Role of deep brain stimulation in modulating memory formation and recall

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Deep brain stimulation (DBS) has become an increasingly popular tool for treating a variety of medically refractory neurological and psychiatric disorders such as Parkinson disease, essential tremor, depression, and obsessive-compulsive disorder. Several targets have been identified for ablation or stimulation based on their anatomical location and presumed function. Areas such as the subthalamic nucleus, globus pallidus, and thalamus, for example, are believed to play a key role in motor control and execution, and they are commonly used in the treatment of motor disorders. Limbic structures such as the cingulate cortex and ventral striatum, believed to be important in motivation, emotion, and higher cognition, have also been targeted for treatment of a number of psychiatric disorders. In all of these settings, DBS is largely aimed at addressing the deleterious aspects of these diseases. In Parkinson disease, for example, DBS has been used to reduce rigidity and tremor, whereas in obsessive-compulsive disorder it has been used to limit compulsive behavior. More recently, however, attention has also turned to the potential use of DBS for enhancing or improving otherwise nonpathological aspects of cognitive function. This review explores the potential role of DBS in augmenting memory formation and recall, and the authors discuss recent studies and future trends in this emerging field. (DOI: 10.3171/2009.4.FOCUS0975)

KEY WORDS • deep brain stimulation • learning • memory

DEEP brain stimulation is becoming established as an effective treatment for a variety of medically refractory neurological and psychiatric disorders. Thus far, it has been largely aimed at treating the “negative” or deleterious aspects of these disorders: in Parkinson disease, for example, DBS is aimed at reducing rigidity and tremor, whereas in obsessive-compulsive disorder it is used to limit obsessive ideations and compulsive behavior.^{22,24,25,30,38} The fundamental premise for this approach is based on the assumption that by disrupting an abnormally active area or pathway, normalization of activity may be regained. Such disruption is largely mediated by direct ablation or electrical stimulation delivered at a constant setting. Despite significant advancement in the use of DBS for treating abnormal symptoms associated with neurological and psychiatric disorders, researchers have paid relatively little attention to the role DBS may play in “positively” enhancing normal behavior. One area in which advancements have been recently made is in augmenting memory formation and recall with dynamic microstimulation delivery.

Neuroanatomy of Learning and Memory

Memory formation and recall play an important role in many aspects of human behavior and are essential for higher cognition. At a basic level, memory formation refers to the ability to acquire new knowledge, and recall refers to the ability to access that knowledge at a later time. Not all forms of memory are identical, however, but are broadly divided into procedural, semantic, and episodic forms. In procedural memory, reflexive or habitual associations are made between sensory stimuli within the environment and behavioral responses, whereas in semantic memory facts are remembered largely independently of their behavioral context. In comparison, episodic memory involves retention of events in one’s own life rather than generalized knowledge and can often be recalled with extraordinary detail after prolonged duration. Not unexpectedly, these different forms of memory are believed to rely on different structures and neuronal pathways within the brain. Although the exact mechanisms responsible for these have yet to be completely elucidated, certain structures have been found to be critically important to their function. These include limbic structures such as the hippocampus and amygdala, dien-

Abbreviation used in this paper: DBS = deep brain stimulation.

cephalic structures such as the hypothalamus and thalamus, and both neo- and subcortical structures such as the prefrontal cortex, basal ganglia, and thalamus.^{11,19,21} Some of these structures and their connections may therefore represent potential targets for augmenting memory formation and recall (Table 1).

Stimulation of the Limbic System and Memory Recall

A growing number of ablative, neurophysiological and imaging studies have indicated that the temporal lobes play a central role in memory. Removal of the bilateral hippocampi and associated structures in patients with epilepsy, for example, leads to profound anterograde amnesia while leaving past semantic and episodic memories largely intact.²⁶ In contrast, stimulation of these structures has been found in some circumstances to augment recall.²⁸ In a recent study by Vignal et al.,³⁷ stimulations were performed in the temporal lobe of individuals undergoing depth electrode recordings for seizure disorders. They reported that stimulation in a number of patients elicited dramatic autobiographical recollection of precise childhood episodes, television advertisements, or life events. These recollections had a highly specific time context and included both recent and remote memories. Interestingly, patients often described recollection of such memories as “spectators” rather than in first person, and in some instances stimulus-induced recollections were similar to memories elicited by seizure onsets themselves. More specific studies have demonstrated that stimulation of the entorhinal cortex reliably elicits episodic scene-reminiscent and context-specific memories in comparison with the perirhinal cortex.⁵ In some individuals, memories were visual objects rather than time-specific scenes and were therefore considered semantic in nature rather than episodic. In these cases, stimulations were delivered in proximity to the medial temporal area TE (Brodman area 20), known to be associated with object recognition as part of the ventral visual stream. In other patients, memories were highly contextualized and were related to a specific episodes and time points in their past, findings that may be consistent with studies in animal models demonstrating subpopulations of cells within the temporal lobe that are highly selective for spatial localization and memory context.^{6,12} Both forms of recall were distinct from the more common but nonspecific emotional or hallucinatory phenomena such as anxiety or fear frequently associated with stimulation of the mesial temporal structures. It is therefore interesting to speculate whether sufficiently precise microstimulation could provide a viable tool for eliciting or suppressing recall of targeted memories. Because the ability to recall semantic facts or episodic events is variably affected by a wide range of disorders including traumatic brain injury, stroke, Alzheimer disease, and Parkinson disease, the potential use of DBS for augmenting memory in these settings may be of particular benefit.^{6,13,23,41}

Stimulation of other areas of the limbic loop has also been shown to elicit selective memory recall. In addition to its function in maintaining physiological homeosta-

TABLE 1: Brain structures thought to be important in processing learning and memory, and that may present potential targets for stimulation

Potential Targets	Presumed Primary Function
hippocampus	semantic/episodic memory
hypothalamus	episodic memory
striatum	associative/procedural memory
anterior cingulate cortex	reward-based & emotional memory
orbitofrontal cortex	reward-based memory
amygdala	fear-conditioning, emotional memory

sis, the hypothalamus plays a role in modulating goal-directed behavior and autonomic functions such as fear and anxiety.^{10,34} Based on initial results in animal models, DBS of the hypothalamus has recently been attempted in individuals for disorders such as obesity and cluster headaches. In a case report by Hamani et al.,¹⁴ the authors implanted bilateral DBS electrodes in the ventral hypothalamus in a patient suffering from morbid obesity. After stimulation of several potential hypothalamic sites, the patient unexpectedly began experiencing déjà vu episodes, recalling familiar scenes such as being in a park with his friends ~ 20 years ago. These autobiographical memories were highly specific: the patient could recollect the color of clothing individuals wore, but he could not decipher what they were saying. Electroencephalographic source localization demonstrated that stimulation in this area led to increased medial temporal activity suggesting that stimulation in this area may modulate limbic circuitry associated with recall. These findings were also consistent with a number of animal studies that have shown that hypothalamic stimulation may modulate memory function and suggest that stimulation of other areas within the limbic pathway may induce selective long-term memory recall.³³

Role of the Basal Ganglia in Memory Formation

Areas of the basal ganglia such as the globus pallidus and subthalamic nucleus are commonly targeted for the treatment of movement disorders because of their known role in motor control and execution. A more recent body of literature, however, suggests that certain parts of the basal ganglia may also play a key role in procedural learning whereby sensory stimuli are associated with motor responses that lead to reward.^{4,16,39} The basal ganglia are a group of subcortical nuclei involved in multiple parallel loops that relay back to homologous areas within the cortex.^{1,15} These loops share common features in that they begin with convergent input from the cortex that project to the neostriatum (caudate and putamen), and then proceed through to the globus pallidus or the substantia nigra pars reticularis, the output nuclei of the basal ganglia. Several functional cortical-subcortical circuits have been described, including the motor and oculomotor loops thought to play a role in movement, as well as the associative prefrontal and limbic loops thought to play a role in memory formation and recall.³

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Based in part on these anatomical observations, studies of neurophysiological responses during movement have shown that striatal neurons can exhibit a variety of cue- and movement-related responses and will fire preferentially in response to movements made in a particular direction.⁷ Many of these cells also exhibit a preparatory, or set, activity that precedes the actual movement, and they often display task-related activity.² Over time, this activity can become associated with conditioned stimuli predicting profitable motor response. These associations can be sustained over days to many weeks on repeated task execution, and they may thus represent correlates of learning at the cellular level.^{9,16} In addition to broad cortical input, neurons in the striatum receive heavy dopaminergic afferents from the substantia nigra pars compacta and ventral tegmental area, both areas of which demonstrate robust responses to actual and expected reward.^{17,36} Consistent with these findings, striatal neurons demonstrate varying degrees of response to reward and will display higher activity in relation to motor selections made when reward is expected.²⁰ Such activity also correlates with changes in behavior during execution of rewarding sensory-motor responses, indicating that it may play an important role in the formation and maintenance of learned associations.⁴⁰

Dynamic Stimulation of the Basal Ganglia During Associative Learning

While the role of the basal ganglia in procedural learning has been supported by studies demonstrating deficits in associative memory formation after lesioning or neurochemical inhibition of the striatum, only recently has dynamic stimulation been examined as a potential tool for enhancing memory formation. In a study described by our group, rhesus monkeys performed an associative learning task while event-related microstimulus pulses were delivered in the anterior caudate and putamen.⁴⁰ During the task, the animals repeatedly learned to associate novel visual images with specific joystick movements in 1 of 4 radial directions. In a separate set of experiments, carbon fiber amperometry was also used to evaluate local dopamine release evoked by stimulation. To examine the effect of stimulation-dependent dopamine release for specific associations, pulses were delivered for 1 of the 2 concurrently learned novel images in each learning block while the animals performed the task. We found that high-frequency, but not low-frequency, microstimulation resulted in a sustained dopamine release in the striatum. A similar release of dopamine was also evoked by stimulation of dopamine projection neurons in the zona incerta, suggesting that the effect was dopamine dependent. Consistent with this, the animals' performance on trials in which novel images were coupled with high-frequency stimulation in the caudate was significantly better than that on nonstimulated trials. This was also associated with an increase in the slope, or the rate of improvement, in the animals' learning performance.

Based on these and similar findings, a number of models regarding the role of the basal ganglia in learning have emerged.^{27,31,40} The most commonly used model is

that of weakly supervised reinforcement learning wherein a learning system is given evaluative feedback based on the correctness of a given response. One of these models specifically employs an "actor" and an adaptive "critic" wherein the actor is the striatum and the critic is the mid-brain dopaminergic output. The output that the critic provides to the actor consists of the temporal difference error in reward indicating whether the association between the previously performed action and the association should be strengthened or weakened. Phasic dopamine release is proposed to result in a selective potentiation of active cortical-striatal synapses or circuits and therefore provides an ideal mechanism by which to modulate learning by extrinsic means. By using DBS in this selective manner, such an approach may provide potential means for enhancing associative learning in individuals with memory disability or brain injury.

Conclusions and Future Directions

While DBS has been traditionally viewed as a tool for delivering a static set of stimulation parameters, recent advances are beginning to allow it to be used in a more versatile manner. By nature, cognitive behavior such as learning and recall is highly dynamic, and therefore dynamic neuromodulatory devices are likely to be required to alter its function. For example, in primates delivery of striatal stimulation only after execution of correct responses has been shown to enhance formation of learned associations whereas delivery prior to motor execution or after execution of incorrect responses has little effect.⁴⁰ More recent studies in humans have also attempted to use continuous neural stimulation for stroke rehabilitation, neuropathic pain, and seizure control.^{8,29} Whereas delivery of continuous stimulation in these cases may be effective, developing the ability to dynamically deliver stimulation in relation to an individual's behavioral state may provide more substantial results. Such approaches would provide a more rational basis by which to modulate neuronal activity in a disease and behaviorally specific manner and is likely to be at least 1 component in the evolution of DBS.

In addition to developing "smart" dynamic tools for delivering stimulation, it is also important that our understanding of the effects of DBS continues to grow. Although microstimulation has been largely assumed to affect behavior via direct excitation or suppression of neuronal activity, recent studies also suggest that DBS may affect memory by alternative mechanisms. In a recent study by Toda et al.,³⁵ for example, rodents received DBS in the anterior thalamus, a central relay area in the limbic memory system. The authors found that in stimulated animals, cell division in the subgranular layer of the hippocampus significantly increased. This was not observed in nonstimulated control groups and suggests that DBS may not only alter neuronal activity but may also enhance neurogenesis in certain areas involved in memory formation.

Our understanding of the effect of DBS on neuronal functioning and its dynamic implementation has proven to be a powerful tool for treating many of the negative aspects of disorders such as Parkinson disease, essential

tremor, depression, and obsessive-compulsive disorder. However, it may also play a potential role in positively affecting cognitive behavior such as memory formation and recall. While such an approach could hold significant promise, it is also important to keep in mind its potential ethical limitations. Memories, in particular, are highly personal and are critical to our personality and conception of ourselves. The manipulation of memory, whether to obliterate unwelcome memories or reinforce fading ones, has implications for who we are as individuals. Therefore, as our ability to deliver real-time dynamic stimulation in the clinical setting grows, a rigorous ethical framework will need to be developed to ensure that such technology can be used in an appropriate and responsible manner.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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