

Could DBS Provide Relief for Huntington's Disease?

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Targeted electrical stimulation via deep brain stimulation (DBS) – an established intervention to manage motor symptoms of neurodegenerative conditions such as Parkinson's disease – may hold promise for Huntington's disease (HD) patients as well.

Cleveland Clinic Neurologic Institute's HD team believes DBS could help maintain independence, relieve suffering and improve quality of life in select patients by modifying the disorder's motor and cognitive effects.

Based on results from other completed observational trials for HD, along with our experience treating neurodegenerative diseases and major breakthroughs in imaging research, especially in patients with HD, our team is planning to pursue a pilot study using DBS to modulate dysfunctional neural circuits.

Essentials of HD

HD is an autosomal dominant neurodegenerative disorder characterized by progressive motor, psychiatric and cognitive degeneration. It invariably leads to neurologic disability and premature death. In the United States, some 30,000 individuals have been diagnosed with HD symptoms (termed manifest disease), and twice as many who have the genetic defect implicated in HD have yet to manifest symptoms.

In individuals who inherit the HD gene mutation, an expansion of a cytosine-adenosine-guanine (CAG) repeat (>40) translates into a polyglutamine expansion that results in production of a neurotoxic mutant protein called huntingtin. The patient's age at the time of motor symptom onset correlates inversely with the number of repeated sequences.

Initial HD manifestations result from preferential degeneration of medium spiny neurons (90 percent of all neurons in the striatum) within the indirect pathway of the basal ganglia. Progression leads to cortical disassociation, whereby established simple and complex skills are decoupled. As a result, the individual can no longer acquire new behaviors and motor tasks and his or her existing abilities deteriorate.

Although research is ongoing, there is no cure available and symptomatic treatment options are limited.

Chorea is primary motor symptom...

Chorea, a randomly distributed and abrupt involuntary movement, is the distinguishing motor symptom of HD. Some individuals present with absence of voluntary movements (i.e., parkinsonism and dystonia), especially later in the disease. The risk of falls from changes in volitional movement is especially distressing for patients and families.

Tetrabenazine is the only FDA-approved agent for chorea associated with HD. The FDA recently accepted a new drug application for [deutetrabenazine](#), an extended-release agent for treating chorea in HD.

...But psychiatric and cognitive symptoms can be equally debilitating

Psychiatric and cognitive symptoms may be as debilitating as HD's motor symptoms. A dysexecutive

syndrome is characterized by difficulties with planning, organizing and cognitive flexibility. Progression to global dementia is relentless and resistant to intervention.

Psychiatric symptoms, which are managed as in the general population, include:

- Affective symptoms (depression, anxiety or mania)
- Thought and perceptual disturbances (delusional ideation and auditory or visual hallucinations)
- Behavioral changes (aggression, disorganization, perseveration or apathy)

Targeting HD with DBS

The idea of using DBS for HD is not new. During the past 10 years, individual cases and studies with small cohorts have been reported. The goal of most of these studies was to reduce the chorea. Safety seems to have been established, but much more knowledge is needed.

When to intervene in HD is a critical question. The success of DBS surgery is related directly to finding the specific brain target and intervening at the optimal time. Operating too early may pose unnecessary risk, whereas intervening after substantial brain degeneration occurs may not be beneficial. New therapies to realign cortical and subcortical structures or reinforce existing neuronal pathways may be possible by adjusting DBS leads implanted at certain nodes within the brain (Figure 1).

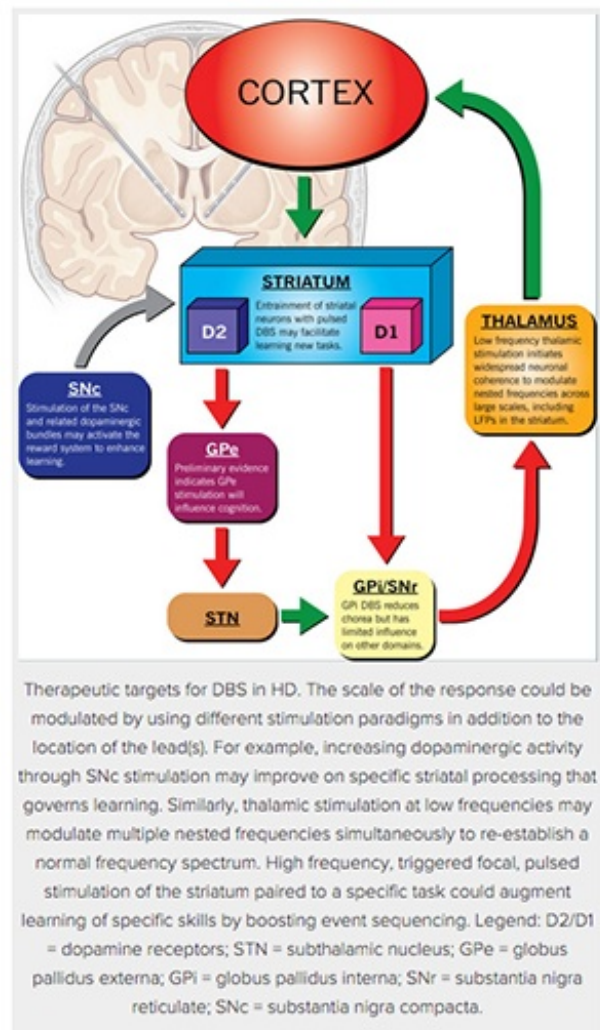
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Because the phenotypic expression of HD is heterogeneous, DBS may benefit only a select group of patients. Determining this subset is paramount to the success of any intervention.

We outline in detail our position regarding the use of DBS for HD in [a paper](#) our team recently published in *Frontiers in Systems Neuroscience*.

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