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STN stimulation

STN stimulation and neuroprotection in Parkinson's disease—when beautiful theories meet ugly facts

P C Warnke

STN stimulation does not halt progression of Parkinson's disease

Repeated claims have been made that inactivation of the subthalamic nucleus (STN) is a neuroprotective measure.[1–3] It was postulated that by suppression of the glutamatergic STN, glutamate mediated excitotoxicity exerted on the substantia nigra could be reduced, if not abolished. The paper by Hilker *et al* in this issue (***see page 1217***) deals with this topic by looking longitudinally at patients who have undergone successful STN stimulation. The investigators have taken the approach of using objective functional imaging employing ^{18}F-DOPA positron emission tomography (PET), an established objective measure of biological progression in Parkinson's disease, which was then correlated with clinical progression. They were able to show convincingly that STN stimulation did not halt the progression of Parkinson's disease.

They have also shown that their technique of STN stimulation was effective both in terms of UPDRS improvement and in reducing L-DOPA or DOPA equivalent drug treatment, and was exactly within the range reported by other groups.

The PET approach to quantify disease progression will allow insights into disease biology and ways of modifying it. A critical point in using sequential PET studies is the reproducibility of quantitative ratios of L-DOPA uptake, especially in the light of huge interindividual differences in uptake in Parkinson patients. Furthermore, accurate repositioning of slices is another crucial point. Finally, patients were examined in the off-drug condition without STN stimulation but the follow up was done with deep brain stimulation turned on, though again in the off-drug condition. We have recently shown that a significant difference in dopamine transporter capacity, though not in dopamine uptake, can be seen between pre-STN stimulation and post-STN insertion but with stimulation turned off.[4] Thus electrode placement resulting in a ''microsubthalamotomy'' could have an effect on its own.

Nevertheless STN stimulation is like other traditional functional neurosurgical ablative techniques in producing symptomatic relief without affecting the biology of the disease.

What is the cause of the discrepancy between the experimental findings and this clinical study that rules out neuroprotective effects? The experimental papers used an artificial model of Parkinson's disease—that is, the 6-OHDA model which does not reproduce all the features of the disease. Furthermore in that model, STN ablation with kainic acid is used instead of STN stimulation to show the potential neuroprotective effects of STN suppression on the substantia nigra.

The paper by Hilker *et al* also raises questions about the focus of future neurosurgical approaches in Parkinson's disease. The investigators point out quite correctly that STN stimulation, which can be carried out bilaterally, has been found to be beneficial in numerous retrospective studies. However, it clearly only provides symptomatic benefit and therefore falls into the realm of traditional functional neurosurgical approaches such as STN ablation. In this context it is worthwhile asking whether the current prospective randomised controlled trial (the PD Surg trial) comparing bilateral STN stimulation with the best medical treatment is a wise investment of money. Very likely the study is going to prove the obvious. New attempts have been made by several neurosurgical groups to modify disease biology in Parkinson's disease and by doing so to achieve actual neuroprotection. These include attempts at the direct infusion of glial cell line derived neurotrophic factor (GDNF) using convection enhanced delivery, which seems to have long term effects in the same range as STN stimulation and looks very promising.[5 6] In addition, while still in the experimental phase the elegant approach of converting the excitatory glutamatergic STN by means of gene therapy into an inhibitory GABAergic nucleus—which is currently being tested in patients after successful results in an experimental Parkinson's model—also looks promising.[7 8]

Besides the worthwhile clinical information gained from Hilker's paper, another of its merits is to point out that, while STN stimulation is highly effective and beneficial in patients with Parkinson's disease, we should be looking for more sophisticated means of attacking the disease biology and hopefully modifying it.

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Correspondence to: Professor Peter C Warnke, The University of Liverpool, Department of Neuroscience, The Walton Centre for Neurology and Neurosurgery, Lower Lane, Liverpool L97LJ, UK; p.c.warnke@liv.ac.uk

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Acute stroke prognosis

DWI and acute stroke prognosis: a simple approach

V Di Piero

Analysis of DWI lesion patterns may identify stroke patients at high risk of complications

In the paper by Bang *et al* in this issue (***see pages 1222–8***), the authors deal with the possibility of predicting clinical outcome in stroke patients by considering the diffusion weighted imaging (DWI) lesion patterns. This is a new approach to MRI findings which gives more emphasis to the location of DWI alterations than to their volume or number.

Although thrombolysis is the most effective treatment for acute stroke, it is still limited to a few patients because of its strict temporal therapeutic window. It follows that most therapeutic efforts are devoted to controlling the neurologic and medical complications. Therefore, early identification of patients at high risk of complications could potentially help to differentiate acute stroke therapies by selecting those patients who should be monitored and treated more aggressively. Early identification could also thus help to allocate medical resources better.

A simple evaluation of the DWI lesion pattern showed that patients presenting with internal borderzone infarcts have a more unstable hospital course. This subgroup of stroke patients may have a particular pathophysiological condition, probably linked to a precarious haemodynamic state associated with the occurrence of large artery disease.

If these internal borderzone infarcts are located in the supraventricular and paraventricular areas, we might hypothesise an unstable penumbral state. This should mainly involve the white matter which has been recently shown to present areas of potentially salvageable tissue as well as similar resistance to ischaemia of grey matter.[1] In addition, a PET comparative study has shown that a DWI lesion may contain not only tissue destined for infarction but also penumbral areas that may still be saved.[2]

Another major early neurological complication is stroke recurrence, with a fatal outcome in about one fourth of cases. Kang *et al* demonstrated by serial DWI studies that ''radiological'' recurrences occurred in about one third of patients in the acute phase of stroke.[3] In other words, stroke appears to be a ''dynamic'' phenomenon not limited to a single event but the result of multiple local or distant ischaemic insults. In their study, recurrences occurred mainly in patients with large vessel atherosclerosis and were frequently clinically silent. Looking at clinically manifested recurrences, Bang *et al* have showed that a DWI alterations pattern of small cortical infarcts suggested a higher risk of recurrent strokes.

Recent sophisticated imaging studies have indicated the possibility of closer insights into the pathophysiology of acute ischaemic stroke and its relationship with clinical features. However, such studies frequently require dedicated devices and research teams. A simple approach such as analysis of DWI lesion patterns might provide additional useful criteria to identify a subgroup of patients at high risk of neurological complications who should be strictly monitored. If these observations are confirmed, they may provide new opportunities for a better definition of individual therapeutic interventions in the acute phase of ischaemic stroke.

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Correspondence to: V Di Piero, Department of Neurology, viale dell'Università 30, Rome 00185, Italy; vittorio.dipiero@uniroma1.it

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