

## Brief Report

## TRANSIENT ACUTE DEPRESSION INDUCED BY HIGH-FREQUENCY DEEP-BRAIN STIMULATION

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**C**ONTINUOUS high-frequency stimulation of the basal ganglia was recently introduced for the treatment of patients with advanced Parkinson's disease.<sup>1</sup> This treatment seems to be most effective when the electrodes are placed in the subthalamic nuclei.<sup>2,3</sup> Among the 20 patients treated successfully by bilateral subthalamic stimulation at our center, 1 woman had transient acute depression when high-frequency stimulation was delivered to the left substantia nigra, 2 mm below the site where stimulation alleviated the signs of Parkinson's disease. We describe here the results of detailed studies of the induction of major, reversible depression in this woman.

### CASE REPORT

A 65-year-old right-handed woman with a 30-year history of Parkinson's disease, who had severe rigidity, severe akinesia, and moderate tremor while resting, despite treatment with 900 mg of levodopa, 2.5 mg of pergolide, and 3 to 5 mg of lorazepam daily, and disabling dyskinesias induced by levodopa underwent bilateral implantation of electrodes in the region of the subthalamic nuclei for stimulation therapy. She had no history of psychiatric disorders or depression, even after the onset of Parkinson's disease, nor had she had mood fluctuations while she was receiving levodopa. The quadripolar electrodes implanted under stereotactic guidance<sup>3</sup> were connected by a cable under the scalp extending to a programmable pulse generator placed under the skin in the subclavicular area, like a cardiac pacemaker. Each electrode had four contacts numbered 0 to 3 from bottom to top, over a length of 7.5 mm, permitting a choice of the most effective sites of stimulation in the target region.

To identify the optimal site, the effect of stimulation through

each of the four contacts of each electrode was evaluated 10 days after surgery and 12 hours after the most recent dose of levodopa, according to our standardized protocol.<sup>3</sup> Briefly, the voltage for stimulation was increased in increments of 0.1 V, from 0 to 5 V, with a five-minute plateau after every additional 0.5 V, until a satisfactory reduction in symptoms of Parkinson's disease was obtained or an adverse effect, such as dysarthria, dystonic contraction, or paresthesia,<sup>2,4</sup> occurred. In most patients, stimulation through one or two contacts of each electrode improves parkinsonian symptoms, whereas stimulation through the other contacts has no effect or has adverse effects.

During this postoperative evaluation, the patient's face expressed profound sadness within five seconds after a continuous monopolar 2.4-V rectangular current with a pulse width of 60  $\mu$ sec and a frequency of 130 Hz was delivered for seven minutes through contact 0 of the electrode implanted on the left. Although still alert, the patient leaned to the right, started to cry, and verbally communicated feelings of sadness, guilt, uselessness, and hopelessness (Fig. 1), such as "I'm falling down in my head, I no longer wish to live, to see anything, hear anything, feel anything. . . ." When asked why she was crying and if she felt pain, she responded: "No, I'm fed up with life, I've had enough. . . . I don't want to live any more, I'm disgusted with life. . . . Everything is useless, always feeling worthless, I'm scared in this world." When asked why she was sad, she replied: "I'm tired. I want to hide in a corner. . . . I'm crying over myself, of course. . . . I'm hopeless, why am I bothering you. . . ." She had no hallucinations, nor were there any changes in her motor or cognitive symptoms of Parkinson's disease. The depression disappeared less than 90 seconds after stimulation was stopped. For the next five minutes the patient was in a slightly hypomanic state, and she laughed and joked with the examiner, playfully pulling his tie. She recalled the entire episode. Stimulation, performed at least twice, through the other contacts of each electrode did not elicit this psychiatric response.

Unlike stimulation through contact 0 of the electrode on the left, stimulation through upper contacts 1 and 2 of the left electrode and contact 2 of the right electrode reduced the motor symptoms of Parkinson's disease on the contralateral side. The patient was therefore treated with continuous bilateral stimulation through contacts 1 and 2 of the left electrode (2.4 V; pulse width, 60  $\mu$ sec; frequency, 130 Hz) and contact 2 of the right electrode (2.6 V; pulse width, 60  $\mu$ sec; frequency, 185 Hz). This treatment was sufficiently effective that drug therapy was discontinued one month after surgery. During treatment, the patient's score for dyskinesia dropped from 9 to 0 (range of possible scores, 0 to 13), and her score for motor fluctuation dropped from 5 to 0 (range, 0 to 7), as measured by parts IVA and IVB, respectively, of the Unified Parkinson's Disease Rating Scale,<sup>5</sup> a scale in which the highest score indicates the most severe disability, and 0 indicates no disability.

### RESULTS

Stimulation through contact 0 of the left electrode was repeated twice on two successive days (20 and 21 days after surgery) to verify the reproducibility of the depressive episode. Informed written consent was obtained from the patient for the study, and the procedure was recorded on videotape. Stimulation was performed in the same manner as during the original episode, after both the left and the right electrodes had been turned off for one hour. On the first day, stimulation was performed 12 hours after the most recent dose of levodopa. On the second day, a 200-mg dose of levodopa was administered one hour before the study to obtain maximal improvement of motor signs. The patient was not aware of whether the stimulation was real or simulated.

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**Figure 1.** Videotaped Images of the Patient's Facial Expressions during Depression Elicited by High-Frequency Stimulation through an Electrode Implanted in the Left Subthalamic Region for Treatment of Parkinson's Disease.

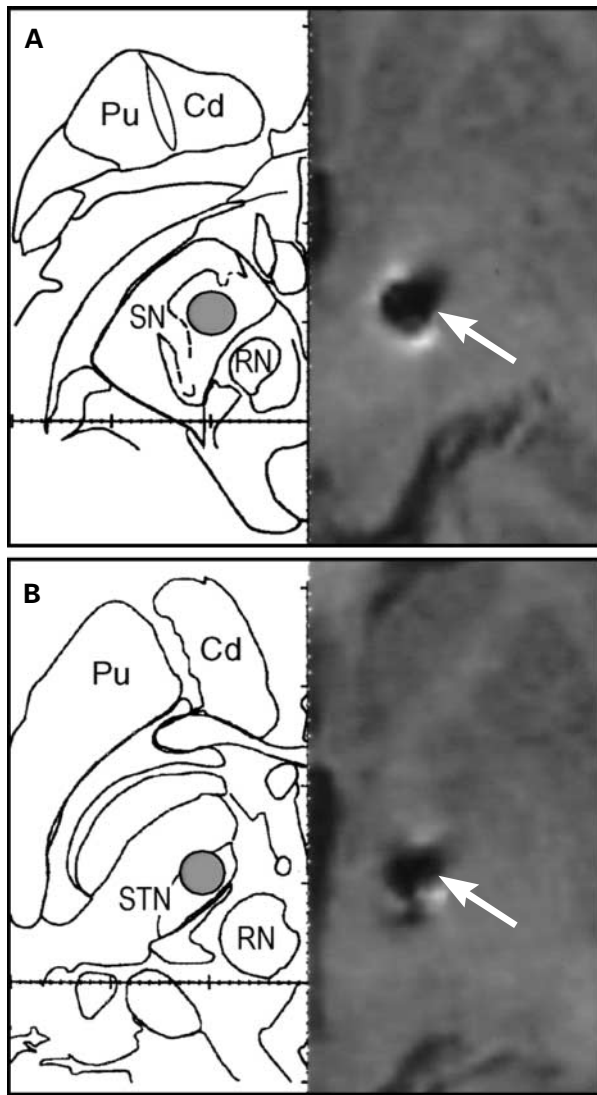
Only stimulation through contact 0 of the electrode placed on the left side caused depression. The actual time of each recording is indicated on the photograph. Panel A shows the patient's usual expression while receiving levodopa. Panel B shows a change in the facial expression 17 seconds after stimulation began. Panel C shows the patient crying and expressing despair 4 minutes and 16 seconds after the start of stimulation. Panel D shows the patient laughing 1 minute and 20 seconds after the stimulator was turned off.

On the first day, after bilateral stimulation was stopped, the patient's parkinsonian symptoms increased (the score on part III of the Unified Parkinson's Disease Rating Scale rose from 10 to 35 on a scale of 0 to 108), but her mood did not change. When current was applied through contact 0 of the left electrode, the patient's facial expression changed within a few seconds and she became extremely depressed, as she had during stimulation through the same contact 10 days after surgery. When stimulation was stopped, the patient's mood returned to normal within one minute. The next day, after motor improvement in response to levodopa (the score on part III of the Unified Parkinson's Disease Rating Scale was 15), stimulation through contact 0 of the left electrode again elicited symptoms of depres-

sion without altering the parkinsonian symptoms; at this time the patient was agitated instead of akinetic, she cried more, and she moved her arms and head more than on the previous day. Simulated onset or cessation of stimulation had no effect on the patient.

The positions of the contacts of the electrode were determined on magnetic resonance images with the help of the Schaltenbrand and Wharen atlas.<sup>6,7</sup> Contact 0 of the left electrode was located in the central substantia nigra, including part of the pars compacta and pars reticulata (Fig. 2A). Contacts 1 and 2 of the left electrode, used for continuous antiparkinsonian therapy, were located in the subthalamic nucleus (Fig. 2B).

Eight months after surgery, two hours after stimulation was turned off, positron-emission tomogra-



**Figure 2.** Anatomical Localization of Left Contact 0, through Which Stimulation Induced Depression (Panel A), and Left Contact 2, through Which Stimulation Improved the Motor Symptoms of Parkinson's Disease (Panel B).

The arrows on the right indicate the position of the artifact corresponding to the contacts on axial volumetric,  $T_1$ -weighted, three-dimensional magnetic resonance images reformatted in a plane parallel to the commissural line.<sup>6</sup> The circles on the left show the location of the contacts on corresponding sections of the Schaltenbrand and Wharen atlas<sup>7</sup> in mirror image: contact 0 was placed in the center of the substantia nigra, and contact 2 in the subthalamic nucleus. Cd denotes caudate nucleus, Pu putamen, RN red nucleus, SN substantia nigra, and STN subthalamic nucleus.

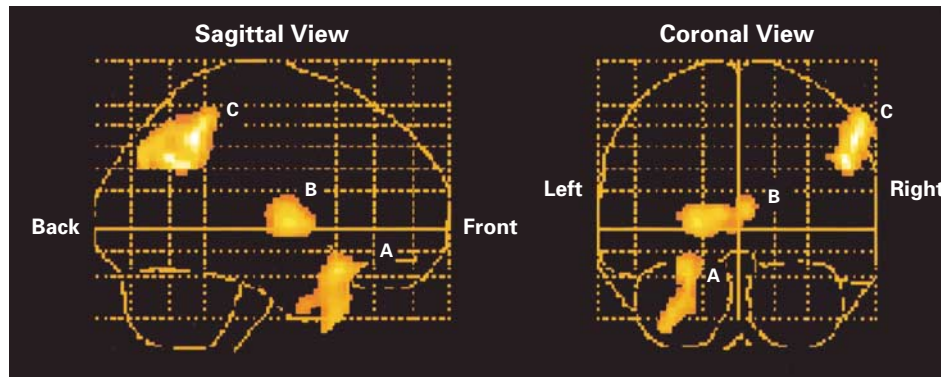
phy with oxygen-15-labeled water was performed (ECAT-HR+, Siemens, Erlangen, Germany).<sup>8</sup> Five images were recorded after five minutes of stimulation through contact 0 of the left electrode, and five more images were recorded eight minutes after stimulation was stopped, in a randomized fashion, with the patient unaware of whether the stimulation was real or simulated. Data were analyzed with the statistical mapping program SPM 96 (Wellcome Department of Cognitive Neurology, London).<sup>9</sup> During stimulation, the patient noted both acute sadness, although less severe than during previous sessions, and the sensation that her body was being sucked into a black hole. This illusion of bodily motion was not accompanied by hallucinations or confusion. A significant increase in blood flow was detected in the right parietal lobe, in the left orbitofrontal cortex, in the left globus pallidus, and also in the left amygdala and anterior thalamus (Fig. 3).

None of the other 19 patients treated by subthalamic stimulation at our center had symptoms of depression during the systematic postoperative evaluation of the effect of stimulation through each contact of the electrodes.

#### DISCUSSION

The syndrome elicited in this patient by stimulation of the left substantia nigra fulfilled most of the nine criteria for major depression, as defined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*<sup>10</sup>: profound sadness, feelings of emptiness and worthlessness, markedly diminished interest and pleasure, agitation (with levodopa) or inhibition (without levodopa), fatigue, decreased concentration, inappropriate guilt, and a morbid interest in death. The other two criteria — weight change and sleep disorder — would not be applicable to short episodes, such as those elicited in this case. The symptoms could not be explained by pain or an increase in the severity of the parkinsonian symptoms. The depression, which was selectively caused by stimulation through contact 0 of the left electrode, was independent of the patient's motor symptoms and of levodopa therapy; stimulation-dependent, beginning abruptly when stimulation started and resolving within one minute after stimulation ceased; reproducible; and not induced by simulated stimulation.

Contact 0 of the left electrode was located in the central part of the substantia nigra, 2 mm below contacts 1 and 2, which were in the subthalamic nucleus. When the subthalamic nucleus was stimulated, the symptoms of Parkinson's disease improved, but the patient's mood was not altered. Since stimulation is considered to affect only a few cubic millimeters of neural tissue,<sup>1,2</sup> the depression probably resulted from the stimulation of afferent, efferent, or passing fibers within the substantia nigra or from the



**Figure 3.** Brain Regions Activated during an Acute Episode of Depression Induced by High-Frequency Stimulation of the Left Substantia Nigra.

Regional cerebral blood flow was measured by positron-emission tomography with [ $^{15}\text{O}$ ]water. There were foci of activation in the left orbitofrontal cortex (Brodmann's area 47), spreading to the left amygdala (A); in the left globus pallidus, spreading to the anterior thalamus (B); and in the right parietal lobe (Brodmann's area 40) (C).

inhibition of these fibers; the effects of high-frequency thalamic<sup>1</sup> or subthalamic<sup>2</sup> stimulation are similar to those of thalamotomy in humans or subthalamotomy in nonhuman primates.<sup>11</sup>

The neural networks involved in this particular case have not been clearly identified, although neurons containing norepinephrine, serotonin, and dopamine and neurotransmitters suspected to be involved in depression<sup>12</sup> are present in the substantia nigra. Medial noradrenergic bundles and serotonergic fibers from the dorsal raphe nucleus can be ruled out because of their distance from the site of stimulation. Decreased dopaminergic neurotransmission, thought to have a role in the depression associated with Parkinson's disease,<sup>13</sup> is unlikely to have been responsible, for two reasons. First, contact of the left electrode could not have affected projections from dopaminergic neurons dorsal to the subthalamic nucleus, because they were too far from the area of stimulation. Second, the patient was not depressed when her parkinsonism was severe (i.e., when dopamine concentrations in the striatum would have been at their lowest) or when it was maximally improved by levodopa. Stimulation may have affected the activity of nigral  $\gamma$ -aminobutyric acid–employing (GABAergic) neurons innervating the ventral nuclei of the thalamus,<sup>14</sup> which project to the prefrontal and orbitofrontal cortices.<sup>15</sup> Dysfunction of these systems has been implicated in mood disorders<sup>16,17</sup> and in self-induced sadness in normal subjects.<sup>18</sup> Lesions of the left basal ganglia are associated with depression in patients who have had strokes.<sup>19,20</sup>

The results of positron-emission tomography revealed activation of the left orbitofrontal cortex, a finding consistent with involvement of the nigrothalamic pathway, which extends to the left amygdala

and limbic structures and is implicated in the processing of unpleasant feelings.<sup>21,22</sup> Activation of the left pallidum may result from retrograde stimulation of GABAergic projections from the external pallidum to the substantia nigra.<sup>23</sup> The reason the right inferior parietal lobe was activated is not known but may be related to the patient's sensation of motion, since this brain region contains "maps" used to orient bodily movement in space.<sup>24</sup>

The fact that depression was not elicited by stimulation of the right side in this patient or by stimulation of any sort in the other patients might be explained by differences in the anatomy of the subthalamic region, or by differences in the placement of the electrodes. Stimulation of a restricted site in the upper midbrain can cause acute major depression, and our findings provide a basis for further studies to elucidate the neural networks involved in depression.

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