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# The impact of deep brain stimulation on the nonmotor symptoms of Parkinson's disease

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**Abstract** Deep brain stimulation (DBS) is a well-established therapy for patients with advanced Parkinson's disease (PD) with clear benefits on many of the motor symptoms. The effects of DBS on the nonmotor symptoms are less well examined. Emergence of tools to measure the nonmotor burden in PD is now allowing a more objective assessment of impact of DBS on such symptoms. Here we review the pertinent evidence and conclude that, as a therapy, DBS has a major potential to contribute towards the holistic care of PD patients.

**Keywords** Deep brain stimulation · Nonmotor symptoms · Parkinson's disease

## Deep brain stimulation, Parkinson's disease and nonmotor symptoms

Deep brain stimulation (DBS) is a functional neurosurgical technique allowing accurate placement of small electrodes into specific target areas deep in the brain (Benabid et al. 1987). This allows delivery of electrical signals, generated by a small implantable pulse generator, which then modulate pathological neural circuits to produce clinical effects. Subthalamic nucleus (STN) and globus pallidus interna (GPi) represent the targets most commonly used. There is now ample evidence on effectiveness of DBS to improve motor symptoms of advanced Parkinson's disease (PD) with significant and long-lasting benefits in tremor, rigidity and bradykinesia (Ashkan et al. 2004; Deuschl et al. 2006; Krack et al. 2003; Williams et al. 2010).

PD, however, is much more than a motor disorder. Nonmotor aspects of PD, such as sleep disturbance and delirium, are evident in the early descriptions by James Parkinson (1817) but have received limited attention by the medical community until recently. As we move forward into the twenty-first century, our patients demand and deserve a holistic approach to their management. This necessitates a thorough understanding of their disease and specific needs. The National Institute of Clinical Excellence (2006) published the UK guidelines for the management of PD. The document identified mental health problems, depression and dementia, falls and potential fractures, sleep disturbance, autonomic disturbance and pain as the main nonmotor features of PD. A major limiting factor in assessing, and therefore management, of the nonmotor burden in PD has been the lack of an effective measuring tool.

The Nonmotor Symptoms Screening Questionnaire (NMSQuest) was the first comprehensive instrument aimed to overcome this limitation (Chaudhuri et al. 2006). NMSQuest is a self-completed 30-item validated questionnaire which allows rapid assessment of nonmotor symptoms. Martinez-Martin et al. (2007) used NMSQuest to quantify nonmotor burden in 545 patients with PD.

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Nocturia (61.9 %), urinary urgency (55.81 %) and constipation (52.48 %) were most frequently reported. Overall 98.4 % of patients reported at least one nonmotor symptom, highlighting the prevalence of the problem. A more objective scale, Non-Motor Symptoms Scale (NMSS) was developed by Chaudhuri et al. (2007) to allow accurate measurement of nonmotor symptoms, assess evolution over time and gauge impact of treatment. NMSS is rated by a health professional and scores symptoms for both severity and frequency. The scale consists of 9 domains of cardiovascular/falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous (including pain, sweating and smell). Importantly, NMSS is shown to be a good predictor of health-related quality of life of PD patients as measured by PDQ-39 summary index (Martinez-Martin et al. 2011).

Current evidence indicates that nonmotor symptoms have a greater impact on quality of life of PD patients than the motor symptoms (Martinez-Martin et al. 2011; Hinnell et al. 2012). Thus, a therapy modality can only be considered holistic and truly effective if it addresses the specific problems posed by both the motor and nonmotor symptoms of PD.

## Does deep brain stimulation improve nonmotor symptoms of Parkinson's disease?

There is a limited literature on DBS and nonmotor symptoms of PD. A recent review by Fasano et al. (2012) provided a summary of the effects of DBS in PD which included both motor and nonmotor features. With respect to individual studies, Zibetti et al. (2007) reported their 2-year follow-up data on 36 PD patients treated with bilateral STN DBS. Unified Parkinson's Disease Rating Scale (UPDRS) was used to assess motor symptoms. For nonmotor aspects, those UPDRS items relating to nonmotor symptoms were analysed separately with the addition of two supplementary pieces of information obtained from patients' charts on constipation and urological function. Within the limitations of a study not using a specific nonmotor assessment tool, sleep quality and constipation were shown to be significantly improved after the surgery.

Pain is a major cause of nonmotor morbidity in PD. Kim et al. (2008) studied pain in 29 PD patients at baseline and then 3 months after STN DBS. They later reported on 21 of the original cohort followed up for 24 months (Kim et al. 2012). Pain was evaluated in terms of severity, location and type. There was significant improvement in pain following surgery which was more pronounced at 24 months compared to 3 months ($P < 0.001$). Dystonic pain responded the best (100 %) followed by central (54 %), musculoskeletal (27 %) and neuropathic/radicular (17 %) pain. The number of painful body parts also reduced from 2.7 at baseline to 1.8 at 3 months and then 1.7 at 2 years. Of note, however, 43 % of patients following surgery developed new, mainly musculoskeletal, pain which was not present at the baseline. The new pain may represent unmasking of pre-existing pain by motoric improvement following DBS or be a result of progression of skeletal degenerative disease with advancing age. Even when the new pain was taken into account, the pain scores remained lower after DBS compared to the baseline.

Autonomic symptoms also significantly contribute to the nonmotor burden in PD. Winge et al. (2007), in a prospective study of 16 PD patients treated with STN DBS and assessed at a median of 2.5 months before surgery and 6 months after, reported significant improvements in the symptoms of overactive bladder although urodynamic parameters did not change. Arai et al. (2012) evaluated gastric emptying in 16 patients with PD at baseline and 3 months after STN DBS and showed a significant improvement.

Motor and nonmotor fluctuations are a disabling feature of advanced PD, The positive effects of STN DBS on dyskinesia and motor fluctuations are well documented (Krack et al. 1997). Witjas et al. (2007) studied the effect of bilateral STN DBS in 40 PD patients before and 1 year after surgery. A structured interview and questionnaire were used to extract 54 items divided into 4 categories of nonmotor fluctuations: pain/sensory, cognitive, dysautonomic and psychic. After surgery, the mean number of different types of nonmotor fluctuations decreased from 15.6 to 6.6 ($P < 0.001$). The pain/sensory category showed the largest improvement (84.2 %) followed by cognitive (70.5 %), dysautonomic (63 %) and psychic (29.6 %). The improvement reached significant levels in all categories.

Systematic studies specifically focusing on the effect of DBS on nonmotor symptoms of PD are rare and controlled studies are as yet to be done. Nazzaro et al. (2011) applied NMSQuest to 24 PD patients 1 year after bilateral STN DBS. Of the 30 items assessed by the questionnaire, symptoms were reported less frequently in 27. The mean number of nonmotor symptoms reported before surgery decreased significantly from 12 to 7 after the operation with the autonomic symptoms responding the best. Of particular relevance, this improvement in nonmotor symptoms was associated with significant improvement in quality of life.

Our group recently published its results following administration of NMSS to 10 PD patients treated with bilateral STN DBS (Reich et al. 2011). NMSS was applied 1–3 months before surgery and then 3–6 months after the operation. The total NMSS score was reduced by 36 % after surgery ($P < 0.03$) with significant improvements in 5

domains of sleep/fatigue, mood/cognition, urinary, sexual function and miscellaneous. Lack of significant improvement in some domains such as cardiovascular/falls or attention/memory was thought to represent a floor effect given the already low pre-operative scores in these domains which left little room for further improvement. The low pre-operative scores in these domains reflected our stringent exclusion criteria for STN DBS such as significant memory impairment and frequent falls. Of note, there were no domains in which nonmotor symptoms deteriorated after surgery.

Hwynn et al. (2011) applied both the NMSS and NMSQuest to 10 PD patients treated with only unilateral DBS, 9 implanted at the STN and 1 at the GPi. The mean time between the pre- and post-operative testing was 12.1 months (range 1–25 months). Data from the NMSQuest showed that pre-operatively, the commonest nonmotor symptoms were gastrointestinal (100 %), sleep (100 %) and urinary (90 %), whilst after surgery, sleep (90 %), urinary (90 %) and cognition (60 %)-related symptoms were most prevalent with sleep, gastrointestinal and cardiovascular/falls items showing the best response to surgery. When NMSS was used, miscellaneous, cardiovascular/falls and mood/cognition domains showed the greatest improvement following surgery, with the improvement reaching significance for the first two domains. The observed difference between our study and Hwynn's data with respect to the cardiovascular/falls domain may reflect the difference in DBS inclusion criteria between unilateral and bilateral procedure, with the former potentially posing less risk for post-operative deterioration in balance and, therefore, more likely to be applied to patients with some impairment in this domain, removing the floor effect described above.

The acute effect of DBS on motor symptoms, with improvements particularly in tremor, rigidity and bradykinesia within seconds or minutes of stimulation onset, is well known (Ashkan et al. 2004). Wolz et al. (2012) recently reported the immediate effect of bilateral STN DBS on nonmotor symptoms in 34 PD patients assessed at a median of 13 months following surgery. All patients were tested after an at least a 12-hour drug free period both with the STN DBS off or 3 h after turning the electrodes on. Structured interview and visual analogue scale were used to assess 10 nonmotor symptoms of dysphagia, anxiety, depression, fatigue, excessive sweating, inner restlessness, pain, concentration/attention, dizziness and bladder urgency. When the DBS electrodes were turned on, there was an overall improvement in the severity of nonmotor symptoms with the most significant improvements in fatigue ($P < 0.001$), inner restlessness ($P = 0.001$), depression ($P = 0.005$) and dysphagia ($P = 0.005$) symptoms. Of note, there were no correlations between changes observed in the nonmotor symptoms and motor improvement or demographics. Furthermore, there was no evidence that STN DBS worsened the nonmotor symptoms.

Although beyond the scope of this paper, a note is warranted on the potential complications of DBS. Both motor and nonmotor adverse events may arise following the surgery. In terms of the latter, transient psychiatric and mood disturbance such as depression, hypomania and delirium have been reported as acute consequences of the surgery which usually settle shortly after (Krack et al. 2003). Long-term mood and cognitive changes including apathy (Thobois et al. 2010), impaired verbal fluency (De Gaspari et al. 2006) and impulse control disorders (Shotbolt et al. 2012), particularly in the context of STN DBS, have also been described. The exact mechanism remains unclear but may include lesioning effect of the fronto-striatal circuits along the trajectory of the electrode, sub-optimal positioning of the electrodes, current spread to adjacent structures or non-judicial post-surgical medication adjustment.

## Conclusion

There is now an increasing recognition of the relevance of nonmotor symptoms of PD and especially their influence on patients' quality of life. With the advent of tools to measure the nonmotor burden, we now have the means to evaluate the effect of various therapies. In the last 2 decades, DBS has emerged as an effective treatment for the motor symptoms of advanced PD. The limited evidence thus far indicates that DBS can also significantly improve many nonmotor symptoms. More prospective studies with larger patient numbers, specifically to include nonmotor assessment measures, are however needed to finally establish the role of DBS in holistic care of our patients.

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