

## Invited commentary

### Obesity in Parkinson's disease patients on electrotherapy: collateral damage, adiposity rebound or secular trends?

Whether obesity should be considered as a disease is debatable, but it is undeniable that it provokes the development of debilitating diseases that include type 2 diabetes, CVD and some forms of cancer. Consequently, emerging evidence that functional brain surgery for alleviating the clinical symptoms of Parkinson's disease – by electrode implantation for deep-brain stimulation – results in a relatively high prevalence of overweight and even obesity may sound like jumping from the frying pan into the fire.

First described in 1817 by James Parkinson in his essay on 'The shaking palsy', Parkinson's disease is a chronic and progressive neurological disorder characterised by rigidity of the limbs, trunk and face, tremor when awake and resting, abnormal body posture and difficulties in initiating voluntary motor activity (akinesia). The clinical manifestation of the syndrome usually begins in the fifth decade of life, and results from degeneration and premature death of brain cells that produce dopamine, a neurochemical that plays an important role in the control of motor functions (Samii *et al.* 2004). Hailed as one of the miracles of modern medicine after its introduction to treat Parkinson's disease in the late 1960s, levodopa, which is taken up by dopaminergic neurons where it is made into dopamine, is particularly effective in restoring the ability to initiate movement. But after an initial satisfactory response to levodopa (or to dopamine agonists), many patients develop motor fluctuations that are difficult to control. They alternate between a state of severe parkinsonism (the 'drug-off' period when the medication is not working) and a state of improved mobility (often accompanied by dyskinesia) during the 'drug-on' period when the medication is working. The patients become susceptible to malnutrition, since both the disease symptoms and the medication side-effects (nausea, vomiting) can limit food intake, while involuntary movements and the development of muscle rigidity can lead to marked elevations in 'resting' energy expenditure (Markus *et al.* 1992). Parkinson's disease patients are four times more likely to report weight loss exceeding 4 kg than matched control subjects, and to have lower BMI, triceps skinfold thickness and percentage body fat, which correlate significantly with weight change and the stage of the disease (Beyer *et al.* 1995). Despite the fact that these complications become increasingly common and disabling with longer durations of the disease and of exposure to levodopa, the latter remains the most potent antiparkinson drug and is the backbone of treatment throughout much of the disease course.

Attempts to alleviate the 'levodopa syndrome' have led to a resurgence of surgical treatments centred upon the ablation of deep brain structures. Indeed, before levodopa, thalamotomy was found to reduce contralateral tremor, while pallidotomy variably improved motor symptoms in Parkinson's disease. The renewed interest in functional brain surgery has now shifted to high-frequency stimulation of deep-brain targets, which causes

less irreversible brain trauma than ablative surgery. Among the anatomical targets for such brain electrotherapy, bilateral stimulation of the internal segment of the globus pallidus or the subthalamic nucleus has emerged as being particularly effective at relieving motor symptoms. These procedures provide considerable clinical benefits, in terms of both improvement in primary symptoms (tremor, bradykinesia and muscle rigidity) and resolution of side-effects of chronic pharmacological treatment (dyskinesia). It also permits a 50 % or more reduction in the levodopa dosage required for satisfactory symptom control (Lang, 2003; Samii *et al.* 2004). Although poorly documented, there are also reports that many patients show modest weight gain (Moro *et al.* 1999; Gironell *et al.* 2002; Romito *et al.* 2003), which is thought to be consequential to the improvements in involuntary movements and in mood, and hence in the normalisation of energy intake and energy expenditure to the pre-disease (and pre-weight loss) level. Whether deep-brain stimulation of the bilateral subthalamic nucleus (referred to as STN-DBS) is superior to bilateral globus pallidus stimulation in patients with Parkinson's disease is unclear, but recent reports that excessive weight gain is common in patients treated by STN-DBS are likely to fuel further the on-going debate about the best stimulation target for this disorder.

Indeed, two independent retrospective studies – one from Italy (Barichella *et al.* 2003) and the other from France (Macia *et al.* 2004) – that have evaluated body weight changes in STN-DBS-treated Parkinson's patients up to 14 months after electrode implantation report an average weight gain of 9.3 kg and 9.7 kg, respectively. Comparison of the distribution of BMI before and after the procedure indicates a clear shift from underweight and normal weight towards overweight and even obesity. It is clear that explanations as to why more than 25 % of patients gained between 10 and 16 kg in a year, and weighed more than they ever had in their lifetime, go well beyond the normalisation of body weight to pre-disease levels. Given the close correlation observed between changes in motor scores and body weight gain assessed at 3 months and a year after surgical intervention, the question arises as to whether STN-DBS intervention – perhaps through interference with nearby hypothalamic areas involved in controlling appetite and energy expenditure – could underlie this apparent dysregulation of body weight. However, weight overshooting based upon 'collateral damage' from STN-DBS therapy seems unlikely, judging from a follow-up of the French study published in a previous issue of this journal (Perlempine *et al.* 2005). In the follow-up, resting energy expenditure, substrate oxidation and daily energy intake were compared in STN-DBS-treated patients, in non-operated patients (awaiting surgery) and in a group of healthy controls. Although 1 year after STN-DBS electrotherapy the operated patients showed lower resting energy expenditure as well as lower

fat and protein oxidation than the non-operated patients, no significant differences were found in resting metabolism or in energy intake between STN-DBS-treated patients and healthy controls. Thus, STN-DBS therapy did not seem to perturb energy intake and energy expenditure beyond levels found in healthy individuals, and excessive weight gain following such electrotherapy would seem to be related to changes in the cardinal manifestations of Parkinson's disease itself, rather than to secondary changes resulting from the surgery.

A more likely scenario, at least among STN-DBS-treated patients who may have lost a substantial amount of weight during the course of the disease, is that the improvements in motor functions in the months immediately following electrotherapy led to an unmasking of autoregulatory mechanisms that normally operate to restore body fat and fat-free mass through increases in hunger and/or through adaptive reductions in energy expenditure (Dulloo *et al.* 1997; Dulloo & Jacquet, 1998). These mechanisms are thought to underlie the phenomenon of disproportionate rate of fat recovery and fat overshooting, i.e. 'adiposity rebound', which has been observed during follow-up studies of famine victims of World War II, and documented in longitudinal studies of experimental starvation and re-feeding in man (see Table 1).

In their classic Minnesota Experiment of semi-starvation and re-feeding, Keys *et al.* (1950) described this phenomenon as 'post-starvation obesity'. It has, in more recent years, been traced to the asymmetry in body fat and fat-free mass recovery consequential to mechanisms that suppressed thermogenesis specifically for accelerating recovery of fat mass, and not fat-free mass (Dulloo *et al.* 1997; Dulloo & Jacquet, 1998; Weyer *et al.* 2000). Thus, in Parkinson's patients who may have lost a considerable amount of body fat during the course of the disease, the efficacy of the STN-DBS in normalising motor functions may, paradoxically, have disinhibited intrinsic mechanisms of adiposity rebound that underlie the syndrome of 'post-starvation obesity'. These same mechanisms, in particular those that suppress thermogenesis in favour of accelerating specifically fat recovery (or catch-up fat), also confer to the phase of weight recovery its particularly high sensitivity to the development of hyperinsulinaemia and insulin resistance (Dulloo *et al.* 2002; Crescenzo *et al.* 2003), thereby putting the patient at risk for obesity and type 2 diabetes.

Finally, secular changes in body weight and adiposity might also be relevant in explaining weight overshooting in the STN-DBS-treated Parkinson's patients, given disease duration of 10–15 years before the start of electrotherapy. During this period, an increase in the prevalence of overweight and obesity of similar magnitude among the general population of the same age range (50–70 years) is not unusual. This 'secular trend' factor may assume even greater significance given recent findings – from two prospective epidemiological studies – that increased adiposity

during middle adulthood is associated with an elevated risk for Parkinson's disease later in life, notably 15–30 years later (Abbott *et al.* 2002; Chen *et al.* 2004). These epidemiological associations between midlife adiposity and later Parkinson's disease, whose cardinal signs are largely due to the loss of dopamine-producing neurons in the substantia nigra area in the brain, together with clinical observations that obesity is associated with depletion of striatal dopamine D<sub>2</sub> receptor availability (Wang *et al.* 2001), suggest that nigrostriatal system disorders are associated with both Parkinson's disease and obesity (Abbott *et al.* 2002). It has also been proposed that either obesity down-regulates dopamine D<sub>2</sub> receptors, perhaps to compensate for increased dopamine concentration associated with overeating, or lower dopamine D<sub>2</sub> receptor availability may lead to overeating and obesity. In either case, the lower dopamine D<sub>2</sub> receptor availability may predispose those with a tendency to fatness to later risk for Parkinson's disease (Chen *et al.* 2004). In this context, the efficacy of STN-DBS in normalising motor functions in some Parkinson's disease patients some 10–20 years after clinical diagnosis of the disease may also have allowed their inherent predisposition to obesity to manifest itself.

Whatever the exact explanations for weight overshooting in STN-DBS-treated Parkinson's disease patients, the subthalamic nucleus is likely to become a new centre of attraction for investigations towards understanding how body weight is regulated, and how some individuals become more prone to obesity than others.

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**Table 1.** Post-starvation weight overshooting in man

Study	Type of energy deprivation	n	Weight overshoot (kg)
Benedict (1907)	Total fast	5	2.7
Benedict <i>et al.</i> (1919)	Semi-starvation	11	3.1
Keys <i>et al.</i> (1950)	Semi-starvation	12	3.6*
Martin & Demole (1973)	Food rationing	700	6.5

\* Excess weight was accounted for by fat, measured by hydrostatic weighing.

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