Deep Brain Stimulation for Amelioration of Cognitive Impairment in Neurological Disorders: Neurogenesis and Circuit Reanimation

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Abstract
Acute (e.g., traumatic brain injury or stroke) and chronic (e.g., dementia or Parkinson’s disease dementia) neurological disorders that involve cognitive impairment and dysfunctional neural circuits always lead to a dreadful and costly experience for patients and their families. The application of deep brain stimulation for the treatment of neuropsychiatric disorders has shown great potential to modulate pathological neural circuits and trigger endogenous neurogenesis. We summarize several important clinical and translational studies that utilize deep brain stimulation to improve cognition based on the potentiation of neural plasticity and neurogenesis. In addition, we discuss the neuroanatomy and cerebral circuits implicated in such studies as well as the potential mechanisms underlying therapeutic benefits.

Keywords
deep brain stimulation, neurogenesis, Alzheimer's disease, dementia, learning and memory

Introduction
Deep brain stimulation (DBS) is a promising treatment for movement disorders and some neuropsychiatric disorders. Proposed mechanisms underlying clinical improvement are based on neuromodulation of pathological signal processing in the brain. Although the specific mechanisms by which DBS exerts benefit are still relatively unknown, increasing evidence has shown it might involve multiple physiological mechanisms¹,². Importantly, the modulation of specific neural circuits via DBS also results in increased neurogenesis, synaptic plasticity, and cell survival by upregulating specific genes³–⁵. Over the last decade, several studies have advanced the application of DBS and have shown the ability to improve learning and memory by targeting particular brain structures at specific time points⁶. In this review, we highlight several pivotal brain regions and their connecting circuitry to provide insights into the underpinnings of how DBS may augment cognition to overcome pathology-induced deficits.

DBS in Neurological Disorders
Medial Temporal Structure
Early case studies that focused on the removal of hippocampal structures to treat epilepsy were the first to reveal the importance of medial temporal lobe function to memory⁷–⁹. In line with these studies, experiential memory phenomena (déjà vu) were associated with medial temporal lobe seizures. Following previous reports about temporal lobe stimulation inducing feelings of familiarity, Bartolomei was the first to show that specific entorhinal cortex stimulation could cause more déjà vu or context-specific memories¹⁰.

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The concept was further exemplified by another study utilizing stimulation of the medial temporal lobe in epileptic patients, which evoked autobiographical memories. These studies suggest that the medial temporal lobe plays a vital role in declarative memory function. Functional imaging studies show activation of the medial temporal lobe (including the entorhinal cortex) exclusively happened during memory encoding. Furthermore, neuronal recordings of the medial temporal lobe have revealed the correlation between memory strength and neuronal activity and spike timings and local field potential during engagement of a learning task. Capturing activation patterns in the medial temporal lobe have further advanced our understanding of how the structures function during mnemonic processes. Based on these results, the activation of large neural networks within the medial temporal lobe seems to be strongly correlated with encoding or retrieving memory and neuromodulation of these areas may facilitate cognitive processes to improve these functions.

Given the prerequisite role of medial temporal structures in memory encoding, these areas have been under vigorous investigation to explore whether the influence of neural activity could lead to better cognition. Suthana et al. demonstrated spatial navigation enhancement in epileptic patients when stimulation was applied to the entorhinal cortex while patients learn the location of spatial landmarks. In addition, the power of the theta rhythm increased after electrical stimulation in all four patients’ entorhinal cortex; theta rhythm is considered to be the electrophysiological hallmark for improvement of spatial learning. In contrast, direct stimulation of the hippocampus, a key structure in the spatial memory circuit, did not reveal similar improvements in spatial learning, indicating that stimulation of the cortical afferent input into the hippocampus might be more effective as a target for DBS to improve cognition. This phenomenon not only suggests memory is supported by the hippocampus but also indicates that disruption of local neuronal circuits within the hippocampus could result from stimulation of hippocampal neurons above the threshold. Recent rodent studies have shown that encoding and mnemonic processes of memory could be manipulated or enhanced when hippocampal electrical stimulation matched hippocampal activity. With optogenetic manipulation, reactivating or deactivating hippocampal neurons that are activated during learning results in specific memory recall or erasure. These studies demonstrate the importance of temporal and physiological properties of electrical stimulation, having the ability to disrupt or enhance cognitive function.

**Fornix and Hypothalamus**

A critical aspect of how DBS affects the brain depends on its location within the pathological neuronal circuitry. In the case of Parkinson’s disease, electrodes are implanted in the subthalamic nucleus (STN) or globus pallidus (GP), which are implicated in neural circuits involving motor control, to ensure maximal clinical benefits on patients’ motor symptoms. When DBS is used to treat psychiatric disorders (e.g., obsessive-compulsive disorder) the target brain regions include the ventral capsule/ventral striatum or limbic portion of the STN. These areas further highlight that DBS not only influences the regional deep nuclei but also could be viewed as circuit modulators of afferent to efferent target neurons. Studies done in humans to elucidate the mechanisms of learning and memory rely on epileptic patients with implanted recording and stimulation electrodes in the brain to identify epileptic foci. This situation also provides an opportunity to explore whether electrical stimulation enhances spatial memory in epileptic patients. A serendipitous finding showed that a morbidly obese patient implanted with fornix/hypothalamus DBS electrodes had stimulation-responsive autobiographical memory recall. Following this unexpected evoked memory, fornix DBS was tested in a double-blinded study to see if it would increase memory recollection. In addition, fornix DBS also increased activity in the ipsilateral mesial temporal lobe as shown on standard low-resolution electromagnetic tomography (sLORETA), demonstrating that DBS in the fornix could drive activity in the medial temporal lobe throughout the limbic circuit.

To explore the evidence of fornix DBS for treating patients with Alzheimer’s disease (AD), Laxton et al. followed six patients with mild AD implanted with DBS systems targeting the fornix and hypothalamus. After 1 year of DBS treatment, the severity of AD, as assessed by the Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-Cog) subscale, improved or ceased to progress with DBS. sLORETA revealed specific activation of the mesial temporal lobe structures of patients immediately after DBS. At longer latencies, activation patterns shifted to the posterior cingulate and medial parietal lobe. In line with this, a positron emission tomography study in the same report also demonstrated metabolic reversal of reduced cortical glucose utilization in the temporal and parietal lobes of patients with AD, providing more evidence on how DBS facilitates activation of remote limbic areas and potentiates memory improvement. These results suggest that DBS can improve memory through modulation of neural activity within memory circuits involving the fornix and hypothalamus. Working within this framework, fornical DBS was explored to treat Rett syndrome, a childhood intellectual disorder. In a rodent model of Rett syndrome, 2 weeks of DBS treatment ameliorated the deficit of contextual fear memory and spatial learning in a Morris water maze. In addition to behavioral improvement, the study further demonstrated that DBS enhanced hippocampal neurogenesis and improved long-term potentiation, potentially revealing a new underpinning of cognitive enhancement from DBS.

Continuous or open-loop electrical stimulation is the dominant form of clinically applied DBS. However, converging evidence suggests that patterned stimulation can
increase the efficiency of DBS to augment signal processing in the brain. The utilization of theta burst stimulation in the fornix showed improved spatial memory benefit over conventional continuous DBS. This dynamic stimulation also quickly normalizes decreased theta-gamma comodulation in amnesic animals. Another report using traumatic brain injury in a rodent model confirmed that patterned stimulation of the fornix using intermittent bursts in the theta range could also rescue cognitive impairment. Results of this nature may arise due to the inherent theta frequencies of the hippocampus, whereby theta-frequency phase locking of single neurons in the hippocampus has been linked to memory retrieval capability. Given the immediate reversal of the electrophysiological abnormality, burst pattern stimulation (200 Hz in 100-ms trains, 5 trains/sec, 100 μs, 7 mA) of the fornix was able to show faster improvement of spatial memory, further highlighting the importance of stimulation parameters settings with DBS.

**Basal Ganglia**

The basal ganglia are associated with motor control and execution and have been primarily targeted in movement disorders. DBS, therefore, emerges as a promising treatment, and GP DBS could suppress abnormal overactivity in the motor cortex and associated motor circuits. In addition, the basal ganglia are also composed of multiple parallel loops tied to associative and limbic circuits, which all point to a prerequisite role for the basal ganglia in learning and memory. Neuronal firing within the dorsal and ventral striatum has been shown to encode animal and human behavior during tasks involving the evaluation of expectations (e.g., reward responses). For example, neural activity in the caudate nucleus is positively correlated with the rate of learning during an associative learning task. Even delivery of microstimulation to the caudate nucleus (dorsal striatum) during the reinforcement period increased the learning rate.

In contrast, neurophysiological evidence showed that neuronal activity of the nucleus accumbens (NAc) in non-human primates increased during the go-cue (initial) stage of a visual-motor associative learning task, indicating these neurons are associated with exploitation in reward-based reinforcement learning. This evidence suggests that the ventral striatum is associated with the central representation of reward and therefore plays essential roles in controlling motivation for goal-directed behavior. Taking advantage of spatially and temporally precise functions of the dorsal and ventral striatum in associative learning, Katnani et al. first adopted temporally coordinated DBS in the NAc and caudate nucleus for non-human primates. The results showed that both temporally specific DBS in the NAc and caudate nucleus could reach significantly better learning performance, compared with stimulation to each target alone. This finding not only highlights the close coordination between ventral and dorsal striatum in associative learning but also highlights different roles involved in behavioral initiation (motivational relevance) to encoding rewarding outcome probability.

**Mechanisms of DBS for Cognition Improvement in Neurological Injuries**

**Stimulation and Activation of Cognitive Circuits**

Although the precise mechanism of fornix and hypothalamus stimulation is as yet unknown, axonal activation within the fornix provokes widespread downstream connected neural structures, including the impaired default mode network in AD. Several animal studies have also shown that electrical stimulation within the limbic circuit may influence cognitive function and induce memory recall. Stimulation was even proposed to activate the Papez circuit; whether DBS of the fornix, hypothalamus, or mamillary-thalamic tract, or all are responsible for memory enhancement remains to be elucidated. Furthermore, the effectiveness of using DBS to enhance cognition could depend on which nuclei are targeted, and therefore, different electrical parameters are used. Through exploration of animals with dementia, we might provide the optimal stimulating parameters and target selection for humans with neurodegeneration and memory impairment.

DBS has been proven to enhance spatial learning memory in both rodents and humans, and the effect is event related. An essential aspect of both studies with entorhinal stimulations to enhance spatial memory all indicate the importance of stimulation during the learning phase when recruitment of cognitive circuit and plasticity formation are demanded. Future studies are necessary to compare the effectiveness of applying stimulation at different stages of the memory process, from learning, encoding, and storing to retrieval.

**Incorporation of Neurogenesis Into Memory Circuits**

Impairment of neurogenesis is associated with the severity of cognitive impairment in AD. Although stem cell-based approaches might be a potential treatment, significant obstacles for cell transplantation remain as we strive to understand controlling stem cells. Nonetheless, stimulation of the entorhinal cortex induced neurogenesis of the dentate gyrus and subsequent recruitment of these ‘new neurons’ within hippocampal circuits, which showed promise for cognitive augmentation. Formation of specific spatial navigation was only improved at 6 weeks rather than at 1 week after stimulation in this study, and this delay-dependence explains why adult-generated dentate granule cells are necessary to mature and integrate into the cognitive circuit supporting water maze memory. Few studies using direct electrical stimulation of the hippocampus in rodents and humans have shown negative results for subsequent memory acquisition. These findings imply that manipulation or modulation of neural activities within cognitive circuits may be
more effective than direct stimulation of memory storage sites, such as the hippocampus, to improve memory.

Anterior thalamus (AT) DBS has been shown to activate the cerebral cortex in epileptic patients. Given that the AT directly connects with the hippocampus, AT DBS in rodents also revealed increased hippocampal neurogenesis and resulted in better cognitive performance. Recruitment of newly formed neurons implicated in the cognitive process indicates the importance of stimulation duration, and it may take time to ensure long-term plasticity and identify the significant difference in humans. Based on the causal relationship between improvement of learning and memory and expedited neurogenesis in the hippocampus after DBS, some studies have tried implantation of stem cells or neurotrophic factor to reach similar enhancement of cognition.

Future Applications

Given the dynamic nature of the mnemonic learning process, from information encoding to memory retrieval, how we harness DBS and cell repair in a versatile fashion is a prerequisite to achieving enhancement of cortical plasticity and leading to improvement of implicated cognitive circuitry. Traditionally, targeted neural excitation or inhibition via electrical current, mostly from DBS or cortical stimulation devices, rely on continuous stimulation, and it is hard to modulate these settings according to simultaneous neural activity detection. Technological advances in neural interfaces are providing more dynamic devices, which combine precise spatial and temporal resolution of neural signals and high fidelity and longevity of stimulation characteristics. For example, cortical reorganization within the motor cortex resulting from recorded action potentials in one location to deliver electrical stimuli to distant sites has been proven through autonomously artificial connection cortical implant. This approach could ensure the causal relationship between dynamic cognitive demand and stimulation to boost cognitive demand function.

Conclusions

The heterogeneity of neurological diseases with cognitive impairment indicates that their origins may lie in the dysfunction of multiple brain regions. The development of novel treatments to improve cognition is anticipated upon the identification of neural substrates within the cognitive circuit. Neuromodulation and the ensuing neurogenesis have emerged as a potential treatment of specific contexts of memory function. Our understanding of how neuromodulation works could help decipher the memory process and ameliorate dysfunctional neural circuits for patients’ impaired cognition.

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