Title

Letter to the Editor: Indirect bypass in nonmoyamoya intracranial arterial stenosis. Author reply.

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Letters to the editor

Deep brain stimulation for dystonia

To The Editor: The authors of a recent paper in the *Journal of Neurosurgery* suggest that subthalamic nucleus (STN) deep brain stimulation (DBS) for dystonia is superior to pallidal DBS (Schjerling L, Hjermind LE, Jespersen B, et al: A randomized double-blind crossover trial comparing subthalamic and pallidal deep brain stimulation for dystonia. Clinical article. *J Neurosurg 119:*1537–1545, December 2013).[1] Microelectrode recording (MER) was employed to guide lead implantation for both nuclei. A crossover design with 6 months' stimulation at each target was planned, with blinded clinical evaluation after each stimulation period. Only 8 of the 12 included patients completed the study protocol.

Figure 2 presents a diagram of lead location within the globus pallidus internus (GPi) that is based on postoperative imaging. This figure contradicts the claim that "Most electrodes were positioned near the intended location (… posteroventral in the GPi)…." In this figure, also chosen to grace the cover of the December issue of the journal, the majority of leads lie outside the posterolateral third of the nucleus and a number are within the anteromedial third of the internal pallidal segment.[1]

Despite the use of MER, the majority of pallidal leads do not appear to have reached the intended anatomical target. The conclusion that STN DBS may be more efficacious for dystonia than posteroventral GPi DBS is therefore inaccurate. However, an alternative conclusion does present itself: correct interpretation of postoperative stereotactic imaging documenting actual (as opposed to intended) lead location is an essential part of every DBS procedure.

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Disclosure

Mr. Zrinzo and Prof. Hariz report having received travel expenses and honoraria from Medtronic and St. Jude Medical for speaking at meetings. Prof. Blomstedt reports stock ownership in Mithridaticum AB.

Reference

1. Schjerling L, Hjermind LE, Jespersen B, Madsen FF, Brennum J, Jensen SR, et al: A randomized double-blind crossover trial comparing subthalamic and pallidal deep brain stimulation for dystonia. Clinical article. **J Neurosurg 119:**1537–1545, 2013

Response: We would like to thank Zrinzo, Blomstedt, and Hariz for their interest in our article, demonstrating that the STN may be an interesting target for DBS in dystonia, in comparison with the current standard, stimulation of the GPi. In our study, we implanted DBS electrodes bilaterally in the STN and the GPi in 12 patients with dystonia. In a randomized double-blind trial, 2 periods of stimulation of either target were compared. There was clinical effect of stimulation in either target, but no statistically significant difference in the clinical effect between the 2 targets. There was a trend indicating superior effect of STN stimulation, and in some patients superior effect was obtained by simultaneous stimulation of both the STN and the GPi.

The strength of our study is that it is a randomized controlled study. The weakness of the study is, as pointed out by Zrinzo et al., that the study population was rather small. We were careful not to conclude beyond the statement that DBS of the STN in our study proved to be a safe and promising target in the treatment of patients with dystonia. We did not, as indicated by Zrinzo et al., claim that STN stimulation was superior to GPi stimulation in dystonia.

Zrinzo et al. question whether the placement of electrodes within the GPi in our study was in the correct part of the GPi for optimal effect in dystonia. We find the precise location of the electrodes within a given nucleus to be very important and therefore welcome the debate. Our study started in 2002, and since then the awareness that posteroventral placement of electrodes within the GPi is optimal has increased. In our study, postoperative MRI demonstrated that in 2 patients the electrodes passed more anteriorly, and although one of those patients had marked effect on dystonic symptoms, both patients experienced suboptimal effect compared to the effect achieved with STN placement. In all the other patients, the electrodes passed through the center or posterior portion of the GPi. It should be noted that with a classical trajectory from the coronal suture, an electrode passing through the center of the GPi terminates in the posteroventral portion (Fig. 1).

We are aware of the important article co-authored by Zrinzo and Hariz, two of the authors of this letter to the editor: "Effect of electrode contact location on clinical efficacy of pallidal deep brain stimulation in primary generalised dystonia," published in 2007.[1] In that article, it was concluded that posteroventral stimulation provided the best overall effect of dystonic symptoms, a statement that we agree with.

As this discussion reveals, correct localization of electrodes in the GPi is more complex than in the STN. This supports one of the conclusions in our article, that

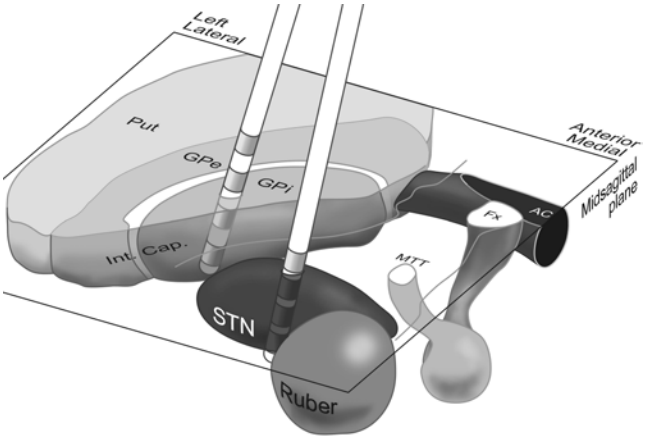

Fig. 1. Three-dimensional drawing showing the basal ganglia cut approximately at the level of the anterior commissure (AC). Two electrodes are visualized well placed in the GPi and STN. Fx = fornix; GPe = globus pallidus externus; Int. Cap. = internal capsule; MTT = mammillothalamic tract; Put = putamen; Ruber = nucleus ruber.

the more simple identification of the STN makes it a suitable target in dystonia, if indeed further studies prove STN simulation to be as effective as GPi stimulation.

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Deep brain stimulation without microelectrode recording

To The Editor: With regard to optimal targeting for deep brain stimulation (DBS) and the use of microelectrode recordings (MERs), Burchiel et al.[1] (Burchiel KJ, McCartney S, Lee A, et al: Accuracy of deep brain stimulation electrode placement using intraoperative computed tomography without microelectrode recording. Clinical article. *J Neurosurg 119:*301–306, August 2013) and numerous other authors[3] have made important contributions to the debate, but unfortunately have made serious logical errors. First, with respect to the repeated use of the term "accuracy," the more appropriate term is "precision." The latter refers to the reproducibility of the action and the former refers to the validity of the action; that is, how often the action results in the true condition. For example, an action can place a DBS lead in the wrong position but do it with a high degree of reproducibility. For these authors to use the term "accuracy" appropriately, they would have to assume that the initial targeting was exactly the valid target. Therein lies the second error.

The valid target is that which results in the maximum benefit and the minimum risk. It is not a foregone conclusion that the anatomical targets available on MRI or CT studies have a one-to-one correspondence to the valid target as defined. To be sure, determining the accuracy relative to the valid target is highly problematic. One option is to use a more accessible surrogate such as the physiologically defined optimal target.[2] Such studies raise questions as to the variability of the physiologically defined optimal target and anatomical targets that can be visualized on MRI or CT—which relates to the third error, the presumption that the valid targets can be visualized on MRI or CT studies.

For any imaging (including electrophysiological imaging) to be useful, the target must have some contrast with adjacent nontargets in the physical modality used by the scan, be it proton density, radiodensity, or patterns of neuronal action potential discharges. Contrary to the presumption of Burchiel et al.[1] and many others, the subthalamic nucleus is not the target. Rather, it is the sensorimotor region of the subthalamic nucleus and the other regions of the subthalamic nucleus that must be avoided. There is nothing on the MRI or CT studies that can differentiate the sensorimotor region from the others, whereas MERs can. This is tacitly admitted by Burchiel et al. and many others by their having to resort to coordinates relative to the anterior and posterior commissure for their targeting in the case of thalamic DBS.

The sources of error that affect accuracy and precision are multiple, including those arising from the methods and those inherent in the intrinsic biological variability. The problem is that as of yet there has been no way to differentiate the contributions made by the various sources of error. The critical issue is that improved surgical techniques may reduce one source of error but not the others, and if the biological variability is significant, then MERs are the only way currently to deal with that variability.

Most reasonable persons would agree that the use of MERs increases the risks and costs of DBS surgery. However, the use of MERs may reduce the risk of reoperation in the event of failed placement or (possibly worse) only partial benefit that makes it difficult to recommend lead revision. But the risks are only one aspect of the decision whether and how to pursue DBS. The other side of the equation is benefit, and how the surgical methodologies impact benefit. Unfortunately, this question is very difficult to answer.[2] Furthermore, development of systems that will enable any neurosurgeon anywhere to provide image-guided and MER-mapped DBS lead placement by offloading the required expertise is nearly complete, thus obviating one concern about MERs reducing accessibility.

All sides of the continuing open debate have limitations. For the future resolution of this important question, premises (both implicit and explicit) and arguments must be clearly and accurately stated.

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Disclosure

Dr. Montgomery consults for FHC, Inc.

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Response: No response was received from the authors of the original article.

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Indirect bypass in nonmoyamoya intracranial arterial stenosis

To The Editor: We read with great interest the article by Dusick et al.[4] (Dusick JR, Liebeskind DS, Saver JL, et al: Indirect revascularization for nonmoyamoya intracranial arterial stenoses: clinical and angiographic outcomes. Clinical article. *J Neurosurg 117:*94–102, July 2012). The authors used indirect revascularization (mainly encephaloduroarteriosynangiosis [EDAS]) to treat 13 patients with symptomatic intracranial arterial stenosis in whom medical management had failed and for whom endovascular therapy was unsuitable or had failed over a 9-year period. In 3 of their patients a definitive etiology of intracranial atherosclerosis could be determined. In 1 patient the area of stenosis looked like a healed area of arterial dissection. The other 9 patients were considered to have a vasculopathy of unknown origin. The authors concluded that indirect revascularization appears to be a safe and effective method to improve blood flow to ischemic brain caused by intracranial arterial stenosis.

As mentioned in the article, optimal treatment of intracranial arterial stenosis has not been fully elucidated.[1,14] Even with maximal medical therapy, symptomatic intracranial arterial stenosis has a high recurrent stroke rate (as high as 15% in 2 years and as high as 25% in high-risk groups).[3,16,17] In patients with intracranial arterial stenosis, the presence of poor collateral circulation increased by 6-fold the risk of stroke in the compromised vascular territory.[10] It is clear that these patients are in need of better alternatives for treatment and that enhancing collateral circulation may play a significant role in reducing the risk of stroke or death. However, neither endovascular angioplasty and stenting[11] nor direct revascularization proved to be a benefit over best medical management.[5,13]

Although the authors mentioned the limitations of their study (the relatively small number of cases and its retrospective nature), we agree with their conclusion that indirect revascularization could be a safe and effective means to improve blood flow to ischemic brain caused by intracranial nonmoyamoya stenotic disease, based on both the literature and our practice. Hallemeier et al.[8] described the baseline clinical features and outcomes in adults with moyamoya phenomenon treated at a single North American institution. The data suggest a potential benefit with surgery (mainly EDAS) if a diagnosis could be made earlier. Goyal et al.[6] studied the clinical characteristics and outcome in adults with idiopathic basal arterial occlusive disease without moyamoya collateral vessels. They found that the clinical features and outcome in these patients are similar to those reported in large case series of North American patients with moyamoya phenomenon. Their data suggest a common origin for the basal arterial occlusive process and a variable ability to form moyamoya collaterals.

In addition to cases in which EDAS is an effective operation in the treatment of moyamoya disease, we believe it is effective in intracranial arterial stenoses with unknown origins. We have followed 42 patients with intracranial nonmoyamoya stenotic or occlusive disease treated by EDAS since 2006 (data not published). Approximately three-fourths of the patients achieved direct spontaneous anastomoses from superficial temporal artery (STA) to middle cerebral artery (MCA), and many of them demonstrated middle meningeal artery (MMA) to MCA anastomoses. More than 85% of the patients experienced clinical improvement. Interestingly, even in those who did not develop good anastomoses from external carotid artery (ECA) to MCA, clinical improvement was found in the follow-up period. Based on our observation, moyamoya features do not definitely determine the ability to form STA-MCA anastomosis after the EDAS operation. At the same time, we found that clinical improvement could be achieved even without the formation of anastomosis. In addition, many patients improved clinically soon (several hours or days) after the operation, despite the fact that the STA did not immediately develop anastomosis. The mechanism should be further researched.

Komotar et al.[9] concluded that indirect bypass does not promote adequate pial collateral artery development and appears to be of limited utility in patients with symptomatic internal carotid artery (ICA) or MCA stenoocclusive disease and secondary hemodynamic failure. Dusick et al. thought that Komotar's patients represented a different group from their own because Komotar's cohort presented with complete intracranial occlusion (in what appears to be 11 of the 12 individuals). However, our patients with complete ICA or MCA occlusion demonstrated formation of anastomosis as well as patients with ICA or MCA stenosis. Meanwhile, in 10 of Komotar's patients, the pathology of the artery was located at the canal segment, not the end segment of ICA. The origin of disease in Komotar's patients might be different from that of patients with the moyamoya phenomenon. However, even when the artery pathology was located at the canal segment, anastomosis could be achieved in our patients.

Some authors have advocated[7] combined direct bypass

with indirect revascularization to treat patients with intracranial nonmoyamoya stenotic or occlusive disease. However, it needs to be emphasized that none of the patients with clinically severe disease could recover completely, and the major purpose of the operation is to prevent recurrent stroke. Therefore, safety is the foremost demand of the operation. Compared to direct revascularization, the EDAS procedure is technically less demanding. The operating time for EDAS is much shorter, and the procedure is much less invasive. Indirect bypass might in theory avoid rapid flow reversal while slowly providing additional flow to distal vascular beds at risk. Furthermore, in contrast to direct bypass, indirect bypass may be safer, generally less complicated, possible in patients with a poor donor STA, and may augment a greater region of cerebral perfusion. There is almost no need for antiepileptic therapy. In our practice, we achieved clinical improvement in most of the patients and robust revascularization without severe complication.

A deficiency of the article is that the authors did not mention cognitive function in their patients. It is reported in the literature that 3 months after stroke attack, approximately 30% of patients developed dementia.[2,12,15] Stroke may lead to consequent cognitive disorder in 50%–75% of patients. We found that many patients with incomplete stroke due to nonmoyamoya intracranial arterial stenosis suffered from cognitive disorders by different degrees, and that the cognitive function improved by different degrees after EDAS operation. Future studies should include cognition assessment for these patients.

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Disclosure

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Response: We appreciate the insightful comments by Tong et al. regarding our paper. We are encouraged by their early (unpublished) positive experience with EDAS as a treatment for intracranial arterial stenosis, which parallels not only the results we reported in the *Journal of Neurosurgery,* but also the most recent results in our expanded cohort. Since publishing that early experience we have continued to have great interest in expanding the application of EDAS for stenoocclusive disease of nonmoyamoya origin, and we are currently enrolling patients

in a Phase II trial of EDAS and intensive medical management for intracranial arterial stenosis of atherosclerotic origin (ERSIAS [EDAS Revascularization in Patients with Symptomatic Intracranial Arterial Stenosis]). We expect that the findings of that trial will serve as a solid foundation to develop a pivotal Phase III study to test the efficacy of these treatments compared to intensive medical management alone.

Several observations of Dr. Tong and colleagues are of particular interest. They mention that some patients improve clinically following EDAS even if they do not form substantial, angiographically visible anastomoses to intracranial vessels. Although the large majority of our patients do form collateral vessels that are visible on angiograms at 3–6 months after EDAS, we too have had a few patients who ceased having ischemic symptoms after surgery despite a relatively reduced number of collaterals on angiograms. We are investigating the hypothesis that the process of collateral formation from EDAS is mainly guided by hypoxia, and that the neovascularization only occurs where it is needed. In those cases with relatively reduced new EDAS vessels, we have observed an increase in leptomeningeal channels providing flow from adjacent vascular territories, such as the anterior cerebral artery (ACA) or posterior cerebral artery (PCA). This reinforces the concept that in contrast to a direct bypass anastomosis, in which the flow is forced into a vascular bed, after EDAS the more gradual process of neovascularization allows flexible revascularization as needed.

Likewise, Tong et al. report early improvement in symptoms after surgery despite the fact that new blood vessels may not have grown in that short a time. Many of our patients who have frequent transient ischemic attacks (TIAs) before surgery stop having them within days or weeks of surgery. However, it should be noted that in our paper we did report that 3 patients continued to have ischemic symptomatology (although no strokes) up to 3 months postoperatively. This raises the point that despite the overall good results of EDAS for intracranial stenosis, vigilance and continued optimization of intensive medical management should continue throughout the postoperative period to reduce the risk of TIA or stroke until a more robust neovascularization develops.

We also agree that the mechanism by which some patients improve within hours or days of surgery is unclear and needs to be further explored. Interestingly, Perren et al.[2] obtained very early angiograms after indirect revascularization in patients with moyamoya and found a substantial degree of visible revascularization in as little as 4 days following surgery. Although we do not routinely perform postoperative imaging that soon, we have seen significant revascularization (scores of 2–3) on angiograms at 1–1.5 months after surgery (unpublished data; abstract presentation). A limitation in the study of early collateralization is the resolution of a catheter angiogram, which is close to 200 μm. Therefore, smaller vessels would not be seen on angiography.

As we did in our paper, Tong et al. commented on the paper by Komotar et al.[1] The results of that study differ significantly from our experience for numerous reasons: no intensive medical management was administered and maintained during the operations; patients had severe stenosis of multiple vessels in different vascular territories; and the perioperative management was not performed with a homogeneous, relatively strict protocol. In that study the majority of the patients had occlusions, and in that setting it is difficult to expect sudden improvements induced by EDAS. We have performed EDAS in select patients with complete intracranial vascular occlusions, especially when there is some degree of vascular recanalization with forward flow through the MCA branches. In those cases we have observed the same success that Tong and colleagues describe. We excluded those patients from the study presented in the *Journal of Neurosurgery* to keep the characteristics of the patients' disease as homogeneous as possible. In parallel to the patients in the ERSIAS trial, we are maintaining a detailed registry of all cases treated with EDAS that do not meet the specific trial inclusion and exclusion criteria. In this group, patients with occlusion and forward flow through recanalization or collaterals are included.

Finally, we recognize that cognitive testing is a very important portion of the evaluation of these patients and our current trial includes detailed evaluations in that sphere performed by independent neurologists not involved in the study.

In general, the comments of Tong et al. are in agreement with our findings and their experience appears to parallel our results, including potential application in cases of occlusion, as we have also observed. Further studies to understand the clinical response of these patients and the mechanisms involved in the neoangiogenesis generated by the synangiosis are, in our opinion, of fundamental importance as a potential tool for the treatment of patients with intracranial stenoocclusive disease and stroke.

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Substantia nigra hyperechogenicity and Parkinson's disease surgery

To The Editor: In their article, Pourfar et al.[15] (Pourfar MH, Tang CC, Mogilner AY, et al: Using imaging to identify psychogenic parkinsonism before deep brain stimulation surgery. Report of 2 cases. *J Neurosurg 116:*114–118, January 2012) highlighted the current challenges of estab-

lishing the correct clinical diagnosis of Parkinson's disease (PD) and the potential implications of a misdiagnosis for deep brain stimulation (DBS) surgery. In clinical practice, it is estimated that about 10% of patients with presumed PD are misdiagnosed.[10] Diagnostic accuracy is essential for an appropriate indication of surgery for PD, since patients with atypical parkinsonism usually have a poorer and less sustained response to both levodopa and DBS, and a less favorable outcome than patients with PD.[4,16] Therefore, the identification of specific diagnostic markers for PD can impact clinical decision making.

With the introduction of molecular imaging studies using SPECT or PET, the evaluation of both presynaptic nigrostriatal dopaminergic function and brain metabolic patterns has become possible. Concurrently, advances in transcranial sonography (TCS) have allowed visualization of structural changes in the substantia nigra (SN) of patients with intact skull.[5,8,11] To contribute to this subject, the importance of SN hyperechogenicity for functional neurosurgery is discussed.

Increased SN echogenicity, or SN hyperechogenicity, has been considered a biological marker for PD (Fig. 1). Several studies have reported this ultrasound sign in most PD patients (> 90%). Postmortem analyses in animals and humans have attributed increased amounts of iron, bound to protein other than ferritin, in the SN as a factor for this hyperechogenicity.[2,4,12] Interestingly, it can indicate functional impairment of the nigrostriatal dopaminergic system.[2,13]

Substantia nigra hyperechogenicity can be useful for the differential diagnosis between PD and a number of clinical conditions, such as essential tremor, vascular parkinsonism, multiple system atrophy, and progressive supranuclear palsy; SN hyperechogenicity occurs in the majority of PD patients while it is less frequently encountered in the mentioned conditions.[2,4,5,8,9] According to a prospective blinded study, the sensitivity of this ultrasound sign for idiopathic PD versus atypical parkinsonian syndromes was 94.8%, the specificity was 90%, the positive predictive value was 97.4%, and the negative predictive value was 81.8%.[9]

Substantia nigra hyperechogenicity can only help to manage patients with parkinsonism when both thorough medical history and neurological examination have been performed appropriately, because various conditions can present this ultrasound sign, among them, spinocerebellar ataxias, corticobasal degeneration, parkinsonism associated with *parkin* mutation, and a minority of healthy subjects (10%).[1–5,14]

Recently, it has been demonstrated that intraoperative localization of DBS electrodes by TCS is safe, reliable, and can predict clinical outcome.[4,16] Walter et al.[17] prospectively enrolled 34 patients with DBS of globus pallidus internus, ventrointermediate thalamic or subthalamic nucleus, and verified that TCS had no influence on lead temperature, electrical variables of DBS device, and clinical state of the patients. There was an agreement between TCS and MRI measurements of lead coordinates in the anteroposterior and mediolateral axes. Patients with optimal lead position on TCS presented favorable clinical 12-month outcome (> 50% improvement), while unfavorable outcome (< 25% improvement) was related to suboptimal lead position. It is possible that TCS can be incorporated into DBS surgical technique.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

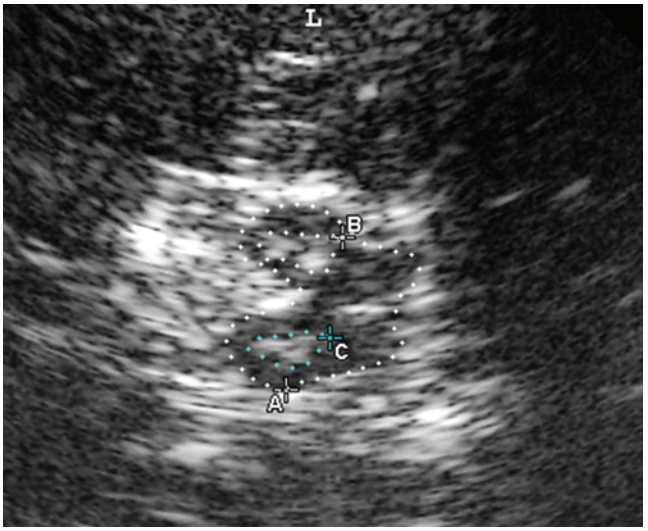

Fig. 1. Midbrain TCS image. The butterfly-shaped midbrain (A) and the SN region hyperechogenicity (left [B] and right [C] substantiae nigrae) are circled for better demonstration.

Future studies must address if SN hyperechogenicity can help to identify PD patients at early stages, or even at preclinical stages, mainly if considered in conjunction with other nonmotor signs of PD, such as depression, olfactory dysfunction, neuropsychological deficits (visuospatial processing, and sequential planning), idiopathic rapid eye movement (REM) sleep behavior disorder, and pain.[5,6,7,11] At present, there is evidence that the combined assessment of motor asymmetry, hyposmia, and SN hyperechogenicity improves diagnostic specificity and allows early diagnosis of PD.[6] In addition, both decreased striatal dopamine transporters uptake and SN hyperechogenicity are risk markers of PD in patients with idiopathic REM sleep behavior disorder.[11] Not surprisingly, in a 37-month 3-center prospective study of 1847 older healthy persons, a highly increased risk for PD was proved in those individuals with SN hyperechogenicity; the relative risk for incident PD was 17 times higher than in subjects with normal SN echogenicity.[3] If all these ideas are true, PD could be identified before manifestation of typical signs and symptoms, allowing development of neuroprotective therapies, and for selected cases, earlier indication of PD surgery.

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Disclosure

The authors report no conflict of interest.

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