

Title: Dyspnea as a Side Effect of Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease

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Abstract

Bilateral subthalamic nucleus deep brain stimulation for Parkinson's disease improves limb function. Unpublished observations from our clinic noted that some subthalamic nucleus deep brain stimulation patients complain of post-operative dyspnea. Therefore, we designed a prospective, longitudinal study to characterize this in greater depth. We used specific questionnaires to assess dyspnea in patients with electrodes in the subthalamic nucleus (n=13) or ventral intermediate thalamus (n=7). St. George's Hospital Respiratory Questionnaire symptom subscale scores were greater in subthalamic nucleus patients (median = 18.60, interquartile range = 40.80) than ventral intermediate thalamus patients (median = 0.00, interquartile range = 15.38) at greater than 6 months post-operatively ($p < 0.05$). Several of the subthalamic nucleus patients exhibited functional impairments as judged by the St. George's Hospital Respiratory Questionnaire impact subscale, the Medical Research Council Dyspnoea Scale and the Dyspnoea-12 questionnaire. There was no correlation between limb function ratings, stimulation parameters, or precise electrode position and dyspnea severity. We have shown, for the first time, that dyspnea can be a side-effect of subthalamic nucleus deep brain stimulation, and that this dyspnea may be highly disabling.

1. Introduction

Deep brain stimulation has been shown to effectively ameliorate the major motor symptoms of Parkinson's disease (Benabid, et al. 1996; Obeso, et al. 2001; Krack, et al. 2003). Deep brain stimulation involves implanting an electrode into a target brain structure and applying electrical stimulation through a subcutaneous pacemaker. Electrical stimulation is reversible and is individually tailored to the particular patient in order to achieve the best clinical results (Bain, et al. 2009). Deep brain stimulation targets for Parkinson's disease include the subthalamic nucleus, ventral intermediate thalamus, globus pallidus interna, and pedunculopontine nucleus. Weight gain (Deuschl, et al. 2006; Locke, et al. 2011; Strowd, et al. 2010), regulation of sweating (Trachani, et al. 2010), dysathria (Deuschl, et al. 2006), and elevation of heart rate and arterial blood pressure (Thornton, et al. 2002) are some side-effects associated with subthalamic nucleus deep brain stimulation. Further evidence for the role of the subthalamic nucleus in cardiorespiratory function comes from electrophysiological, neuroimaging, and clinical studies (Green, et al. 2007; Eldridge, et al. 1981; Hyam, et al. 2012; Pattinson, et al. 2009).

Dyspnea is one of the most difficult to understand respiratory symptoms. For ease of description, dyspnea is generally discussed in terms of three sensory components: air hunger, muscle work/effort, and chest tightness (Herigstad, et al. 2011). The clinical state, however, almost always consists of a complex combination of sensations. Air hunger is the feeling of being starved of air (Moosavi, et al. 2003; Parshall, et al. 2012). Muscle work/effort is believed to be associated with the amplitude of voluntary, cortical

respiratory command (Parshall, et al. 2012). Chest tightness is commonly experienced during bronchoconstriction; asthma patients generally classify their dyspnea in this way (Parshall, et al. 2012). Affective and cognitive components of dyspnea include anxiety, depression, attention, and expectation (Herigstad, et al. 2011). Although these dimensions are useful for describing a model, in reality dyspnea is a complex individual, subjective experience (Hayen, et al. 2013). Therefore, researchers need multiple instruments in the evaluation of dyspnea.

Unpublished observations from our clinic noted that some subthalamic nucleus deep brain stimulation patients complain of dyspnea. Therefore, we designed a prospective, longitudinal study to characterize this in greater depth. The aim of this study was to see if subthalamic nucleus deep brain stimulation is related to dyspnea and to begin to examine the quality of dyspnea. Ventral intermediate thalamus deep brain stimulation patients were used as controls, since the ventral intermediate thalamus has not been implicated in cardiorespiratory control.

2. Methods

2.1 Subjects

13 patients treated with deep brain stimulation in the subthalamic nucleus for Parkinson's disease at the John Radcliffe Hospital in Oxford, UK, were recruited prior to surgery. In addition, 7 Parkinson's disease patients with ventral intermediate thalamus electrodes were recruited as a control group. Patient age, time since diagnosis, stimulation parameters, and electrode configuration are presented in Supplementary Table 1. The study conformed to the Declaration of Helsinki, and the Oxfordshire Research Ethics Committee C (Study No. 05/Q1605/47) gave ethical approval. Consent was provided by all patients before the study. Patients were excluded if they were unable to fill out the questionnaires for cognitive reasons, including executive dysfunction and dementia. Patients with a pre-existing diagnosis of respiratory disease (obstructive conditions, restrictive conditions, vascular diseases, or infectious diseases) or cardiac disease associated with sensations of breathlessness were also excluded.

2.2 Surgical Technique and Electrode Localization

Our surgical technique was as follows; under local anesthetic and sedation, a Cosman-Roberts-Wells stereotactic frame was attached to the patient's head and a stereotactic computed tomography (CT) scan was performed. This was fused to a pre-operative Magnetic Resonance (MR) sequence, using the Radionics Image Fusion™ software (Radionics, Burlington, Mass.). The subthalamic nucleus was targeted visually on a T2 or T2 FLAIR sequence with the dorsolateral aspect being chosen. The ventral intermediate thalamus nucleus was based on the midcommissural point on a T1 sequence (AP -3-5mm, Lateral +/- 12-14mm, Vertical 0mm). 2.7mm twist drill craniostomies were used for

access, a Radionics TC™ electrode (Radionics, Burlington, Mass) was used to make the tract and measure impedance. The deep brain stimulation electrodes (Medtronic 3389® for subthalamic nucleus and 3387® for ventral intermediate thalamus, Medtronic, Minneapolis, USA or St. Jude Medical 6146® or 6147® for subthalamic nucleus and 6142® or 6143® for ventral intermediate thalamus, St. Jude Medical, Inc., Secaucus, USA) were inserted to target and awake stimulation confirmed effect. Depth was adjusted according to best response and side-effects were tested. The electrodes were secured using a Codman titanium bioplate® and either externalized for testing or connected to the implantable pulse generator that was inserted into an infraclavicular subcutaneous pocket. Externalized electrodes were implanted in a second stage operation one week later. For electrode localization, a post-operative stereotactic CT scan was fused to the MR as above. Coordinates relative to the mid-commissural point for all active contacts, those contacts optimized for the best clinical result, and for the electrode tips were calculated. The subthalamic nucleus was also visually located and all active contacts and electrode tips were noted as either in or out of the visually-defined subthalamic nucleus.

2.3 Respiratory-Related Questionnaires

2.3.1 St. George's Hospital Respiratory Questionnaire. The St. George's Hospital Respiratory Questionnaire is a 50-item self-report quality of life measure of respiratory health (Jones, et al. 1992). This questionnaire can be divided into three component scores: symptoms, activity, and impact, each scored from 0 to 100. The symptom subscale considers symptoms in terms of frequency and severity. The activity subscale considers activities that are limited by dyspnea. The impact subscale considers social functioning and psychological disturbances resulting from dyspnea. The subscales can be

combined to give a total score (0 to 100). This questionnaire is reliable, valid, and very widely used in respiratory research, allowing comparisons with many other studies.

2.3.2 Medical Research Council (MRC) Dyspnoea Scale. The MRC Dyspnoea Scale is a measure of how dyspnea affects quality of life (Bestall, et al. 1999). It consists of five statements which describe nearly the entire range of disability due to dyspnea from Grade 1 (not troubled by breathlessness) to Grade 5 (too breathless to leave the house). Patients select one grade to represent their dyspnea-related disability. This is the most widely used dyspnea scale and is very easy to administer.

2.3.3 Dyspnoea-12. The Dyspnoea-12 is a 12-item self-report measure of dyspnea which can be divided into a physical aspect section and an affective aspect section (Yorke, et al. 2010; Yorke, et al. 2011). Scores range from 0 to 36 (0 to 21 for the physical section and 0 to 15 for the affective section) and are presented as percentages of the total score of each section. A slightly different wording of the questionnaire was used, instructing patients to respond to statements based upon “breathing during the past few days”, rather than “these days”. Thus it worked well with our goal of assessing dyspnea over a period of time.

2.3.4 The Center for Epidemiologic Studies Depression Scale. The Center for Epidemiologic Studies Depression Scale is a 20-item self-report depression screening questionnaire (Radloff 1977). Scores range from 0 to 60, and a score of 16 or greater is indicative of clinical depression. Depression is a common coexisting problem with dyspnea (Herigstad, et al. 2011).

2.3.5 State-Trait Anxiety Inventory. The State-Trait Anxiety Inventory contains two 20-item self-report questionnaires for state anxiety and trait anxiety (Spielberger, et al.

1970). Scores on each questionnaire range from 20 to 80 and they can be analyzed together or separately. Anxiety is also a common coexisting problem with dyspnea (Herigstad, et al. 2011).

2.3.6 Fatigue Severity Scale. The Fatigue Severity Scale is a 9-item self-report measure of fatigue severity (Krupp, et al. 1989). Scores range from 9 to 63. Fatigue is another common coexisting problem with dyspnea.

2.3.7 Catastrophic Thinking Scale. The Catastrophic Thinking questionnaire is a 13-item self-report measure of dyspnea-specific anxiety. Scores range from 0 to 52. This questionnaire was slightly adjusted from the Catastrophizing about Asthma Scale (De Peuter, et al. 2006), which was validated for asthma after adaptation from the Pain Catastrophizing Questionnaire (Sullivan, et al. 1995). Our adjustments allowed the questionnaire to address dyspnea more generally. We felt justified in rewording the items for this purpose since dyspnea is a major symptom of asthma and since dyspnea, like asthma and pain, is influenced by cognitive elements which do not correlate very well with measures of physical respiratory dysfunction (Herigstad, et al. 2011). We adapted the ‘exacerbation’ scale of the Catastrophizing about Asthma Scale by replacing the words ‘asthma attack’ with ‘breathlessness’ and by slightly rewording a few items to obtain a meaningful phrase (Supplementary Figure 1).

2.3.8 Questionnaire Timing

The St. George’s Hospital Respiratory Questionnaire was administered pre-operatively one day before the surgery to 8 subthalamic nucleus patients and 7 ventral intermediate thalamus deep brain stimulation patients. Post-operative questionnaires were administered at least 6 months after surgery and detailed timing is presented in Table 1.

Patients were asked to provide answers based upon the time since the surgery, reflecting an average state with stimulation turned on.

2.4 Clinical Ratings of Parkinson's Disease

The Unified Parkinson's Disease Rating Scale was administered pre-operatively by a movement disorder specialist nurse at a median of 3.00 months (interquartile range = 3.5 months) for subthalamic nucleus and 4.00 months (interquartile range = 2.5 months) for ventral intermediate thalamus ($p = 0.688$). The motor (part 3) scores from the Unified Parkinson's Disease Rating Scale during the on and off medication assessments were used as ratings of limb function. In addition, the total Unified Parkinson's Disease Rating Scale on and off medication were used as measures of disease severity.

2.5 Statistical Analysis

Comparisons were made using Mann-Whitney U tests, using the two-tailed significance values. Correlations were made using Spearman's rho correlation tests. A p value < 0.05 was considered significant. A Bonferroni correction was applied to the electrode localization and stimulation parameter correlations due to the high number of tests. All results are displayed with the median and interquartile range. Statistical analyses were conducted using the Statistical Package for the Social Sciences v. 20 (SPSS Inc., Chicago, IL, USA).

2.6 Neuroimaging Reanalysis

Previously published data, presented in Pattinson, et al. Neuroimage 2009 and Pattinson, et al. J.Neuroscience 2009 was reanalyzed to look for subthalamic nucleus involvement during various respiratory maneuvers.

3. Results

3.1 Subjects

There were no significant differences in patient age or time since diagnosis between subthalamic nucleus and ventral intermediate thalamus patients (p values > 0.05) (Supplementary Table 1). In general, medication regimens were not changed during the postoperative period. In cases where specific medications were changed, no known respiratory side effects of those medications could be found.

3.2 Subthalamic Nucleus vs. Ventral Intermediate Thalamus Questionnaire Scores

Post-operative St. George's Hospital Respiratory Questionnaire symptom subscale scores were found to be significantly higher in subthalamic nucleus patients than in ventral intermediate thalamus patients ($p = 0.035$) (Table 3, Figure 1, and Figure 2), but pre-operative scores showed no difference ($p = 0.832$). Furthermore, post-operative impact subscale scores were increased in subthalamic nucleus compared to ventral intermediate thalamus deep brain stimulation patients ($p = 0.046$), but pre-operative scores were similar between the two groups. The activity subscale score showed no difference between the two groups post-operatively ($p = 0.117$). The total St. George's Hospital Respiratory Questionnaire score also showed no difference between groups ($p = 0.077$).

The Dyspnoea-12 (total score, physical subscale, and affective subscale), Medical Research Council (MRC) Dyspnoea Scale, The Center for Epidemiologic Studies Depression Scale, the State-Trait Anxiety Inventory, the Fatigue Severity Scale, and the Catastrophic Thinking Scale all showed no differences between subthalamic nucleus and

ventral intermediate thalamus deep brain stimulation patients post-operatively (p values > 0.05) (Table 2).

3.3 Stimulation Parameters and Electrode Localization

No significant associations between any of the deep brain stimulation parameters and St. George's Hospital Respiratory Questionnaire symptom subscale scores were found in subthalamic nucleus patients (Supplementary Table 2). Parameters were evaluated individually for left, right, and average stimulation. Stimulus parameters for some patients changed during the postoperative period, but the parameters were stable during at minimum the preceding week before administering the respiratory questionnaires.

Subthalamic nucleus deep brain stimulation patients' St. George's Hospital Respiratory Questionnaire symptom subscale scores were correlated with electrode tip and active contact coordinates relative to the mid-commissural point. The electrode tip is the absolute end of the electrode, and the active contact coordinates are where the center of electrical stimulation occurs from the electrode (a few mm from the electrode tip). There were no significant correlations between any of the electrode tip or active contact coordinates in any of the three dimensions and scores on the St. George's Hospital Respiratory Questionnaire symptom subscale (Supplementary Table 3) (all p values > 0.05). Due to inter-individual variability in brain nuclei locations, St. George's Hospital Respiratory Questionnaire symptom subscale scores were also examined with respect to visually located subthalamic nucleus deep brain stimulation electrode tips and active contacts. There were no significant differences in St. George's Hospital Respiratory

Questionnaire symptom subscale scores based upon whether the active contact or electrode tip in either the right or left subthalamic nucleus was determined to be in the visually located subthalamic nucleus (all p values > 0.05).

3.4 Parkinson's Disease Severity and Limb Function Ratings

To examine if there was a relationship between severity of Parkinson's disease and dyspnea in subthalamic nucleus deep brain stimulation patients, we correlated pre-operative Unified Parkinson's Disease Rating Scale scores to St. George's Hospital Respiratory Questionnaire symptom subscale scores. No correlation reached statistical significance. St. George's Hospital Respiratory Questionnaire symptom subscale scores correlated with motor scores (Unified Parkinson's Disease Rating Scale part 3) off medication: $r = 0.316$, $p = 0.317$. St. George's Hospital Respiratory Questionnaire symptom subscale correlated with total Unified Parkinson's Disease Rating Scale off medication: $r = 0.323$, $p = 0.306$. Correlations between St. George's Hospital Respiratory Questionnaire symptom subscale scores and on medication Unified Parkinson's Disease Rating Scale scores are also not significant ($r = 0.496$, $p = 0.101$).

4. Discussion

We have demonstrated an increase in dyspnea following surgery in subthalamic nucleus deep brain stimulation patients treated for Parkinson's disease. This result, combined with subthalamic nucleus fMRI studies (Figure 3), suggests that the subthalamic nucleus may play a role in respiratory control.

Results from the St. George's Hospital Respiratory Questionnaire impact subscale show that dyspnea is highly disabling and therefore clinically important in subthalamic nucleus deep brain stimulation patients. Furthermore, the average Dyspnoea-12 score from the five subthalamic nucleus patients who scored the highest on the questionnaire is comparable to the score from a cohort of Chronic Obstructive Pulmonary Disease patients with a mean MRC grade 2.6 (Yorke, et al. 2010). Using age-matched general population reference norms, the mean post-op St. George's Hospital Respiratory Questionnaire symptom subscale score of the same five patients (the five highest scoring on the Dyspnoea-12) falls above the 90th percentile (Ferrer, et al. 2002). The mean MRC Dyspnoea Scale score of these five patients was 3.60. Thus, dyspnea in these patients is a highly disabling limitation carrying functional impairments.

It is still unclear what neurophysiological mechanisms can cause dyspnea in subthalamic nucleus deep brain stimulation patients. Yanase et al. (2008) reported a case study of a deep brain stimulation patient who developed severe dyspnea due to a fixed epiglottitis directly linked to subthalamic nucleus stimulation. It is conceivable that the subset of subthalamic nucleus deep brain stimulation patients in the current study also developed

reduced mobility of the epiglottis. Current spread into neighboring areas may be a different mechanism for dyspnea following subthalamic nucleus deep brain stimulation. It is possible that the dyspnea presented in the current study does not relate to actual respiratory changes, but rather to alterations in dyspnea perception. Stimulation of the subthalamic nucleus might interfere with feedforward respiratory afferents, leading a mismatch between expected respiratory signaling and feedback from respiratory muscles and chemoreceptors, causing the perception of dyspnea. Alternatively, changes in respiratory physiology, such as bronchoconstriction, upper airway control, or disturbed respiratory muscle control, could explain the observed dyspnea. Future research should aim at elucidating the mechanism underlying subthalamic nucleus deep brain stimulation dyspnea.

In response to the findings presented in this paper, we looked at previously published functional magnetic resonance imaging data during various respiratory maneuvers to see if the subthalamic nucleus was involved. The subthalamic nucleus exhibits a blood oxygen level dependent fMRI response to respiratory stimulation with CO₂ and breath holding (Figure 3). Furthermore, a positron emission tomography study from the early 2000's suggests increased cerebral blood flow in response to hypercapnia, potentially within the subthalamic nucleus, although the subthalamic nucleus was not explicitly mentioned (Liotti, et al. 2001). Together these findings provide some neuroimaging evidence that the subthalamic nucleus is involved with respiration.

Several important points need to be considered for a careful interpretation of the results of this study. First, this study focused on patients at greater than 6 months post-operatively. It will be important to better determine the dyspnea state of patients at the time of implantation and immediately after implantation in the future. It will also be important to test whether the Unified Parkinson's Disease Rating Scale, a measure of disease severity, is worse in the post-operative period. Secondly, it is difficult to draw conclusions about incidence and severity of dyspnea because the availability of patients appropriate for deep brain stimulation surgery limited the possible number of patients. Thirdly, each questionnaire was not administered on every occasion to each patient since many patients who did not suffer from dyspnea did not complete the entire questionnaire set. Finally, it is possible that patients were primed to notice and exaggerate dyspnea with the neurosurgery team due to the consenting process. However, this is unlikely because dyspnea was first noticed observationally without prior discussion with the patients. Patients' expectations of future dyspnea was not assessed prior to surgery.

It is important for neurosurgeons to be aware of dyspnea as a potential side effect of subthalamic nucleus deep brain stimulation so that patients can be adequately followed up. Patients may not complain of dyspnea with the neurosurgery team unless prompted. Indeed, several of the patients in this study remarked that they would not have thought to mention breathlessness on their own with the neurosurgery team, and they were surprised to discover that it may be related to deep brain stimulation.

In summary, we have shown, for the first time, that dyspnea may be a side effect in patients treated with deep brain stimulation of the subthalamic nucleus for Parkinson's disease. This dyspnea carries functional limitations and is clinically important.

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Figure Titles and Captions

Figure 1. Pre-operative and post-operative St. George's Hospital Respiratory Questionnaire scores (symptom subscale, activity subscale, impact subscale, and total score) for subthalamic nucleus (STN) and ventral intermediate thalamus (VIM) deep brain stimulation patients. Data is presented in Table 3. Error bars are $\frac{1}{2}$ of the interquartile range. * : $p < 0.05$.

Figure 2. Pre-operative and post-operative St. George's Hospital Respiratory Questionnaire symptom scores for individual deep brain stimulation patients. *A*) Subthalamic nucleus (STN) patients. Note that 2 of the subthalamic nucleus patients had a score of 0 pre-operatively and post-operatively. *B*) Ventral intermediate thalamus (VIM) patients. Note that 3 of the ventral intermediate thalamus patients had a score of 0 pre-operatively and post-operatively. Also, note the absolute difference in scores between subthalamic nucleus and ventral intermediate thalamus patients.

Figure 3. Blood oxygen level dependent (BOLD) fMRI response in the subthalamic nuclei in response to respiratory various respiratory maneuvers. These data are fully presented in Pattinson et al Neuroimage 2009 and Pattinson et al J.Neuroscience 2009. Here, the original data has been displayed only to illustrate the involvement of the STN.

The boundaries of the STN were defined from the standard space STN atlas (<http://www.nitrc.org/projects/atag/>) derived from Forstmann 2012 and are illustrated in white.

The location and extent of STN is illustrated in the first column. The second column demonstrates BOLD response to respiratory stimulation with CO₂, the third column the BOLD response to breath holding, and the fourth column the reduction in positive BOLD response during breath holding with simultaneous administration of the opioid remifentanyl. In each case CO₂-induced vasodilatation was accounted for (see original articles for full details).

The images consist of a color-rendered statistical map superimposed on a standard (MNI) brain. The gray region on the CO₂ stimulation scans delineates the coverage for the brainstem scanning (limited field of view used).

Significant regions are displayed with a threshold of $Z < 2.3$, with a cluster probability threshold of $p < 0.05$ (corrected for multiple comparisons). Abbreviations: L, left; R, right; A, anterior; P, posterior.

Supplementary Figure Titles and Captions

Supplementary Figure 1. Catastrophic Thinking for dyspnea questionnaire. As discussed in the methods section (2.3.8.)