

# NEUROLOGY

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*Neurology* 2006;66:1799-1800

DOI: 10.1212/01.wnl.0000227468.17113.07

**This information is current as of June 29, 2006**

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.neurology.org/cgi/content/full/66/12/1799>

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Print ISSN: 0028-3878. Online ISSN: 1526-632X.





## STN DBS in PD

### Selection criteria for surgery should include cognitive and psychiatric factors

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Brain stimulation in the awake patient was systematically used by Penfield to map cortical functions during epilepsy and tumor surgery.<sup>1</sup> Although it was initially thought that such stimulation activated circuits much like turning on a tape recorder, electrophysiologic mapping during stereotactic surgery showed that high-frequency stimulation could temporarily disrupt normal neural activity and produce a functional lesion.<sup>2</sup> This eventually led to the use of deep brain stimulation (DBS) to replace Vim thalamotomy for the treatment of tremor.<sup>3</sup>

Now hailed as the holy grail of treatment for advanced Parkinson disease (PD), dystonia, and tremor, but also applied to the treatment of chronic pain, Tourette syndrome, depression, Huntington disease, obsessive-compulsive disorder, and epilepsy, DBS is established as a major technique in functional neurosurgery. The pathophysiologic basis of DBS is proposed to be the induction of a functional lesion, a cancellation of error messages, or perhaps the liberation of transmitter either locally or at a distance from the point stimulated.<sup>4</sup> Subthalamic nucleus (STN) DBS allows the reduction of dopaminergic medication by approximately 50% and provides long-term improvement of motor symptoms.<sup>5</sup> Stimulation of other brain targets (e.g., the globus pallidus internus) is of less benefit and does not reduce the need for dopaminergic medication.<sup>6</sup> This raises the question as to whether (and to what extent) STN DBS activates dopaminergic function in the brain. Like dopaminergic medication, STN DBS is a symptomatic treatment that does not prevent disease progression, as evidenced by the comparison of preimplant motor scores with those measured after 5 years of continuous stimulation.<sup>5</sup>

Dopaminergic treatment was introduced in the 1960s as a symptomatic remedy for motor symptoms

of PD.<sup>7</sup> It was later observed that long-term administration of levodopa produces motor complications, such as fluctuations and dyskinesias.<sup>8</sup> More recently it has been recognized that some patients under long-term dopaminergic replacement treatment suffer behavioral and psychological symptoms (so-called “dopamine dysregulation syndrome”).<sup>9</sup> There are intriguing similarities between behavioral reactions following STN DBS and those of chronic dopaminergic medication.<sup>10,11</sup>

In this issue of *Neurology*, two papers analyze neuropsychological, behavioral, and psychological outcome of patients with PD treated with STN DBS implants and show that nonmotor features may compromise the benefit of DBS. Smeding et al.<sup>12</sup> describe a prospective controlled study of STN-implanted patients with PD. DBS induced an executive dysfunction, characterized by reduced verbal fluency (found in virtually all previous studies), impaired naming speed, reduced selective attention, and delayed verbal recall. Although follow-up was only 6 months, the innovative study design (with a control group consisting of nonimplanted patients with PD) convincingly shows that bilateral STN stimulation worsens executive function. The effect sizes were in the medium to large range (Cohen's *d*). STN-implanted patients were emotionally labile, and 9% had significant psychiatric complications. A recent meta-analysis<sup>13</sup> found that large effect sizes (in the range of 1.5 SD), typically in the domain of verbal fluency, could be easily demonstrated, even at low power. However, more subtle effects, still of considerable magnitude (0.75 SD), were more difficult to detect consistently. This suggests that only certain individuals are susceptible to postoperative decline.

Schüpbach et al.<sup>14</sup> observed that despite improvement of motricity, activities of daily living and qual-

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Disclosure: The authors report no conflicts of interest.

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ity of life and social adjustment measures did not improve, affecting the patients' perception of themselves and their body, marital situation, and professional life. Only about half of the patients regained their previous employment. These data challenge the concept that STN implants should be performed "not too early, nor too late" in the disease course, and they indicate that thorough psychosocial evaluation should be performed following the clinical selection of a candidate patient for STN DBS. Both papers report psychiatric reactions similar to those observed in dopamine dysregulation syndrome: transient psychosis with mood changes, sexual disinhibition, and pathologic gambling. In most instances, these features were only ascertained through in-depth and unstructured interviews of the patients and caregivers.

These data raise new questions on the selection of appropriate patients for STN DBS. Most implanting centers follow inclusion criteria derived from the recommendations of the CAPSIT panel,<sup>15</sup> where the main emphasis is on the appropriateness of diagnosis and on motor features to predict motor response. There is a need for new consensus guidelines that include nonmotor (neuropsychological, psychological, social, and psychiatric) factors which predict outcome and adaptation after surgery and to identify which psychosocial interventions should be performed before and after implant. STN DBS has generally been considered safe from the neuropsychological viewpoint, because investigations consistently showed only a postoperative decline of verbal fluency, with inconsistent effects on other cognitive tasks.<sup>16</sup> It is not surprising that such artificial stimulation is not entirely benign, since both normal and dysfunctional circuits are disrupted.<sup>17</sup> The use of a control group allowed Smeding et al.<sup>12</sup> to show a decline of executive functions following STN DBS implants. When compounded by the effects of aging, this cognitive decline could accelerate the decline due to dementia and impair social adaptation. In addition to the cognitive costs, STN DBS also produces affective changes in some patients that cannot be attributed to inaccurate lead placement. Intra- and interpersonal adaptation can be difficult, with stressed couples relationships a common complication.<sup>14</sup> With the dramatic reduction in medications, some patients become apathetic and listless, so-called "psychic akinesia" in France; others show aggressive or manic behavioral symptoms sustained by medication, STN DBS, or both. The latter effect could be due to a "dopaminergic-like" action of STN DBS. Mood and behavioral changes contribute to exacerbate stressed relationships. Younger patients benefit more from STN DBS, but they are likely to have less advanced PD and therefore could wait longer for surgery. However, the older the patients are, the greater the likelihood that they will develop

a second disease (such as a dementia) that could make them more vulnerable to cognitive impairment following surgery.

One way of making sense of these data is to consider that the behavior seen after successful STN DBS is supported by circuitry outside of the domain of the basal ganglia. While it has proven difficult to predict neuropsychological outcome on the basis of presurgical cognitive profile (it being understood that patients with diagnosed dementia or symptomatic psychiatric disorders are excluded), response to levodopa challenge has been shown to be a good predictor of motor outcome.<sup>18</sup> Lacking are comparable predictive tests in the cognitive and psychiatric domains. As DBS technology is applied to more treatment-refractory conditions in both neurologic and psychiatric practice, caution is needed in patient selection, as well as in monitoring outcome.

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