Effects of subthalamic nucleus (STN) stimulation on motor cortex excitability

To the Editor: We agree with Däuper et al.1 that STN stimulation may modulate cortical excitability.2 However, the study by Däuper et al.1 raises several concerns related to methodology, results, and discussion.

Regarding the methodology, information on the age of the control group is not provided—age, however, is a crucial factor for motor evoked potentials. For a valid comparison the age group of the controls should be matched with the age of the patients. Besides, the reproducibility of the total voltage time integral may be questionable, considering the intertrial variability (see figure 1 in their article) and considering that only a few trials were averaged (possibly preselected from more trials by an unblinded observer). Movement of coil position and angle against the individual's vertebrae may also have increased data variability. Moreover, patients with predominantly akinetic-rigid PD are not able to cooperate as well as controls in silent period (SP) studies requiring maintenance of a constant muscle tone. Consequently, the SP is frequently interpreted by small amounts of EMG in patients with PD.4

Regarding the results, previous studies suggest that STN stimulation restores intracortical inhibition (ICI), similar to the effect of dopaminergic drugs5,6 and has no effect on the SP.7 In contrast to these results, Däuper et al. did not report restoration of ICI by dopaminergic drugs alone, but ICI was reduced with stimulation “on”/medication “on” in the same amount as with stimulation “off”/medication “off” (see figure 2 in their article).1 Different stimulation paradigms only partially explain these inconsistent results. Finally, in the discussion of their results the authors raise the question, “How can the increase of the SP during stimulator “on” be explained?”2 Modulation of other indirect connections not mentioned in Däuper et al.’s article, like disinhibition of the dorsal midbrain anticonvulsant zone via the substantia nigra, may also influence motor excitability.2 Furthermore, high-frequency stimulation does not only inhibit STN neurons but simultaneously excites axons within the STN.2 Antidromic activation of cortico-subthalamic collaterals of the pyramidal tract may lead to cortical modulation (for example via retrograde activation of collaterals to cortical GABAergic basket cells) as well as spinal modulation (via nigrospinal pathways or via collaterals to spinal alpha-motoneurons and activation of Renshaw cells). This could also explain a modulation of intracortical and spinal inhibitory mechanisms by STN stimulation.

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Reply from the Authors: We appreciate the critical comments on our paper “Effects of subthalamic nucleus (STN) stimulation on motor cortex excitability.” The authors of the letter have several concerns that we would like to address.

Regarding methodology, we agree that age has a substantial influence on motor cortex excitability. We will publish a paper focusing on this issue in the near future. We have examined two different age groups in this study using paired-pulse transcranial magnetic stimulation (3 vs 13 ms interstimulus interval) and found that intracortical inhibition was significantly greater in older subjects.8 This result, however, is different from previous reports9 suggesting a decrease of intracortical inhibition with on-
Predictors of effective bilateral subthalamic nucleus stimulation for PD

To the Editor: Charles et al. make an important contribution with their article describing possible predictors of deep brain stimulation (DBS) of the subthalamic nucleus efficacy for PD. While DBS is highly effective and FDA approved, the procedure has considerable risks. Effective predictors could favorably shift the risk-to-benefit ratio. Unfortunately, the analysis performed is of little value and potentially misleading. A more appropriate analysis would be to report the area under the receiver–operator characteristic curve, which relates the specificity and sensitivity of the tests to age and levodopa responsiveness. The goal of any predictive task not only is to avoid surgery for those patients not likely to benefit but also to avoid withholding surgery from those that would. Visual inspection of the data represented in the graphs provides little confidence that either age or levodopa responsiveness will have sufficient specificity and sensitivity to be an effective predictor that can be used for patient selection.

In addition, the study of predictors was limited to a retrospective correlational analysis. Correlation is a mathematically optimizing procedure that will find a correlation, even if spurious. Thus, it remains unclear how generalized are the regression analyses performed. That is why it is so important to apply the predictive regression equations in a prospective manner. Often, dividing the sample population into two groups, the first to develop the regression equations and the second to prospectively test those equations, can do this. The large majority of times, the specificity and sensitivity of predictors protectors fall when tested prospectively.

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Reply from the Authors: We thank Dr. Montgomery for his comments and share his concern about the importance of adequately selecting parkinsonian patients for surgery. Dr. Montgomery’s remark deals with the use of regression and correlational analyses to study the predictive factors of outcome from bilateral subthalamic nucleus stimulation. While it is true that the regression analysis of the data is retrospective, the original patient enrollment, treatment, and data collection were performed prospectively. The calculation of the sensitivity, specificity, and confidence intervals would need considerably more patients, hardly compatible with this type of therapeutic procedure. The receiver–operating characteristic curves proposed by Dr. Montgomery are frequently used to assess the usefulness of diagnostic markers, but the method also has some disadvantages. We think that univariate analysis is one of the most appropriate statistical methods for our study. We agree with the necessity of validating our model in another prospective study. We do not know if “the large majority of times, the specificity and sensitivity of protectors fall when tested prospectively,” but it has been shown that it is not always true.

Most studies of the surgical treatment of PD found that outcomes from surgery are better in patients with levodopa-responsive motor symptoms. Welter et al. also used regression analysis in their series of parkinsonian patients treated with subthalamic nucleus stimulation. In keeping with our results they found that the outcome of STN stimulation was excellent in levodopa-responsive forms of PD. Our results are consistent with the classic inclusion criteria for subthalamic nucleus stimulation and imply that the decision to operate on the oldest patients and/or patients with levodopa-resistant motor symptoms should be carefully weighed. The other lesson from our experience is that parkinsonian patients with severe levodopa-induced motor complications may still be surgical candidates if a fair levodopa response is maintained, i.e., if their best on-motor score is low. This result is clinically sensible. The relative young age at the time of surgery could have been expected as a good predictor because young-onset PD is characterized by a good response to levodopa with minimal on-period axial or motor symptoms except fluctuations and dyskinesias. Moreover, surgery-related complications are more frequent in an elderly population.

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References


Correction

GDAP1 mutations in CMT4: Axonal and demyelinating phenotypes? The exception “proves the rule”

In the recently published editorial titled “GDAP1 mutations in CMT4: Axonal and demyelinating phenotypes: The exception “proves the rule,” (Neurology 2002;59:1835–1836) the authors inadvertently misstated a mutation. The text should have stated “myotubularin-related protein-2 (MTMR2).”
GDAP1 mutations in CMT4: Axonal and demyelinating phenotypes? The exception "proves the rule"

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