducted a
larger study (40-patient cohort) of entorhinal cortex electrical stimulation (50 Hz) that demonstrated impairment of spatial and verbal memory. One reason for the possible contradictory findings is that the 2 studies used different spatial memory tasks. Another potential difference is that the study by Suthana and colleagues utilized a longer stimulation paradigm.

While the SANTE trial and entorhinal cortex stimulation case series utilize gamma frequency stimulation, there is evidence that theta frequency stimulation may be beneficial in patients with epilepsy, as seizures can result in decreased theta activity and memory deficits. In one case series (4 patients), fornical theta burst stimulation was used to improve memory. In this study, there was a suggestion that visual-spatial memory was improved with theta burst stimulation, but there was no effect on verbal memory. This suggests that a frequency target, in addition to an anatomic target, may be warranted in DBS treatments for memory disorders.

**DBS for traumatic brain injury**

TBI is a heterogeneous disease with multiple sequelae and outcomes. Affected patients may have significant short-term memory, working memory, episodic memory, and semantic memory deficits in mild, moderate, and severe injuries. These deficits have been correlated with decreased metabolism in prefrontal and frontal cortical regions of patients with TBI. Moreover, during free recall, memory retrieval, and recognition tasks, patients exhibited less frontal cortical activation and more posterior cortical activation than controls.

There may be a role for DBS in patients in the vegetative state. TBI leads to a reduction in hippocampal theta activity and spatial working memory deficits. Preclinical TBI studies have shown that spatial working memory was improved with medial septal nucleus theta frequency (7.7 Hz) stimulation, while gamma frequency stimulation did not improve spatial working memory. And, theta burst (200 Hz in 50-ms trains, 5 seconds per train) fornical stimulation improved learning and memory in rodents. These results suggest that septohippocampal stimulation, particularly within the theta band, may be a potential target for memory DBS neuromodulation in patients with TBI.

**Referring patients for DBS trials**

DBS trials for memory have their own unique challenges compared with other DBS indications, such as movement disorders. As in DBS for movement disorders, a multidisciplinary team is necessary, including psychiatrists, neuropsychologists, neurologists, and neurosurgeons. Particularly when researching cognitive decline, it is important to have clinicians experienced in dementia and to have patients with reliable caregivers who can report on daily activities and function throughout the study. Equally as important, it is necessary for patients and their families to understand the risks and benefits involved in the study, including the possibility of infection, brain injury, and electrode lead fracture or migration.

To reduce confounding variables, these patients should be taking stable doses of their medications, such as acetylcholinesterase inhibitors and N-methyl-D-aspartic acid receptor antagonists. Moreover, it is important to assess patients with rating scales such as the Clinical Dementia Rating Scale and the Alzheimer Disease Assessment Scale for patients with AD. As with any DBS procedure, the patient must not have any contraindications for MRI because preoperative and postoperative MRI scans are necessary for operative planning and lead confirmation.

While DBS trials for cognition have demonstrated promising results, future studies are needed to identify the optimal stimulation paradigms. Moreover, better understanding of physiology and potential biomarkers may help identify targets to modulate. These biomarkers may enable a more targeted approach. As technology advances, biomarkers may lend themselves to responsive neurostimulation, in which the device monitors brain signals and provides stimulation in response to abnormal electrical events. This may lead to decreased battery use and potentially fewer adverse effects. Moreover, advances in technology may improve the performance, size, and battery life of the internal pulse generators.

**Conclusion**

The initial DBS case reports for memory demonstrated an immediate recall effect; however, there are multiple memory circuits. Moreover, there are different types of memory, and it is important to identify which memory subtype DBS will be likely to affect. Memory is associated with significant functional connectivity among various regions of the brain. Stimulating one node may not necessarily improve the disrupted network or may even cause further interference. This may necessitate determining which of the nodes is functioning inappropriately. In addition to anatomical locations associated with memory, different frequencies in different locations are thought to be important in memory. Therefore, it is important to identify anatomically and physiologically relevant DBS targets.
Another caveat to neuromodulation for cognition is that the effect of DBS may not be immediate. Frequent and long-term monitoring and evaluation may allow for more refined analysis. However, with repeated testing and evaluation, there may be improvement just from practice and attention to the memory deficits. There may also be a placebo effect from DBS, and expectations must be tempered. Rigorous experimental design is necessary to account for these confounding factors. Therefore, randomized controlled trials with appropriate matched groups are imperative. Despite these challenges and the complex circuitry involved with the various types of memory, there is still significant evidence for the promising role of DBS in cognition.

**FIGURE.** The Papez circuit is a neural circuit proposed to be important...

**TABLE.** Case series and DBS trials for memory in Alzheimer disease, Par...

**SIGNIFICANCE FOR THE PRACTICING PSYCHIATRIST**

**Disclosures:**
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**References:**


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