Expectation and the Placebo Effect in Parkinson's Disease Patients With Subthalamic Nucleus Deep Brain Stimulation

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Abstract: To determine whether the degree to which a patient with Parkinson's disease expects therapeutic benefit from subthalamic nucleus–deep brain stimulation (STN-DBS) influences the magnitude of his or her improved motor response, 10 patients with idiopathic Parkinson's and bilateral STN-DBS were tested after a 12-hour period off medication and stimulation. Four consecutive UPDRS III scores were performed in the following conditions: (a) stimulation OFF, patient aware; (b) stimulation OFF, patient blind; (c) stimulation ON, patient aware; and (d) stimulation ON, patient blind. Statistical significance ($P = 0.0001$) was observed when comparing main effect ON versus OFF (mean ON: 32.55; mean OFF: 49.15). When the stimulation was OFF, patients aware of this condition had higher UPDRS motor scores than when they were blinded (mean: 50.7 vs. 47.6). With the stimulation ON, UPDRS motor scores were lower when the patients were aware of the stimulation compared with when they were blinded (mean: 30.6 vs. 34.5). The interaction between these levels was significant ($P = 0.049$). This variation was important for bradykinesia and was not significant for tremor and rigidity. The authors conclude that the information about the condition of the stimulation enhanced the final clinical effect in opposite directions. The results presented support the role of expectation and placebo effects in STN-DBS in Parkinson's disease patients. © 2006 Movement Disorder Society

Key words: placebo; nocebo; Parkinson's disease; subthalamic nucleus; deep brain stimulation

Parkinson's disease (PD) is among the disorders in which the placebo effect can play a significant role.[1–4] Functional imaging studies have demonstrated that this effect is related to dopamine release in the striatum.[5] This dopamine release appears to be linked to expectation of reward (i.e., clinical benefit), which is in turn mediated by dopamine release in the ventral striatum.

Since the initial description of high-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) for the treatment of severe PD in 1995,[6] many centers have reported efficacy and the safety of this procedure.[7–10] Despite its clinical success, the mechanism underlying the effects of STN DBS in PD remains unknown.[11] Only two previous studies have been published describing the role played by expectation in the outcome of movement velocity in parkinsonian patients treated with effective STN DBS.[12,13] The objective of this study is to determine whether the degree to which patients with Parkinson's disease expect therapeutic benefit from STN DBS influences the magnitude of their improved motor response.

PATIENTS AND METHODS

This study was approved by the University of British Columbia Clinical Research Ethics Board (C98-0404). Ten patients with idiopathic Parkinson's disease who had received bilateral STN DBS were enrolled in the study. Disabling motor fluctuations with severe bradykinesia and dyskinesias secondary to the chronic use of antiparkinsonian medication were the main indications for surgery. There were two women and eight men whose mean age was 61 years (range, 42–78 years). The mean duration of the symptoms before surgery was 14 years (range, 6–23 years). All underwent microelectrode-guided placement of bilateral deep brain stimulation electrodes (model 3389; Medtronic, Minneapolis, MN) in the subthalamic nuclei, connected to an implantable pulse generator below the left clavicle (Kinetra, model 7428; Medtronic).

The stimulation parameters and reduced level of medications were then optimized over several months. At the moment of the study, the mean dose of L-dopa and dopamine agonist in the form of L-dopa equivalents that the patients were receiving was 690 mg (range, 200–1,300 mg). Patients were then tested for this study after a 12-hour period of no antiparkinsonian medications and no stimulation. Four consecutive Unified Parkinson's Disease Rating Scale (UPDRS) scores were performed in the following conditions: stimulator OFF and patient aware that the stimulation was OFF; stimulator OFF and patient unaware whether the stimulation was ON or OFF; stimulator ON, patient aware; stimulator ON, patient blind. The four conditions were randomly assigned. The stimulator remained OFF or was switched OFF for 10 minutes after each evaluation. The patients were evalu-

ated after 15 minutes of the stimulation using the motor score of the UPDRS. STN stimulation typically improves rigidity and tremor in less than 1 minute and the majority of improvement in bradykinesia gradually builds over several minutes.[14] To blind the examiner to the experiment's condition, the stimulator was switched ON or OFF by a different investigator. Our experience when programming the settings for the optimal DBS parameters has shown that some patients are aware almost immediately when their stimulation is switched ON and this could potentially unblind them. This same phenomenon is typically not described when the stimulation is switched OFF. In order to minimize this risk of unblinding, during the four conditions of the test, the patient was blinded by placing the programmer (N'vision programmer model 8840; Medtronic) on the patient's chest, turning the DBS ON briefly then randomly pressing the ON or OFF button.

Statistical Methods

Repeated-measures analyses of variance were carried out on the total UPDRS data, as well as on the tremor, rigidity, and bradykinesia subscores. Main effects consisted of aware vs. blind and ON vs. OFF. The interactions between the main effects were also tested. A P value of < 0.05 was considered significant.

RESULTS

The mean UPDRS motor scores in the various conditions were as follows: blind OFF = 47.6 ± 12.2; blind ON = 34.5 ± 13.2; aware OFF = 50.7 ± 16.6; aware ON = 30.6 ± 13.05.

The repeated measures of the analyses of variance (ANOVA) with a priori comparisons between ON vs. OFF (main effect), aware vs. blind (main effect), and the interaction between these showed $P = 0.0001$ (main effect, ON vs. OFF). This means that the bilateral STN DBS was effective in controlling the features of the disease assessed by the UPDRS, whether or not the patients were aware of the function of their stimulators.

There was no significant main effect of aware vs. blind ($P = 0.7733$). However, awareness of stimulation had an opposite effect for the OFF vs. ON condition, with a significant interaction effect ($P = 0.049$). Thus, as shown in Figure 1, when the stimulation was OFF, patients aware of this condition had higher UPDRS motor scores (clinically worse) than when they were blinded (mean, 50.7 vs. 47.6). With the stimulation ON, UPDRS motor scores were lower (clinically better) when patients were aware of this compared to the blinded state (mean, 30.6 vs. 34.5).
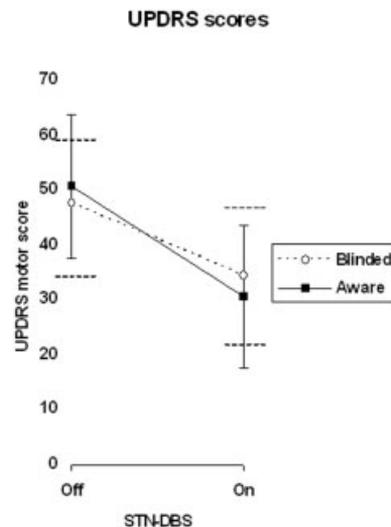

FIG. 1. UPDRS motor scores in patients aware or blinded to whether their STN stimulation was ON or OFF. Square and solid line show the improvement in UPDRS scores during the aware condition. Open circle and dashed line show the improvement in UPDRS scores during the blinded condition. The interaction is statistically significant ($P = 0.049$).

The analyses of tremor, rigidity, and bradykinesia subscores, determined from the specific issues of the UPDRS motor score describing these features, showed that some interactions, individually, were no longer significant, specifically for tremor and rigidity ($P = 0.23$ and 0.10, respectively). For bradykinesia, we found a marginally significant interaction ($P = 0.059$). Under the blind condition, the mean OFF was 17.3 ± 3.56, and the mean ON was 12.4 ± 2.63, while when aware of the stimulation, the mean OFF was 19 ± 4.78 and the mean ON was 10.4 ± 3.40 as shown in Figure 2.

DISCUSSION

Since the initial studies reporting the efficacy of STN DBS,[6] several studies have confirmed its benefits and safety,[7–10] but none has been able to describe precisely the possible mechanism of action of this therapy. Current pathophysiological models of basal ganglia organization suggest that PD is a state characterized by hyperactivity of the glutamatergic excitatory action of the STN over the globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNr) that propagate an excessive inhibitory influence in the thalamus, cortex, and brainstem.[15] Therefore, the simplest hypothesis is that the high-frequency stimulation reduces or inactivates either the neurons of the STN or their excitatory glutamatergic projections. On the basis of theoretical considerations, there are a number of possibilities. First, the neurons could be held in a depolarized state, in which they could
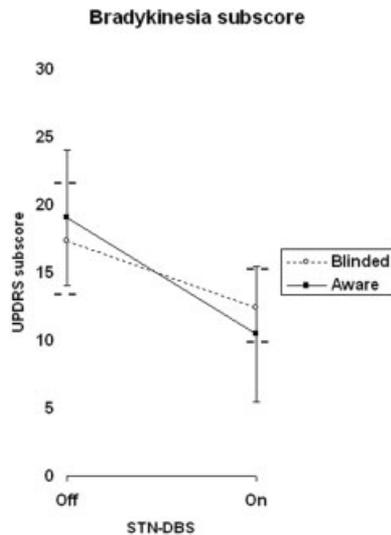
FIG. 2. The subscore analysis for bradykinesia showed a marginally significant interaction ($P = 0.059$) between the aware (square and solid line) and blind effect (open circle and dashed line).

not produce action potentials. Second, the neural network could be disrupted by the additional nerve impulses generated by the stimulation. Third, the stimulation might produce net inhibition either by activation of inhibitory neurons or by the properties of the network itself when driven at high rates.[11]

The results presented here support the hypotheses that STN DBS in PD is associated with a placebo effect. The interaction of the scores obtained in the UPDRS between the aware and blinded conditions was significant. This suggests that the certainty of the clinical benefit (i.e., reward) given by the information about the condition of the stimulation enhanced the final clinical effect in opposite directions. Thus, clinical benefit was heightened when the patients were advised that the stimulation was ON, whereas clinical worsening was further potentiated when the patients were advised that the stimulation was OFF, a response modulated by a nocebo effect. The UPDRS motor score has been defined as sensitive to detect changes coincident with this placebo and expectation manipulation.[16]

A recent analysis of the literature of STN DBS clinical trails by De la Fuente-Fernández[17] suggested that the magnitude of the effect of the STN DBS (i.e., ON–OFF) is significantly higher when the patients are aware of the stimulation condition than when they are blinded to it. Following this line of analysis, in our study, the magnitude of the effect of the active STN DBS was 20.1 (i.e., 50.7–30.6) when the patients were aware of the stimulation, and 13.1 (i.e., 47.6–34.5) when they were blinded to the stimulation (Fig. 3). Furthermore, in this analysis,

the magnitude of the placebo effect can be considered as the difference between the effects of the STN DBS when the patients are aware and when they are blinded to the stimulation. According to this observation, the magnitude of the placebo effect is 7.0 (i.e., 20.1–13.1) and represents an equivalent of 34.8% (7.0/20.1) of the magnitude of the active STN DBS effect when the patients were aware of the stimulation. This agrees with the 39% mentioned by De la Fuente-Fernández[17] in his report.

There are several theoretical reasons why an increase in dopamine release could account in part for the relief of the clinical features in PD treated with STN DBS. First, patients for STN DBS are generally selected on the basis of dystonic and freezing *off* periods responsive to treatment to L-dopa.[18,19] Second, dopaminergic medications may be reduced by almost 50% in PD patients after STN DBS.[20] Third, STN DBS tends to increase dyskinesia, which is generally associated with the chronic use of large amounts of dopaminergic drugs.[21] Animal models support this notion, as some authors report that high-frequency stimulation of the STN causes release of dopamine in the striatum of the rat.[22] However, several studies using PET with [^{11}C]raclopride in humans treated with STN DBS for PD have failed to demonstrate dopamine release in the human striatum.[23–25] Interestingly, this imaging modality has been used to demonstrate that the placebo effect in PD is related to dopamine release in the striatum.[26] Furthermore, this placebo-induced dopamine release is linked to the anticipation of therapeutic benefit, and this expectation of reward is mediated by dopamine release in the ventral striatum.[27] The magnitude of the placebo effect observed in this study suggests that this effect can be related to dopamine release in the dorsal and ventral striatum enhanced by the expectation of the clinical benefit.

Among the three most important features of PD evaluated with the UPDRS motor score, rigidity, tremor, and bradykinesia, the one that displayed a marginally significant interaction between being aware or blinded to the
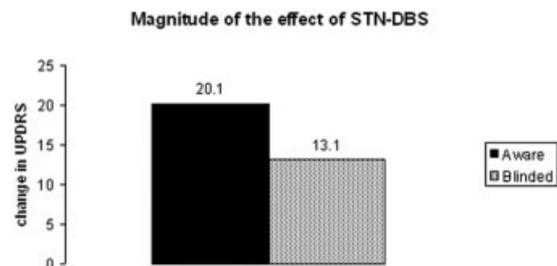

FIG. 3. The magnitude of the effect of the active STN DBS was 20.1 (i.e., 50.7–30.6) when the patients were aware of the stimulation, and 13.1 (i.e., 47.6–34.5) when they were blinded to the stimulation.

stimulation was bradykinesia. We have previously described in a fluorodopa PET study that bradykinesia is the sign that most correlates with striatonigral degeneration and lack of dopamine in the striatum.[28] The fact that bradykinesia was responsive to our expectation manipulation supports the notion that this placebo effect was a dopamine-mediated response.

There are still some questions regarding the specificity or nonspecificity of the placebo effect.[29] The specificity of the placebo effect relies either on the information given to the patient (for example, placebos can have opposite effects on heart rate or on blood pressure depending on whether they are given as tranquillizers or as stimulants[30]) or on the previous experience of the patient with the active drug or therapy. In both cases, the effect is mediated by the expectation of the clinical benefit to be obtained. In this study, all the patients were familiar with the beneficial effect of the STN DBS, and such previous experience may have enhanced their expectation.

The motor function displayed a significant worsening when the patients were advised that the stimulation was OFF, in comparison with the blinded OFF condition (UPDRS, 50.7 vs. 47.6). Benedetti and colleagues[13] have previously analyzed motor function in 10 patients with idiopathic PD receiving STN DBS, who displayed a significant decrease of movement velocity when told that they were going to deteriorate. In both studies, negative expectations yielded negative outcomes, a situation that has been called the nocebo effect.[31]

In conclusion, STN DBS exerts a beneficial effect in patients disabled by PD regardless of whether they are aware of the stimulation condition. However, significant variations in the UPDRS scores were noticed when the patients were aware or blinded to the stimulation condition. As suggested by Colloca and colleagues,[32] this is a kind of response observed between overt therapy vs. covert treatment. This variation was more important for bradykinesia, and not significant for tremor and rigidity, supporting the notion of a dopamine-mediated response underlying the expectation response. The results presented support the role of expectation and placebo effects in STN DBS in PD patients.

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Surface Electromyography Shows Increased Mirroring in Parkinson's Disease Patients Without Overt Mirror Movements

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Abstract: **Patients with Parkinson's disease (PD) may present mirror movements (MM). Transcranial magnetic stimulation data indicate that these movements reflect an abnormal enhancement of the "physiological mirroring" that can be observed in healthy adults during complex and effortful tasks. It was hypothesized that, in PD, enhanced mirroring is caused by a failure of basal ganglia output to support the cortical network that is responsible for the execution of strictly unimanual movements. If so, it is likely that subtle alterations of voluntary unimanual motor control are also present in PD patients without overt MM. We tested this hypothesis by using surface electromyographic (EMG) techniques in 12 mildly to moderately affected PD patients without overt MM, and in 2 control groups (12 age-matched and 10 young healthy volunteers). Subjects performed unilateral phasic thumb abduction during a sustained tonic contraction of the opposite abductor pollicis brevis. All patients were tested *on* dopaminergic therapy. On a separate day, 7 of 12 patients were re-tested after withdrawal of medication. During this task, involuntary mirror-like increase in surface EMG of the tonically abducting thumb was significantly larger in PD patients than in age-matched or young healthy volunteers. *Off* therapy, mirroring was slightly greater than *on* medication, although this difference was not significant. Our findings suggest that dysfunction of unimanual motor control is a general feature of PD. It is likely that this deficient movement lateralization contributes to an impairment of non-symmetrical bimanual movements in PD.** © 2006 Movement Disorder Society

Healthy adults are usually able to perform strictly unimanual movements, although electromyographic (EMG) techniques may reveal subtle mirroring in the opposite hand (mirror hand), particularly during complex and effortful tasks.[1] Namely, involuntary mirror EMG activity may be recorded when they maintain a slight level of background isometric muscle contraction in the mirror hand while performing voluntary phasic contractions with the homologous muscle of the other hand. This "physiological" mirroring likely is caused by overflow activation from the task motor cortex to the mirror motor cortex.[1]

During intended unimanual movements, patients with Parkinson's disease (PD) may present motor overflow, that is, movements that are mirror reversals of the contralateral voluntary ones (mirror movements, MM).[2–5] Vidal and colleagues[3] and Espay and associates[4] documented MM in untreated patients with early PD and nicely demonstrated that this phenomenon is associated with asymmetric Parkinsonism. However, these purely observational studies did not provide direct information on the pathophysiological mechanisms underlying MM in PD.[3,4] Recent transcranial magnetic stimulation data suggest that, in PD, MM reflect an abnormal enhancement of the physiological mirroring.[5] It was hypothesized that enhanced mirroring in PD is caused by a failure of basal ganglia output to support the cortical network that is involved in enabling the corticospi-