

30,000 spirals from several multicenter (mainly tremor) studies around the globe. Because of our patent, we were rather cautious with the publication of preliminary results. Various reasons caused an additional delay until submission (2006) and publishing (2010).² Up to that time, we had not found the article by Miralles et al³ from 2006, although we have consistently updated our references (eg, Elble et al⁴). In retrospect, we, unfortunately, have no explanation for why this article³ (unintentionally) escaped our literature search.

Concerning the similarities of both methods,^{2,3} as averred in the letter by Miralles et al,¹ many may be considered trivial (eg, a scanner is naturally the device for digitizing drawings) or represent basic knowledge (eg, polar coordinates and mathematical modeling) or stem from common scientific literature (eg, Bain and Findley⁵).

Other points that are suggested to be “similarities” are in fact fundamental methodical differences—they are partly even misrepresented. Thus, Miralles et al¹ misquoted in their letter: “. . . ‘best-fit spiral curve,’ which is a low-pass filtered version of the original spiral . . .” (this procedure would indeed leave spirals—but without any tremor information). The original text from our article² is: “. . . ‘best-fit spiral curve’ is calculated with an interpolation process (‘moving window’- technique) . . . working similar to a high-pass filter. . .” (indeed our result² is a horizontal line with overlaid perpendicular tremor).

Bain and Findley’s instructions⁵ already defined in 1993 how to evaluate tremor amplitudes from drawn spirals by “rating the perpendicular displacement of the track from the intended trajectory.” We transferred these original instructions into a computerized measurement (interpolation process). An auxiliary variable like Miralles et al’s³ “radial error” does not appear in our method.

Our “spiralometry” technique² allows a fully automated evaluation of spontaneously drawn spirals on any blank sheet of paper with standardized blind processing that takes less than 30 seconds per spiral. Our interpolation process only needs the drawn line. For cross-validation, we digitized and evaluated the 32 original spirals from the handbook by Bain and Findley⁵ (see Fig. 5 of our original article²).

In contrast, the tracing test from Miralles et al³ needs a preprinted spiral for evaluation (with this technique, it is therefore not at all possible to evaluate the spirals from Bain and Findley⁵). Furthermore, their analysis³ is limited by an unautomated and nonobjective manual working step that requires a time-consuming (and subjective) human input.

When thoroughly contemplated, although starting with a similar issue, both of our groups’ approaches and solutions show fundamental differences. Ultimately, we act on the assumption that there has been no exchange of information between our 2 laboratories in any direction. All interested readers are encouraged to form their own view on the differences between both articles.

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Early Versus Delayed Bilateral Subthalamic Deep Brain Stimulation for Parkinson’s Disease: Need for Long-Term Clinical Trials

We read with interest a recently published decision analysis on the timing of subthalamic nucleus (STN) deep brain stimulation (DBS) implants in Parkinson’s disease (PD).¹ This model predicts that performing STN DBS in patients with less than 20% off time is associated with increased quality-adjusted life expectancy, compared with patients with more than 40% off time. We recently reported a cohort of PD patients treated with STN DBS 8 years previously² and found remarkable interindividual variability of outcome and variable response of different PD motor symptoms to DBS. At 8 years, rigidity and tremor improved more than gait and even more than limb akinesia, whereas speech did not improve and postural stability worsened.² Furthermore, we observed between-patient variability of outcome at 8 years, raising the issue of differentiating PD subtypes who can best benefit from STN DBS. The simulation by Espay and colleagues¹ is generally in keeping with our findings, but it did not consider UPDRS motor score subitems, which are part of the clinical evaluation of PD patients. The total UPDRS motor score does not allow details to be obtained on individual motor items that are subject to specific variations in the long term. The complexity of real-life scenarios, which also take into account clinical heterogeneity (eg, disease progression),^{3,4} cannot be easily reproduced by simulation models. We believe that long-term randomized controlled trials remain the gold standard for decision making on PD surgery and for the development of guidelines.

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Reply: Early Versus Delayed Bilateral Subthalamic Deep Brain Stimulation for Parkinson's Disease: Need for Long-Term Clinical Trials

We thank Fasano and colleagues for their interest in our report.¹ We are in full agreement that no study methodology, including the simulation modeling underlying many decision analyses, could replace a randomized clinical trial, with appropriate attention to prespecified patient subgroups. However, our decision analysis addressed a question that has not been answered in a clinical trial for logistical and ethical reasons, namely, whether the long-term, possibly disease-modifying benefits of early subthalamic nucleus (STN) deep brain stimulation (DBS) implantation outweigh its procedural risks when carried out in a population not currently considered eligible for surgery. Decision analysis is precisely the type of modeling tool that can help to address these kinds of clinical problems where feasibility is problematic.

Testing the disease-modifying hypothesis of early STN DBS implantation is particularly challenging in a clinical trial because it requires overcoming the ethical concerns of “premature surgery,” as well as bridging 2 major logistical problems: (1) accepting and implementing a common operational definition of “early” disease, which should be early enough for putative neuroprotective interventions, and (2) maintaining a double-blind allocation long enough (3 years? 5 years?) to move beyond the reporting of the short-term “honeymoon” benefits of surgery. The challenges of such a study also include the need for sham surgery and multiple sham programming visits. Our decision analysis provides further rationale for eventually tackling

this clinical question by properly testing this hypothesis in a clinical trial. We acknowledged that our decision model was only a simulacrum that could not possibly match the true complexity of factors considered in “real life.” Decision analytic models require simplifying assumptions, such as using “off time” as the single factor (over the combination of UPDRS scores or other clinical variables) driving the decision to proceed with surgery. The report by Fasano and colleagues is a welcome contribution to our understanding of the long-term effects of STN DBS,² but it cannot answer whether early surgery is capable of yielding greater long-term benefits compared with the current standard-of-care “delayed” intervention. Thus, we agree that a multiyear clinical trial comparing early versus late STN DBS implantation would resolve this important clinical question. We believe results of our modeling and analysis should contribute to allaying apprehensions about designing and carrying out such an effort.

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