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Brain Stimulation for Neurological and Psychiatric Disorders, Current Status and Future Direction.

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Abbreviations: cerebral blood flow (CFB), deep brain stimulation (DBS), high frequency stimulation (HFS), transcranial magnetic stimulation (TMS), rapid-rate magnetic stimulation (rTMS), Parkinson's disease (PD), Centromedian thalamus (CM), subthalamic nucleus (STN), substantia nigra pars reticulata (SNr), Globus pallidus internalis (GPi), ventral intermediate thalamic nucleus (Vim)

Abstract

Interest in brain stimulation therapies has been rejuvenated over the last decade and brain stimulation therapy has become an alternative treatment for many neurological and psychiatric disorders, including Parkinson's disease (PD), dystonia, pain, epilepsy, depression and schizophrenia. The effects of brain stimulation on PD are well described and this treatment has been widely used for such conditions worldwide. Treatments for other conditions are still in experimental stages and large-scale, well-controlled studies are needed to refine the treatment procedures. In the treatment of intractable brain disorders, brain stimulation, especially transcranial magnetic stimulation (TMS), is an attractive alternative to surgical lesioning as it is relatively safe, reversible and flexible. Brain stimulation, delivered either via deeply implanted electrodes or from a surface mounted transcranial magnetic device, can alter abnormal neural circuits underlying brain disorders. The neural mechanisms mediating the beneficial effects of brain stimulation however are poorly understood. Conflicting theories and experimental data have been presented. It seems that the action of stimulation on brain circuitry is not limited to simple excitation or inhibition. Alterations of neural firing patterns and long term effects on neurotransmitter and receptor systems may also play important roles in the therapeutic effects of brain stimulation. Future research on both the basic and clinical fronts will deepen our understanding of how brain stimulation works. Real-time computation of neural activity allows for integration of brain stimulation signals into ongoing neural processing. In this way abnormal circuit activity can be adjusted and thus provide information for optimizing therapeutic brain stimulation paradigms.

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The modern era of brain stimulation treatment started in the 1950's with an early application of deep brain stimulation (DBS) to treat patients with intractable pain. Interest in DBS as a treatment for movement disorders has surged since late 1980s. With the development of new devices such as transcranial magnetic stimulators and refinements in DBS paradigms, brain stimulation has been gradually replacing surgical ablation as a uniquely promising clinical procedure for the treatment of many neurological disorders that are unresponsive to existing therapies.

Movement disorders.

Parkinson's disease.

Although pharmacological dopamine (DA) enhancement has therapeutic benefits for PD, long term use also produces the undesirable side effect of dyskinesia. Both surgical ablation and DBS were explored during 1970's and 1980's. Benabid et al. (1987) reported in 1987 that high frequency stimulation of the ventral intermediate thalamic nucleus (Vim) can suppress the tremor syndrome of PD. During the following decade, we witnessed tremendous interest and great success of DBS treatments in PD.

Currently, the major targets of DBS for PD treatment are the subthalamic nucleus (STN) and the internal segment of globus pallidus (GPi) within the thalamocortical basal ganglia pathways. Stimulation of each of these regions has been shown to varying degrees to improve Parkinsonian signs. However, the mechanisms of DBS action in these regions are poorly understood.

According to the classic model of the direct and indirect pathways of the basal ganglia thalamocortical system (DeLong, 1990), depletion of DA in the substantial nigra exerts dual effects on its projection area, the striatum. DA depletion can produce disinhibition via D₂ receptors and inhibition via D₁ receptors of separate populations of medium spiny neurons in the striatum. Since these two

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populations of cells mediate the direct (D₁ type) and indirect (D₂ type) pathway signals respectively, the net effect of DA depletion is likely to enhance the inhibitory basal ganglia output to the thalamocortical circuit. The similarity of therapeutic effects obtained from DBS and lesions of the STN and GPi are consistent with the hypothesis that DBS may mimic the effects of a lesion by disabling (inhibiting) the nuclei (Figure 1). Some electrophysiological evidence does support this local inhibition theory for the action of DBS. Dostrovsky et al. (2000) recorded neural activity in the GPi during surgical implantation of stimulation electrodes. Profound inhibition was observed at stimulation frequencies ranging from 5 to 300 Hz. High frequency stimulation (HFS) of the STN also produced long lasting inhibition of the STN and substantia nigra pars reticulata (SNr) in anesthetized rats (Benazzouz et al., 2000).

A number of *in vitro* studies have been performed to investigate the channel and membrane property changes induced by DBS. Beurrier et al. (2001) conducted a patch clamp study in brain slices and reported that HFS similar to that used in the clinic to treat PD inactivates the STN. This result was attributed to the blockade of persistent Na⁺, L- and T-type Ca²⁺ currents. Magarinos-Ascone et al. (2002) found time-dependent responses of STN neurons during DBS in an *in vitro* slice preparation. The neurons in the STN initially followed HFS beyond 100 spikes/s. After 10 s of HFS, the cells switched to a burst firing mode and then totally shut down after another 10 s. Like Beurrier et al. (2001) the authors attributed the silencing effect of HFS on STN neurons to the inactivation of Na⁺ mediated action potentials. A recent study by Do and Bean (2003) examined dynamic firing patterns in dissociated rat STN neurons. They found that a resurgent Na⁺ current, together with a persistent Na⁺ current, may be responsible for the generation of high tonic firing and burst firing patterns in STN neurons. These two Na⁺ currents were under the regulation of a slow inactivation process to maintain a constant firing rate. In contrast to the previous findings which suggested that HFS silenced STN cells, Do and Bean (2003) found that 75 Hz stimulation could drive a subpopulation of STN cells to fire at a higher, yet regular

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firing. Thus, the authors suggested that the firing pattern, rather than the firing rate, of the STN neurons could account for the therapeutic effects of DBS. However, caution must be exercised in the interpretation of *in vitro* experiments since normal anatomic connections of STN neurons are severed preclude DBS-induced changes in network processing from being investigated. In addition, the specifically selected stimulation parameters that produce the electrophysiological results in such experiments may not be equivalent to those used in behaving subjects with therapeutic benefits (Chang et al., 2003; Hashimoto et al., 2003).

Recent studies have shown that the effects of DBS on the projection areas of the STN are inconsistent with the simple view that DBS works by inactivation. An increased firing rate in the GPi with stimulation has been demonstrated in behaving primates (Hashimoto et al., 2003). In this study the GPi neurons discharged 3 to 4 ms after the STN stimulation pulse and the effects of DBS on GPi firing rates and behavioral benefits appear to be co-dependent upon stimulus intensity. This correlation between an increase in pallidal neuron firing rates and therapeutic benefits is inconsistent with the classic model of the basal ganglia thalamocortical pathway which predicts that enhanced inhibitory output from GPi would further inhibit the thalamocortical feedback loop and thereby worsen the parkinsonian motor symptoms. Anderson et al. (2003) recorded neural activity in the motor thalamus during high frequency stimulation of the GPi in a monkey model of PD and corroborated Hashimoto's findings by showing a decrease in motor thalamic activity during DBS. These findings raise the possibility that DBS may differentially act on cell bodies and axons in the stimulation sites. This hypothesis was supported by a computer modeling study that indicated that high frequency stimulation can simultaneously suppress cell bodies and excite axons (McIntyre and Grill, 1999). Together with the finding that STN-high frequency stimulation induced increase in glutamate release in the SNr (Windels et al., 2000), these results suggest that the postulated overactivation of basal ganglia output, as

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represented by high firing rates in the GPi and SNr and low firing rate in the motor thalamus in the Parkinsonian condition, may not be the pathophysiological attribute responsive to DBS treatment. Both Hashimoto and Anderson's studies did show, however, a reduced burst firing pattern during DBS, which may support the notion that DBS may exert its therapeutic effects via a modulation of basal ganglia firing patterns rather than by changing firing rates. Similar results have also been observed with a rodent model of DBS (Chang et al., 2002). In summary, these latter findings suggest that DBS induced increases in GPi firing rates and decreases in thalamic firing rates, though abnormal, may effectively interrupt pathogenetic bursts or oscillatory firing patterns and thus improve parkinsonian syndromes.

Dystonia.

DBS has also been tested in other movement disorders such as dystonia and essential tremor. Dystonia is a hyperkinesia disorder characterized by uncontrollable movements of antagonist muscles. Electrophysiologic studies have demonstrated a decrease in neural activity in the basal ganglia output regions, such as the GPi in this condition (Vitek et al., 1999). Such findings are in line with the model of reduced basal ganglia inhibitory output for hyperkinetic disorders, like dystonia. However, a recent study (Hutchison et al., 2003) has challenged this hypothesis by showing similar spike frequencies of GPi neurons in patients with dystonia and patients with PD. The authors attribute the discrepancy of the results to the use of propofol anesthesia, which can significantly reduce spike activity in GPi neurons. As DBS of the GPi has proven to be effective in alleviating dystonia syndromes as well as PD symptoms, the mechanisms underlying GPi stimulation on behavioral improvements are more likely to involve modulation of network firing patterns rather than simple GPi inhibition. However, pilot studies exploring STN stimulation as a treatment for dystonia have pointed to other possible mechanisms. Interestingly, *high* frequency stimulation of the STN worsens dystonia symptoms while *low* frequency stimulation improves these symptoms (Benabid et al., 2001). This result fits well with the hypothesis

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that while high frequency stimulation of the STN may be inhibitory, low frequency stimulation of the STN could be excitatory, which in turn would enhance GPi inhibitory output thus reducing the hyperkinesia associated with dystonia.

Epilepsy.

Approximately 10% of epileptic cases can be classified as medically intractable, unresponsive to drug treatments and without a defined epileptic focus amenable to surgical removal. This significant population of several million patients could potentially benefit from DBS therapy (Figure 2).

Initial attempts to use brain stimulation to treat epileptic patients started in the 1970's. Because the cerebellum has abundant inhibitory GABAergic Purkinje cell output, it was selected as a stimulation site (Cooper et al., 1973). In an open study, Davis and his colleagues found long lasting beneficial effects of cerebellum stimulation on tonic-clonic and complex partial seizures (Davis and Emmonds 1992).

The thalamus is the critical region for relaying neural signals to the cerebral cortex and is thought to be involved in the epileptogenic process. A number of studies have explored the therapeutical potential of thalamic stimulation for epilepsy treatment. Cooper and his colleagues stimulated the anterior thalamic nucleus to treat complex partial epilepsy on the grounds that this region relays limbic signals to the cingulate cortex (Cooper and Upton, 1985). A recent study also showed beneficial effects of anterior thalamic stimulation on generalized tonic-clonic seizures (Lozano et al., 2000). The centromedian thalamus (CM) is another thalamic region that is relevant to epileptogenesis. Velasco et al., (1987) first reported beneficial effects of CM stimulation on seizure control. Later, a long-term study of CM stimulation effects revealed a persistent decrease in generalized tonic-clonic seizures for a period of 7 to 33 months (Velasco et al., 1995). However, a double-blind, cross-over study did not show significant effects of CM stimulation on intractable seizures (Fisher et al., 1992). A recent mapping study

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suggested that this discrepancy of results may be attributable, at least in part, to differing stimulation loci within the CM. Selective stimulation of the ventral lateral part of the CM could recruit and desynchronize the direct current shift response, and this response was directly correlated with desired antiepileptic effects (Velasco et al., 2000). In addition to stimulating potential pathways of epileptic network, recent reports showed that DBS directly targeting the seizure focus had beneficial effects on intractable temporal lobe seizures (Vonck et al., 2002).

The basal ganglia have been hypothesized to be involved in the transition from limbic to generalized motor seizures. Early reports by Hayashi (1952) showed bilateral lesions of either the globus pallidus or SNr blocked clonic convulsion induced by chemical stimulation. An increasing number of reports have been consistent with a role for the basal ganglia in epileptogenesis since the 1980's. Most of studies have focused on the SNr, the output nucleus of the basal ganglia where the direct and indirect pathways converge. Gale was the first to describe a nigral control epilepsy system. The system is thought to control seizures by the nigrotectal pathway. Garant and Gale (1987) reported that bilateral ablation of the superior colliculus in rats abolished the anticonvulsant effect of microinjection of muscimol, a GABA agonist, into the substantia nigra. This result suggests that anticonvulsant effects of nigral manipulation are a result of the disinhibition of neurons in the superior colliculus that receives GABAergic inhibitory input from the SNr. Other basal ganglia structures, either directly or indirectly connected to the SNr, may also influence epileptic seizures. GABA receptor antagonists microinjected into the striatum have been shown to prevent amygdala kindling-induced seizures in the rat (Cavalheiro et al., 1987). A number of recent studies have focused on the role of the STN in epileptic seizures. GABA receptor agonist infusion into the STN significantly reduces flurothyl-induced clonic seizures, probably by decreasing excitatory input to the SNr (Veliskova et al., 1996).

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Based on these anticonvulsant experiments in the basal ganglia, DBS studies have been performed in the basal ganglia to investigate epileptic seizure suppression. Clinical trials have been performed to study the effect of DBS of the STN on intractable epileptic seizures (Chabardes et al., 2002). Animal experiments revealed that DBS of several basal ganglia regions can suppress seizures. The effective stimulation sites included the SNr (Morimoto and Goddard, 1987; Velisek et al., 2002) and the STN (Vercueil et al., 1998). Most of these studies used high frequency stimulation capable of effectively treating PD. Although the neural mechanisms underlying DBS at such frequencies are a matter of debate, the prevalent view favors the local inhibition theory. This view is supported by findings that pharmacological inhibition of the STN and SNr can block seizure expression and that GABA receptor antagonism can block the anticonvulsant effects of SNr stimulation (Morimoto and Goddard, 1987). However, low frequency stimulation (10-30 Hz) of the SNr also inhibited cortical epileptiform spikes. This result was attributed to inhibition of the thalamocortical re-exciting loop (Sabatino et al., 1988). Since epileptiform discharge is characterized by hypersynchronized action potentials, it may be that DBS works by disrupting network synchronization, rather than by simply inhibiting the local circuit. Evidently, in order for stimulation to block seizure activity it needs to be applied to a pivotal structure in the network that gates the propagation of epileptiform activities. Presently, the SNr is an attractive candidate for such a pivotal structure in kindled and chemical induced seizures, however it is not known whether other structures may play a critical role in the propagation of other types of epileptic seizures.

Pain.

Clinical application of DBS to treat intractable pain started half century ago (Pool et al., 1956). Several brain regions have since been identified as promising targets for DBS treatment of pain, including the somatosensory thalamic nuclei (Mazars, 1975), the motor cortex (Tsubokawa et al., 1993),

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the internal capsule (Adams et al.,1974), periaqueductal gray area, pariventricular gray, the raphe nuclei (Oliveras et al., 1978) and other brain regions near the central gray. Based on anatomic and functional characteristics, DBS procedures for the treatment of pain can be generally classified into two categories. The first category is characterized by stimulation of sites around medial mesen-diencephalon regions, such as the periaqueductal gray, pariventricular gray and raphe nuclei. Stimulation of these regions appears to induce the release of endogenous opioids and thereby effectively treat nociceptive, peripheral pain. The second category of DBS pain treatment includes stimulation of the motor cortex, somatosensory thalamus and internal capsule. Stimulation of these sites can more directly attenuate deafferentation and neurogenic pain.

Early studies linked the effects of periaqueductal/pariventricular gray stimulation on pain control to the release of endogenous opioids. Analgesia induced by DBS of the periaqueductal gray can be blocked by the opiate antagonist naloxone (Akil et al., 1976) and increased levels of β -endorphin have been found in the ventricular fluid of patients subjected to DBS of the pariventricular gray (Young et al., 1993). However, other studies have failed to demonstrate a blockade of stimulation induced analgesia with naloxone (Yaksh et al., 1976). A detailed analysis of stimulation sites may provide an explanation for the discrepancy between these results. Cannon et al., (1982) pointed out that naloxone elevated the stimulation threshold in the ventral but not dorsal part of the periaqueductal gray. In the clinic, stimulation has usually been applied to rostral regions of the central grey such as the pariventricular gray in order to avoid undesirable side effects associated with periaqueductal gray stimulation. β -endorphin cell bodies and axons have been found in the arcuate, infundibular and periventricular nucleus of the hypothalamus, periaqueductal gray and other medial brain and brain stem regions. Stimulation of periaqueductal gray releases β -endorphin in periaqueductal gray (Basbaum and Fields, 1984) and activates descending pathways through the raphe nuclei in the ventral periaqueductal gray and inferior to

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the locus coeruleus. Serotonergic fibers from the raphe nuclei and noradrenergic fibers from the locus coeruleus then project through the dorsolateral funiculus to the dorsal horn of the spinal cord (Hosobuchi et al., 1979; Young et al., 1993). This input may activate opioid interneurons which inhibits the conduction of signals from noxious stimuli. This model is supported by the finding that lesions of the dorsolateral funiculus blocked both morphine and periaqueductal gray stimulation induced analgesia (Basbaum et al., 1976).

The mechanisms for the analgesic effects induced by somatosensory thalamus stimulation have not been elucidated. One hypothesis postulated by Mazars is that deafferentation pain is caused by a loss of proprioceptive signals reaching the sensory thalamus. Thalamic stimulation may therefore be able to compensate this loss of sensory input (Mazars, 1975). The somatosensory thalamus relays peripheral sensory signals to the cortex so it is no surprise that stimulation of these critical relay nuclei in the sensory pathway would alter the transmission of sensory signals. Recent studies using brain imaging and electrophysiological methods have further revealed significant roles of the cingular and insular cortices in nociceptive transmission. Neurons in the cingular cortex can be activated by noxious stimulation in experimental animals (Wang et al., 2003) and humans (Hutchison et al., 1999). Positron emission tomography studies revealed an association between increased activity in the anterior cingulate cortex and the affective aspect of pain (Ranville et al., 1997). Because the cingulate cortex receives nociceptive input via the thalamus (Wang et al., 2003), the ascending nociceptive stimuli signals it receives can be altered by thalamic stimulation. In concordance, positron emission tomography studies demonstrated enhanced activity in the anterior cingulate cortex during thalamic stimulation in a patient with chronic pain (Davis et al., 2000).

It may also be that antidromic activation of descending nociceptive modulating pathways mediates analgesia effects of thalamic stimulation. Gerhart et al. (1983) reported that stimulation of the ventral

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posterior lateral thalamus nucleus could inhibit spinothalamic tract neurons in anesthetized monkeys. The response of spinothalamic tract neurons to electrical stimulation of A and C fibers in the sural nerve were reduced during thalamic stimulation. Lesioning of the dorsolateral funiculi bilaterally blocked the inhibitory effects of thalamic stimulation. A correlation between pariventricular gray stimulation and sensory thalamus responses was reported recently (Nandi et al., 2002). Low frequency stimulation (2-25 Hz) of the pariventricular gray produced coincident reduction of 0.2-0.4 Hz thalamic field potentials and relief of pain. Meanwhile high frequency (50-100 Hz) pariventricular gray stimulation neither altered thalamic field potentials nor the pain syndrome. Since the onset of changes in thalamic activity and pain threshold are almost instantaneous, direct neural circuits, in addition to the descending endogenous opioid pathway, are expected to be involved in this pariventricular gray stimulation effects. It is likely that thalamic stimulation could activate both thalamocortical and descending inhibitory pathways to modulate nociceptive processes.

Chronic motor cortex stimulation has been used recently to treat neuropathic facial pain (Rainov and Heidecke, 2003), deafferentation pain (Tsubokawa et al., 1993) and complex regional pain syndrome (Son et al., 2003). Stimulation of the cortical region capable of triggering stimulation induced muscle contraction in the affected limb generated a potent analgesic effect in that limb with the stimulation intensity set below the threshold for muscle contraction. Beneficial effects of motor cortex stimulation on deafferentation pain may be attributable to an inhibition of hyperactivity of deafferented nociceptive neurons and/or activation of non-nociceptive fourth order sensory neurons that inhibit hyperactive nociceptive neurons in the sensory cortex (Tsubokawa et al., 1993). An intact cortical spinal tract seems to be necessary to ensure effective analgesic results of motor cortical stimulation, suggesting that the mechanism involves modulation of the spinal nociceptive reflex (Katayama et al., 1998).

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In spite of extensive research and a long history of clinical application, there is no standard protocol for DBS treatment of pain, partially because of the variety of clinical pain symptoms. Clinical results, target selection and stimulation parameters have varied widely among reports (Levy et al., 1987). Well designed studies with sham-controlled, double-blind procedures and precise, subjective pain measures are needed to make a resounding evaluation of DBS effects on clinical pain management.

Psychiatric disorders.

The recently developed transcranial magnetic stimulation (TMS) technique has been replacing the common practice of electric shock as the preferred alternative in the treatment of a variety of psychiatric disorders such as depression and schizophrenia. TMS is a noninvasive, painless brain stimulation method that uses a magnetically induced current to stimulate the cortical regions of the brain. The method was first introduced by Barker et al. (1985) and has since been widely used as a powerful research and clinical tool. This technique can be used to study many basic central nervous system functions such as motor control, visual processing, neural plasticity, memory, speech and mood.

Depression.

Attempts to use TMS to treat depression started a decade ago. Antidepressive effects of low frequency TMS applied to the vertex were reported in small open studies (Hoflich et al., 1993). These pilot studies led to further exploration seeking better approaches of TMS treatment. Based on the known therapeutic effects of electroconvulsive therapy and evidence of abnormal frontal cortex function in depression, frontal cortex was selected as a target for TMS treatment. A lateralized effect of rapid-rate transcranial magnetic stimulation (rTMS) was discovered in healthy adult human subjects. Left prefrontal cortex stimulation resulted in increased sadness ratings and decreased happiness ratings in comparison with ratings reported with right prefrontal cortex stimulation (Pascual-Leone et al., 1996).

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Early attempts to use rTMS on the prefrontal cortex in medication resistant depressed patients however yielded contradictory results to that seen in the healthy subjects. Right prefrontal cortex stimulation, worsened, rather than improved, mood and anxiety ratings in depressed subjects. However, *left* prefrontal cortex rTMS significantly improved depression scores in depressed patients (George et al., 1998).

With the aim of understanding its action, imaging techniques have been employed to map brain activity during rTMS. A positron emission tomography study revealed opposite effects of high vs. low frequency rTMS of the left prefrontal cortex on regional cerebral blood flow (CBF) in depressed patients. High frequency (10-20 Hz) rTMS significantly increased CBF bilaterally in frontal, limbic and paralimbic regions while low frequency stimulation (1-10 Hz) decreased CBF in selected cortical and basal ganglia regions. The change in mood following the two rTMS frequencies were inversely related such that individual who improve with one frequency worsened with the other (Speer et al., 2000). The mechanism of the lateralized antidepressive effects generated by rTMS of the prefrontal cortex is unclear. But it seems that low and high rTMS of the right and left prefrontal cortices, respectively, can induce similar antidepressive effects (Klein et al., 1999a).

Schizophrenia.

TMS treatment of schizophrenia has been tested recently and produced mixed results. Stimulating the right prefrontal cortex with low frequency rTMS produced only marginal effects on core psychotic symptoms in schizophrenic patients (Klein et al., 1999b). However, successful rTMS treatment of schizophrenic auditory hallucinations has been reported. Hoffman and his colleagues found that 1 Hz rTMS applied to the left temporoparietal cortex significantly reduced auditory hallucinations in medication-resistant schizophrenic patients in double-blind, cross-over and parallel trials (Hoffman et al., 2000). The effect was attenuated by anticonvulsant agents, suggesting that the propagation of neural

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signals from the temporoparietal cortex to a more distributed network is crucial for the therapeutic rTMS effects (Hoffman et al., 2000).

Overall, brain stimulation for psychiatric disorders is still in an early experimental stage. Clinical application of TMS has not been standardized and reports from different groups can not be compared reliably due to the variation in stimulation parameters, experimental designs, patient selection and evaluation criteria. Large scale, long term studies are needed to translate this experimental procedure into standard clinical practice. Furthermore, the mechanism underlying the therapeutic effects of TMS is speculative at most. Better imaging techniques capable of capturing brain activity with high temporal and spatial resolution during TMS will help to define the brain regions activated by the stimulation. Animal models of depression and schizophrenia are important for understanding how TMS works. Several studies have reported TMS-induced changes in neurotransmitter systems. For example, Ben-Shacher et al., (1997) found that a single 25 Hz TMS session in the rat brain increased the DA turn-over rate in the frontal cortex and increased striatal and hippocampal dopamine levels. In addition to modulation of transmitter levels, TMS has been reported to alter the number of monoamine receptors in the animal brain, a single rTMS treatment induced a significant increase in 5-HT_{1A} receptor binding in the frontal and cingulate cortices and the olfactory nucleus (Kole et al., 1999). It should be noted however that caution needs to be exercised in interpreting the results from animal studies due to poor spatial resolution of stimulation sites and questionable behavioral models.

Summary and future directions.

Brain stimulation as a tool for treating neurological and psychiatric disorders has been advanced substantially over the last decade. It has been commonly used in the clinic to treat PD and other movement disorders and has great potential for further applications in epilepsy, pain and psychiatric

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disorders. Not included in this review is another exciting research field, the prosthetic use of brain stimulation to recover lost limb functions. Brain stimulation methods will continuously be advanced as researchers work toward the goal of safe and effective stimulation treatments of neurological and psychiatric disorders. A better understanding of the underlying mechanisms of the therapeutic effects of brain stimulation will be fundamental to achieving this goal.

Even in the case of PD, where DBS exerts remarkable therapeutical effects, there is still plenty of room for improvement. Varying patterns (regular vs. irregular), waveforms (sinusoidal vs. square) and intensities (constant vs. variable) of stimulation pulses should be tested based on the current understanding of the pathophysiological changes in the basal ganglia network associated with the parkinsonian condition. DBS can be programmed individually by feedback signals from close-loop, real time computation of neural network activity. This approach can provide more efficient stimulation with fewer side effects than the indiscriminate regular daily stimulation method currently in use. Furthermore, this brain-computer interface approach has the potential to correct pathological parkinsonian neural circuitry by training neural networks to learn a new motor skill thus achieving some permanent functional recovery.

Current treatments of epilepsy by brain stimulation are performed mostly on regular schedules that are not closely coupled with the onset of epileptic seizures. In clinical epilepsy management, there is nothing more important than precise prediction of impending seizures as unpredicted seizures can cause harm or even death for the epileptic patient. Thus seizure prediction is of the highest priority in epilepsy research and significant progress has been made already over the last 3 decades. Further advances in contingent (closed loop) brain stimulation with accurate seizure monitoring and prediction procedures may be more effective in breaking emerging epileptiform activity in the preictal period and thereby avoiding the side effects of long term medication and indiscriminative brain stimulation.

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Figure legends.

Figure 1. Tentative action of DBS in the basal ganglia thalamocortical pathways to treat Parkinson's disease. **A.** Schematic of the basal ganglia thalamocortical pathways in normal condition. Yellow blocks are the basal ganglia structures. Black arrows represent inhibitory projections and red arrows represent excitatory projections. **B.** The basal ganglia thalamocortical pathways in Parkinsonian condition. Degeneration of dopaminergic cells in the SNc results in a disinhibition of dopamine D₂ receptor mediated indirect pathway and an inhibition of D₁ receptor mediated direct pathway in the striatum. Alterations of neural activity in both pathways result in an increase in inhibitory output of the basal ganglia and thus inhibit the thalamic nuclei, this in turn will reduce excitatory thalamic inputs to the cortex. **C.** Tentative action of DBS of the STN and GPi to treat Parkinson's disease. High frequency stimulation of both the STN and GPi is postulated to induce local inhibition and restore normal basal ganglia output, thus alleviating the Parkinsonian symptoms. Other theories about the action of DBS exist, see text for detailed discussion. (EPN=entopeduncular nucleus. GPe=external segment globus pallidus. GPi= internal segment globus pallidus. SNc=substantia nigra pars compacta. SNr=substantia nigra pars reticulata. STN=subthalamic nucleus. VA=ventral anterior thalamic nucleus. VL=ventral lateral thalamic nucleus).

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Figure 2. Neural circuits involved in limbic (hippocampus, amygdala and piriform cortex) and tonic-clonic (superior colliculus, reticular formation and brain stem structures) seizures and action of brain stimulation on the circuits to treat epileptic seizures (stimulation sites were marked by black).

Stimulation of the cerebellum may activate inhibitory projections from Purkinje cells to the thalamus and spinal cord (via reticular formation and red nucleus) thus alleviating tonic-clonic seizures.

Stimulation of basal ganglia structures such as the STN and SNr may alter the activity in the amygdalohippocampal circuit, thalamus, superior colliculus and other brain stem structures to inhibit epileptic seizures. Anterior and centromedian thalamic stimulations may interrupt epileptiform activity relaying to the cortices thus suppressing epileptic seizures.

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Footnotes:

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