Long-term effects of Deep Brain Stimulation in Parkinson’s Disease

The history of stereotactic neurosurgery for treatment of Parkinson’s disease has a remarkable track record. The traditional lesion method, employed and refined over half a century, seemed to have reached its end with the advent of l-dopa medication. But, paradoxically, levodopa-induced motor fluctuations and dyskinesias led to a renaissance of surgical therapy and the introduction of deep brain stimulation by Alim-Louis Benabid et al. (1987) opened a new therapeutic window for treatment of the late levodopa syndrome. From the beginning it appeared that the effects of stimulation mimic those of stereotactic lesions. Whereas the advantage of the fine tuning of treatment and its reversibility spoke for the new method, its long term efficacy still awaited the test of time. Recently, the Grenoble group reported the results of a 5 year follow-up showing that subthalamic nucleus deep brain stimulation had persistent beneficial effects in 42 patients (Krack et al., 2003).

In this issue of Brain, Rodriguez-Oroz et al. (2005) report results of the first worldwide multicentre study on long term effects of deep brain stimulation. Eight groups enrolled 69 bilaterally implanted patients who were assessed preoperatively and 3–4 years postoperatively. What is particularly valuable is the comparative evaluation of the effects of stimulating the subthalamic nucleus (49 patients) and the globus pallidus, pars interna (20 patients). The globus pallidus, pars interna was the first target structure for deep brain stimulation, but subsequently published data seemed to favour the subthalamic nucleus. This tendency is set in perspective by the results presented here revealing similar overall efficacy for both targets. Most impressive was the improvement of the frequency and severity of ‘off’ periods and of dyskinesias in both groups. Whereas the main effects of deep brain stimulation were surprisingly similar at the two stimulation sites, the adverse effects (speech, postural and equilibrium problems) and cognitive impairment along with mood disturbances were more pronounced in the subthalamic nucleus group than in the GPi group. Whether this is due to area-specific differences or to technical reasons such as current spread to surrounding fibres or spatial inaccuracies of electrode placement into the smaller target remains unclear. Differences on the basis of medication between the two groups seem unlikely, because the still relatively high daily levodopa dosages were significantly lower in the subthalamic nucleus group (859 versus 1418 mg per day in the globus pallidus, pars interna group).

Regarding disease progression, there was no significant difference between the UPDRS III motor scores in the off medication states obtained at baseline and at 4 years in the off stimulation condition in both groups. This is mainly attributed to the beneficial long term effects on the cardinal features of Parkinson’s disease: tremor, rigidity and hypokinesia. In contrast, gait, postural stability and speech worsened significantly in both groups. This preferential deterioration of axial features is taken as further support for the frequently addressed issue of disease progression outside the dopaminergic system in the late stages of the disease.

The analysis of the data showed another noteworthy difference: tremor benefited most (subthalamic nucleus 87%; globus pallidus, pars interna 85%), followed by rigidity (59 and 38%), hypokinesia (42 and 30%) and gait (41 and 28%). Both ‘positive’ symptoms, tremor and rigidity (the latter only for subthalamic nucleus stimulation) responded better than the ‘negative’ symptoms. The common denominator of tremor and of the cogwheel phenomenon in rigidity is oscillatory muscle activity in the 3–6 Hz range. Blockage of these pathological rhythms is obviously more efficient from both targets than the modification of hypokinesia and gait frequently attributed to the down-regulation of inhibitory basal ganglia output.

A preferential effect of stimulation on pathological oscillations has repeatedly been emphasized on the basis of electrophysiological data. It has been conjectured that the clinical efficacy of high-frequency stimulation in Parkinson’s disease may result from changes in oscillatory patterning in cortical-subcortical motor loops rather than from depolarizing block (Brown et al., 2001; Levy et al., 2002). Magneto-electroencephalography recordings have revealed low-frequency entrainment of sensorimotor areas thought to play a key role in the pathophysiology of parkinsonian motor symptoms (Timmermann et al., 2003). Electrical stimulation may block or, more beneficially, desynchronize pathological rhythms, as shown in theoretical models (Tass, 2003). How far the deep brain stimulation induced modifications of pathological oscillations underlie the preferential improvement of the oscillatory clinical symptoms of Parkinson’s disease or even change the dynamics of the underlying pathomechanisms by down-regulating abnormally patterned input is unclear. However, along with the alteration of abnormal neuronal discharge rates neuroprotection might be accomplished. Hyperactivity of the subthalamic nucleus
is considered a functional hallmark of Parkinson's disease and there is evidence for subthalamic nucleus-mediated glutamatergic excitotoxicity on neurons of the substantia nigra pars compacta. Deep brain stimulation of the subthalamic nucleus can reduce this glutamatergic drive. Although Rodriguez-Oroz et al., (2005) point out that their data do not allow any conclusions regarding a possible action of deep brain stimulation on disease progression, the stability of the UPDRS III motor scores in the off medication states obtained at baseline and at 4 years (off stimulation) make this an important issue for future studies.

In this context the favourable response to deep brain stimulation in patients with young-onset Parkinson’s disease is of interest. This condition, which makes up ~5% of patients with Parkinson’s disease, is characterized by earlier onset of motor complications and rapid disease progression. Young-onset Parkinson patients who exhibit no behavioural, mood, or cognitive impairment benefit the most from deep brain stimulation of the subthalamic nucleus (Pollack et al., 2002). This group also seems particularly suitable for disentangling the effects of stimulation on motor complications from their eventual action on disease progression. A related issue of major clinical significance is whether a strategy shift from late treatment of symptoms towards earlier intervention would affect the development of the late levodopa syndrome.

Deep brain stimulation is now considered for new applications in a variety of other conditions including chronic pain, epilepsy and psychiatric disorders. The models trying to explain the intended therapeutic effects are still in their infancy. But the unsolved questions about the ways of action and the scope of clinical applications in Parkinson’s disease continue to be one of the most challenging issues for future research on brain stimulation.

**References**


