Pathology of Vessels Supplying the Brain in Patients with Parkinson's Disease

We have read with interest the study by Santangelo et al.,[1] reporting the role of vascular pathology in the neuropsychological profile of parkinsonian patients. The authors evaluated whether the brain's vascular lesion load is associated with neuropsychological variables. They compared the neuropsychological profile of patients affected by Parkinsonism and vascular lesions to that of patients with Parkinson's disease (PD) without vascular lesions. The conclusion was that "regardless of the presence of dopaminergic denervation, cerebrovascular lesions … have an important effect in determining early onset and severity of cognitive impairment in patients with parkinsonism". We agree with the authors that a comorbid cerebrovascular disease (CVD) may have an important impact on impairment of cognitive functions in patients with PD. In this aspect, the PD patients are not fundamentally different from patients without Parkinsonism.

We have recently demonstrated that the pathology of vessels supplying the brain contribute to the disease severity in PD patients even without a CVD.[2] In 57 consecutive PD patients, we measured ultrasound parameters indicating an atherosclerotic disease of the large and small brain vessels. The occurrence of the MRI and clinically manifested CVD was rare (stroke or transient ischemic attack in five patients, only small volume white matter lesions), concurring with results of large epidemiological studies.[3,4] The ultrasonographic examination of extracranial vessels comprised the measurement of the intima-medial thickness (IMT) of the common carotid artery, and the carotid arteries were evaluated for the presence of atherosclerotic plaques. IMT is considered to be a useful sonographic marker of early atherosclerotic affection. Regarding the ultrasonographic examination of intracranial vessels, the resistance and pulsatility indexes (RI, PI) were calculated. These indexes are not just functions of flow resistance; they are also influenced by vascular compliance. The results of a multiple regression analysis revealed a significant association between the IMT and motor, functional, and cognitive impairment (as measured by the Hoehn-Yahr score, Lawton's Instrumental Activities of Daily Living, Barthel Index, Mini-Mental State Examination, and Clock Drawing Test – for details see Rektor et al.[2]). Several cognitive tests (Benton Temporal Orientation Test and the Recognition subtest of the Wechsler Memory Scale III) were significantly associated with the PI.

Our results suggest a possible link between a comorbid and otherwise subclinical atherosclerotic involvement and the degree of motor and cognitive decline caused primarily by disease-related degenerative brain changes. This subclinical brain hypoperfusion may affect the severity of clinical symptoms of PD even prior to the development of CVD.

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Differential Neuropsychological Profiles in Parkinsonian Patients with or Without Vascular Lesions

We are familiar with the interesting study of Rektor et al., which demonstrates that the pathology of brain vessels contributes to the motor and cognitive dysfunctions in Parkinson's disease (PD).[1]

Their conclusions are consistent with ours,[2] despite some methodological differences between the two studies.

First, we enrolled patients with parkinsonism and divided them into three groups based on clinical history and the

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presence of brain vascular lesions and/or dopaminergic denervation as revealed by magnetic resonance imaging and dopamine transporter imaging. Differently, Rektor et al. enrolled patients diagnosed with idiopathic PD. We demonstrated that cognitive impairment is associated with brain magnetic resonance imaging vascular lesions, whereas they demonstrated that some cognitive variables correlated with ultrasound parameters, which is an indirect index of vascular disease. The second methodological difference between the two studies regards dementia. In our study, dementia was an exclusion criterion. Although cognitive impairment was an exclusion criterion in the Rektor et al. study, the Mini Mental State Examination (MMSE) results revealed dementia in six PD patients. The third difference concerns the neuropsychological evaluation. We explored mainly executive functions (cognitive flexibility, logical abstract thinking, spatial planning, set-shifting, and selective attention) and verbal long-term memory, whereas Rektor et al. used a cognitive battery evaluating mainly visuospatial and constructional abilities, verbal long-memory and semantic association.

Despite these differences, the two studies concur that there is a correlation between cognitive impairment and vascular disease in PD patients.

Gabriella Santangelo, PhD,[1,2,3] Carmine Vitale, MD, PhD,[1,3,4] Luigi Trojano, MD,[2] Angelo Antonini, MD, PhD,[5] and Paolo Barone, PhD, MD[1,3]*

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ATP13A2-Related Neurodegeneration (PARK9) Without Evidence of Brain Iron Accumulation

We read the article by Schneider et al.[1] with interest. These authors describe a single patient with a homozygous *ATP13A2* mutation and hypointense signal in the basal ganglia in T_2^*-weighted MRI scan obtained after ~24 years of disease duration, and they suggest the classification of PARK9 within the neurodegenerations with brain iron accumulation.

We recently reported a Brazilian patient with juvenile parkinsonism and a homozygous *ATP13A2* Gly504Arg missense mutation.[2] At the time of our initial report, only brain CT images were available, showing evidence of brain atrophy. A detailed brain MRI study, including T_2^*-weighted sequences, was recently performed in our patient at the age of 29, therefore, 17 years after symptoms onset. The MRI confirmed the presence of moderate generalized brain atrophy, particularly, in the substantia nigra but no hypointense signal in T_2^*-weighted sequences was seen in the basal ganglia or elsewhere in the brain (Fig. 1).

The lack of signal abnormalities in T_2^*-weighted MRI scans 17 years since the onset of symptoms is remarkable, suggesting that brain metal accumulation is not a constant feature in this disease, or that it only occurs very late in the disease course.

It is also possible that brain metal accumulation occurs (or is more likely to occur) in cases with drastic *ATP13A2* mutations leading to total loss of protein function, such as that present in the patient reported by Schneider et al. (homozygous p.Thr367ArgfsX29, causing frameshift and protein truncation), while in some patients with missense

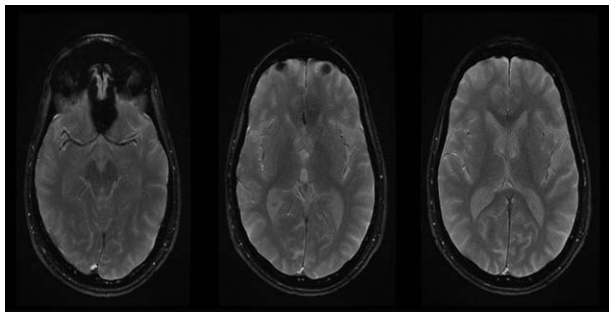

FIG. 1. T_2^*-weighted axial scan (1.5 T) in the Brazilian patient with homozygous *ATP13A2* Gly504Arg mutation shows normal intensity at the level of the substantia nigra and basal ganglia.

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mutations, a residual protein function might be retained and brain metal accumulation might not occur.

The identification of additional patients with pathogenic *ATP13A2* mutations and the acquisition of further, extensive T_2^*-weighted brain MRI studies will hopefully lead to a more complete appreciation of the neuroimaging and nosologic classification of this form.

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Sensory Alien Limb Syndrome in Stroke and Corticobasal Syndrome

We read with interest the article published by Delrieu et al. on a recent issue of *Movement* Disorders,[1] describing cerebral flow studies in patients with predominant non-dominant sensory alien hand syndrome (AHS) and corticobasal degeneration. The authors elegantly described decreased of regional cerebral blood flow over the nondominant thalamus and pointed out the gradual onset and progressive nature as important details in the history for the sensory AHS seen in corticobasal degeneration to differentiate with the symptoms seen in patients with stroke.

Although rarely reported, previous case reports have highlighted that the symptoms can be present more or less abruptly after acute left parietal strokes.[2] However, at least in a very detailed case, which included a video, that we have published in *Movement* Disorders a few years ago, our patient could not precisely report time lag between the stroke and the onset of symptoms.[3] Indeed she was not really aware of the abnormal nature of her symptoms until we diagnosed her condition, which was quite unique as it was position-dependent and markedly enhanced by tactile stimulation as detailed in the video. Therefore, at the same time that we congratulate the authors for providing new evidence about the disrupted cortico-striato-thalamic functioning as the underlying mechanism of sensory AHS, we would like to reinforce that the gradual onset and progressive nature may not differentiate the presentation in corticobasal syndromes versus strokes.

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Reply: Sensory Alien Limb Syndrome in Stroke and Corticobasal Syndrome

We appreciate the careful reading of our manuscript by Gondim. The main aim of our study was to determine the cerebral regions involved in the sensory alien hand syndrome. To do so, we pointed out that there is a significant decrease of regional cerebral blood flow over the nondominant thalamus in patients with corticobasal degeneration (CBD) and sensory alien hand syndrome. Furthermore, we suggested that the presence of sensory alien hand is determinant of a CBD diagnosis when it develops in a progressive way.

We agree with Gondim that the gradual onset and progressive nature of sensory alien hand syndrome may not differentiate the presentation of corticobasal syndromes versus strokes. In CBD, this phenomenon is mostly of gradual onset, as described in previous case reports.[1,2] In contrast, sensory alien hand seen after an acute stroke (in particular after a posterior cerebral artery stroke) can have an acute onset or a progressive as described in the case report of Gondim et al.[3] These data suggest that the type of onset may not always differentiate the presentation of alien hand in CBD versus strokes. Unlike the alien hand syndrome seen in the CBD, the syndrome may improve following stroke in parallel with proprioceptive recovery. Thus, as described in previous case reports, the involuntary movements are considerably reduced during the months following a stroke.[4,5] This suggests that the lack of proprioceptive feedback from the moving limb could lead to an impoverished

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contralesional limb with the development of alien hand. In the natural history of this phenomenon, the possibility of recovery seems to better differentiate CBD versus strokes than the type of onset.

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Bilateral Cerebellorubrothalamic Fibers Stimulation for Essential Tremor?

With interest we read the article by Blomstedt et al.[1] on posterior subthalamic area (PSA) deep brain stimulation (DBS) for essential tremor. We would like to add a case in which the same target was reached as a result of extensive intraoperative testing, after thalamic nucleus ventralis intermedius (Vim) stimulation did not produce a satisfying benefit.

The patient is a 66-year-old woman with medication-resistant head, voice and arm tremor since the age of 35. The total score on the Essential Tremor Rating Scale (ETRS) was 53 (Video Segment 1). The Vim was localized on frame-based magnetic resonance imaging (MRI) at 15 mm lateral, 2 mm superior, and 8 mm anterior to the posterior commisure (PC). Left-sided intraoperative stimulation from 6 mm above to 2 mm below target depth had no benefit. A second, more medial and posterior Vim target was calculated at 13 mm lateral and 6 mm anterior relative to PC. At 4 mm below target depth, slight tremor reduction occurred at 4.5 mA, accompanied by hand paresthesias. We subsequently targeted the Zona Incerta at 7 mm lateral, 3 mm inferior, and 6 mm posterior to the midcommissural point (MCP). Stimulation from 2 mm above to 2 mm below target depth produced slight tremor reduction with a persistent unpleasant feeling. We, therefore, returned to the more medial and posterior Vim target. At 8 mm below target depth, tremor was abolished completely at 2mA, with transient hand paresthesias. For the right side, we only tested this last target. Stimulation at 2 mA, at 6 and 8 mm below target depth, completely abolished tremor, with transient hand paresthesias. The permanent electrodes (3389, Medtronic; Minneapolis, MN) were implanted 8 mm below target depth bilaterally.

After surgery, a marked microlesional effect was noticed. Two weeks later, tremor recurred to preoperative intensity. Bilateral stimulation (monopolar 0-, 3.3 V, 180 Hz, 60 μsec) abolished voice tremor and markedly reduced postural arm and head tremor, with a residual intention component on the right arm (ETRS total score 35, 34% reduction—Video Segment 2). Higher voltages induced dysarthria and paresthesias. The patient complained also of some gait instability, which was not improved by changing stimulation settings. This side effect profile is similar to that reported after bilateral Vim stimulation.

A postoperative computed tomography (CT) was coregistered with the frame-based MRI using Leksell Surgiplan® software (Elekta Instrument AB, Stockholm, Sweden). The left active contact was localized at 9.6 mm lateral, 4.2 mm inferior, and 8.2 mm posterior to MCP, the right at 9.2 mm lateral, 4.1 mm inferior, and 8.7 mm posterior to MCP. On both sides, the active contact targeted the area adjacent to the lateral border of the red nucleus (Fig. 1A), similar to Blomstedt et al.[1] The DBS target within the PSA varies between the different groups, as revised by Blomstedt.[1] According to the Atlas by Schaltenbrand and Wahren, the PSA contains the zona incerta, medial lemniscus, fasciculus Q, and prelemniscal radiation (Raprl), including cerebellothalamic fibers.[2] According to Duvernoy's Atlas,[3] the area immediately adjacent to the lateral border of the red nucleus harbors cerebellorubrothalamic fibers (Fig. 1B). In the stereotactic atlases by Morel and by Mai et al. this area harbors cerebello(rubro)thalamic fibers.[4,5] As these fibers are thought to play an important role in tremor,[6,7] one could hypothesize that the beneficial effect of DBS at this area occurs through cerebellorubrothalamic fibers stimulation.

We agree with Blomstedt et al. that it is not possible to state which PSA substructure contributes to the therapeutic effect. However, since determining the precise relationship between the neuroanatomical location of the active contact and the therapeutic effect is critical, we postulate that the fibers of the cerebellorubrothalamic tract are the structures through which the effect of stimulation is produced.

Additional Supporting Information may be found in the online version of this article.

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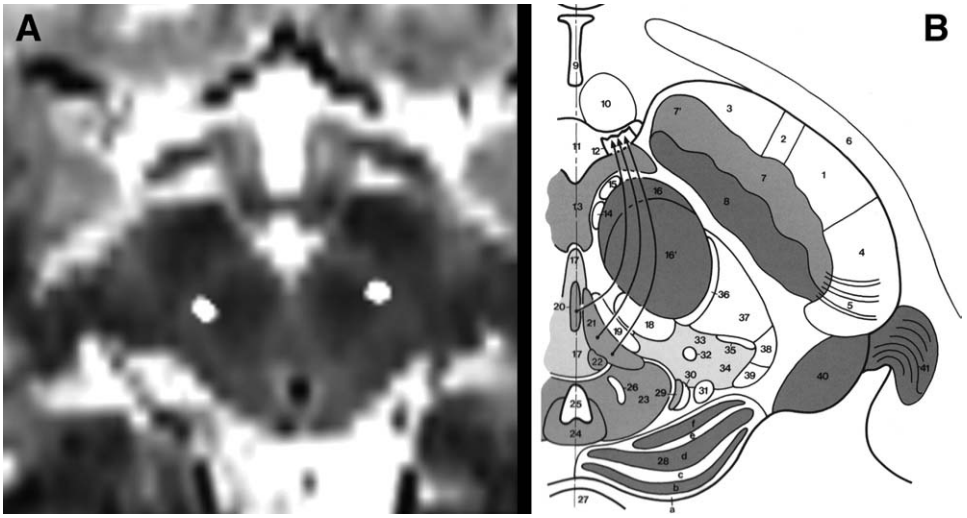

FIG. 1. A: T2-weighted MR image showing the active contacts adjacent to the lateral border of the red nucleus. **B:** Plate from Duvernoy's atlas of the human brain stem and cerebellum (page 88, Fig. 2.20),[3] showing the cerebellorubrothalamic fibers running lateral to the red nucleus.

Eventually, comparing DBS for tremor at the different PSA and thalamic substructures will further elucidate the optimal target.

Legends to the Video

Segment 1. The patient before surgery: postural and action tremor of the arms and head tremor are visible.

Segment 2. The patient after surgery with stimulator switched on: marked reduction of head and arm tremor with residual intention component in the right arm.

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The Influence of Deep Brain Stimulation on Pain Perception in Parkinson's Disease

With great interest, we read the article of Gierthmühlen et al[1] reporting on the effects of deep brain stimulation of the subthalamic nucleus (STN-DBS) on sensory signs and symptoms in Parkinson's disease (PD). Their findings are in line with our own observations in 15 PD patients treated with bilateral STN-DBS (age [mean ± SD]; 64.2 ± 9.9 years; disease duration [mean ± SD], 17.3 ± 4.8 years; duration of STN-DBS [mean ± SD], 37.6 ± 30.5 months; 5 women and 10 men) who we were able to test for thermal detection and thermal pain thresholds. For evaluation of the influence of STN-DBS and L-dopa on thermal perception, testing was carried out in 4 conditions, namely, with STN-DBS turned OFF and with STN-DBS turned ON, in each case tested with and without parkinsonian medication (OFF/OFF − OFF/ON and ON/OFF − ON/ON). Testing was carried out on the body side more seriously affected by PD. For performance of testing, we refer to the literature.[1] In addition, all patients underwent a standardized motor examination with Unified Parkinson's Disease Rating Scale (UPDRS) part III in each condition. At the time of examination, all patients were free of any other disorders with the potential to alter peripheral sensibility. The study received approval from the Ethics Committee of the Medical University Innsbruck, and all subjects gave written informed consent. For data analysis, the Wilcoxon signed rank test and Spearman rank correlation analysis were performed, and $P < .01$ and $P < .05$, respectively, were chosen as levels of significance.

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Table 1. Cold detection thresholds (CDTs), warm detection thresholds (WDTs), cold pain threholds (CPTs), and heat pain thresholds (HPTs) with inactivated neurostimulation in medical off (OFF/OFF), with activated neurostimulation in medical off (ON/OFF), with inactivated neurostimulation in medical on (OFF/ON), and with activated neurostimulation in medical on (ON/ON)

	OFF/OFF	ON/OFF	OFF/ON	ON/ON	*P* (OFF/OFF vs ON/OFF)	*P* (OFF/OFF vs OFF/ON)	*P* (OFF/OFF vs ON/ON)
CDT (°C)	27.3 ± 3.7	27.2 ± 3.2	23.8 ± 7.8	24.1 ± 6.9	ns	ns	ns
WDT (°C)	40.7 ± 4.6	42.0 ± 3.7	40.8 ± 4.9	41.6 ± 4.6	ns	ns	ns
CPT (°C)	12.5 ± 9.4	9.5 ± 9.0	10.8 ± 9.2	11.5 ± 8.0	ns	ns	ns
HPT (°C)	46.3 ± 4.4	47.8 ± 2.8	47.0 ± 3.2	47.1 ± 3.5	ns	ns	ns

Data given as mean ± SD.

Sensory testing did not reveal any influence of STN-DBS or L-dopa on thermal detection thresholds or thermal pain sensitivity in PD patients (see Table 1). Furthermore, no correlation was found between pain thresholds and the severity of motor symptoms, as indicated by UPDRS part III. Mean UPDRS III scores improved from 43.6 to 34.6 on medication, to 27.5 with activated stimulation and to 25 with activated stimulation and medication.

These findings suggest that thermal pain thresholds remain uninfluenced by STN-DBS or L-dopa as also reported by Gierthmühlen and colleagues. At the same time, our findings with L-dopa are discrepant with earlier studies showing modulatory effects of L-dopa on pain sensitivity in fluctuating PD[2] and are also inconsistent with clinical observations on off-period-related pain.[3] These discrepancies highlight the need for future studies on pain modulatory effects of L-dopa in PD.

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Reply: The Influence of Deep Brain Stimulation and Levodopa on Pain Perception in Parkinson's Disease—Implications for Further Scientific and Clinical Work

We thank Spielberger et al for the presentation of their own observations in relation to our published article about the influence of subthalamic nucleus deep brain stimulation (STN-DBS) and levodopa on sensory signs in Parkinson's disease (PD).[1] Congruent with our findings, no influence of STN-DBS or levodopa on thermal pain thresholds in PD was observed, which contrasts with previous studies.[2,3] The discrepant findings not only highlight the need for further investigations on the involvement of the dopaminergic system in pain perception in PD, but also strengthen the need for a better classification of pain in PD considering the different etiologies (nociceptive, neuropathic, related to/independent of motor symptoms, attributable to motor symptoms such as rigor, dystonia, and dyskinesia). Patients with different pain etiologies might respond differently to treatments. Therefore, ideally, homogenous (regarding the prevailing pain etiology) patient samples should be investigated in order to investigate the effect of certain drugs/treatments. However, this requires good classification of pain in PD, but studies focusing on a systematic assessment are rare.[4] Further, not only from a scientific point of view but also from the clinical point of view, it is important to focus on pain in PD, as it is a frequent but still underreported and insufficiently treated symptom in PD.[5] Awareness of this problem should be increased, and clinicians need to draw

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their attention to optimizing nonmotor symptoms such as pain for a better quality of life in PD.

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Quantitative Evaluation of the Drawing of a Spiral on a Paper

We read the article from Kraus and Hoffmann[1] in which the authors present a supposedly new instrumental method to objectively evaluate the drawing of a spiral on a paper through the analysis of its digitized picture obtained off-line with a commercial scanner. We were very surprised that the authors completely ignored our own article[2] published 4 years ago. In it, we reported for the first time that a spiral drawing specimen may be transformed in a numerical series able to be mathematically analyzed thanks to the use of a commercial scanner. The first aim of our work was to conjugate the advantage of obtaining the spiral specimen without any limitations imposed by the use of a digitizing tablet and the possibility of an objective evaluation of the drawing. These are also the most relevant advantages that Kraus and Hoffmann found in their method. The similitude of the article by Kraus and Hoffmann and our article not only resides in the digitization procedure but also in the type of analysis performed on the numerical data. These authors quantified the intensity of tremor as the maximal amplitude between the patient's drawing and the "best-fit spiral curve," which is a low-pass filtered version of the original spiral. This index is basically the same as what we called "radial error" in our article. We also attempted to validate our instrumental method, comparing its results with the clinical score given by 3 neurologists using the same scale[3] that Kraus and Hoffmann used in their article with the same objective. Finally, we developed a mathematical model of the drawing of tremulous spirals to understand the results of our method. The same strategy has been adopted by Kraus and Hoffmann.

An extensive revision of the literature relevant to a particular topic constitutes an important part of scientific work, and it is essential in order to set our own results in the right perspective. Undoubtedly, the article from Kraus and Hoffmann contains valuable information, but it does not propose a genuinely novel idea, considering our preceding article. The importance of their work is to confirm that the digitization of spirals specimens and its subsequent mathematical analysis is a useful method for quantifying the execution of the drawing of a spiral on paper and that this procedure gives relevant clinical information, as we proposed initially.

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Reply: Quantitative Evaluation of the Drawing of a Spiral on a Paper

We are thankful for the possibility of answering the letter from Miralles et al.[1]

We developed our fully automated technique for the evaluation of drawings on paper (graphimetry) in 2002 (patent application 2003). Since then, we have analyzed more than

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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 al[3] from 2006, although we have consistently updated our references (eg, Elble et al[4]). In retrospect, we, unfortunately, have no explanation for why this article[3] (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 Findley[5]).

Other points that are suggested to be "similarities" are in fact fundamental methodical differences—they are partly even misrepresented. Thus, Miralles et al[1] 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 article[2] is: ". . . *'best-fit spiral curve' is calculated with an* ***interpolation process ('moving window'- technique)*** *.* ***. . . working similar to a high-pass*** *filter*. . ." (indeed our result[2] is a horizontal line with overlaid perpendicular tremor).

Bain and Findley's instructions[5] 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's[3] "radial error" does not appear in our method.

Our "spiralometry" technique[2] 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 Findley[5] (see Fig. 5 of our original article[2]).

In contrast, the tracing test from Miralles et al[3] needs a preprinted spiral for evaluation (with this technique, it is therefore not at all possible to evaluate the spirals from Bain and Findley[5]). Furthermore, their analysis[3] 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 previously[2] 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 colleagues[1] 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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