**Letter to the Editor: Thalamic deep brain stimulation may relieve breathlessness in COPD**

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**Text**

The cerebral mechanisms of dyspnoea (breathlessness) are not well understood. Neuroimaging studies of experimentally induced dyspnoea in healthy individuals have identified several cortical areas that might form a neural network for perception of dyspnoea[1], much like those identified for pain perception[2]. However, functional imaging studies alone do not reveal neurophysiological pathways and may miss putative targets for dyspnoea relief. The objective of this study was to assess the effects of Deep Brain Stimulation (DBS) of four different brain nuclei on the sensation of dyspnoea in an individual with Chronic Obstructive Pulmonary Disease (COPD) using an established multidimensional dyspnoea tool[3].

We report the case of a 65 year old right-handed male with pre-existing COPD who underwent Deep Brain Stimulation (DBS) for the relief of a combination of post-stroke pain and post-stroke tremor in the left arm. Pre-operatively, he had a Forced Expiratory Volume in 1s (FEV1) of 0.08L (41% predicted). He had suffered from a haemorrhagic infarct of the right thalamus 6 years previously. Electrodes were implanted in four different brain nuclei on the right; the ventral intermediate nucleus (VIM) and the Globus Pallidus Internus (GPi) for relief of tremor and its dystonic component respectively, Periaqueductal Gray (PAG) and sensory thalamus (ventral posterolateral nucleus (VPL)) for relief of post-stroke pain. His tremor had a dominant frequency of 4.2Hz with a myoclonic component. Tremor score, assessed using the Abnormal Involuntary Movement Scale (AIMS), improved by 53% with stimulation of VIM. A striking and unexpected finding was that VIM DBS abolished his pursed lips breathing associated with pre-existing breathlessness (see video – supplementary data).

As the patient had breathlessness at rest, we had the opportunity to explore the effect of stimulation of each of these brain nuclei on the patient's experience of breathlessness. All studies conformed to the Declaration of Helsinki and the study was approved by the Oxford Regional Ethics Committee (Study number 11 SC 0229). Breathlessness was assessed using a validated multidimensional dyspnoea instrument; Dyspnoea-12 questionnaire [3]. The first assessment (visit 1) was carried out 3 days after electrodes were surgically implanted. D-12 was administered at baseline (all electrodes OFF) and at 20 minutes after each of the GPi, VIM and PAG electrodes were individually switched 'ON' (with all other electrodes 'OFF') in a randomized order. The order of items on the D12 was also randomized. Stimulation of the VPL electrode was not tested at visit 1 because its analgesic effect took 48 hours to manifest. The process was repeated after 11 weeks (visit 2) when data from VPL stimulation were also obtained.

At visit 1, stimulation of the VIM markedly relieved both the 'physical' and 'emotional' components of dyspnoea compared to baseline (all electrodes OFF) (Figure 1). GPi stimulation reduced the D12 physical (intensity) score but slightly increased the D12 emotion (affective) score. PAG stimulation also reduced the D12 physical score but the D12 emotion component score remained unchanged.

At visit 2, baseline physical scores (all electrodes OFF) remained unchanged but GPi, VIM, VPL and PAG stimulation all substantially reduced the physical component of the dyspnoea. The baseline emotion score was zero at visit 2 and the enhancement by the GPi stimulation observed at visit one had disappeared. It should be noted that stimulus parameters were optimised at visit 2 with an increase in amplitude from 3.7v to 7v in the GPi and VIM and 5.5v to 6.0v for the PAG and VPL.

Our findings suggest that unilateral DBS of various brain nuclei currently targeted for neurological symptoms may also relieve the breathlessness associated with COPD; the VIM nucleus of the thalamus being the most efficacious and demonstrating objective clinical signs of improvement (pursed-lips breathing). The reduction in D12 score, that was primarily related to the physical domain, suggests that tremor in our patient may have worsened the dyspnoea (perhaps due to diaphragmatic involvement or increased energy expenditure) and that relief of the tremor itself improved the breathlessness. However, an alternative explanation that warrants further investigation is that DBS of the thalamus may block ascending afferent signals that report the need to breathe in COPD. Comparison of this signal with other afferent signals that report the prevailing level of ventilation is considered to be the mechanism of air hunger, an unpleasant component of dyspnoea[4] that features prominently in COPD[5] Future studies should aim to unravel the contributions of these two alternative explanations of dyspnea relief with DBS of the thalamus. The ideal experiment would be to compare the relief of breathlessness when the patient's hyperactivity is reduced with DBS of the thalamus versus when it is reduced by temporarily paralysing the limb or abolishing the tremor pharmacologically in the DBS 'off' state. The latter is not feasible since the indication for DBS is itself pharmacologically intractable tremor. Whatever the mechanism, these findings raise the possibility of using DBS for dyspnoea, similar to its use for chronic pain.

**Conflicts of Interest:** AG is on the Movement Disorders Executive Advisory Board of Abbott Medical and receives occasional honoraria for teaching courses related to Dorsal Root Ganglion Stimulation (for pain). PR is currently an employee of Abbott Medical (but was not at the time of the study).

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## Legends

**Figure 1 (video).** The video demonstrates that without Deep Brain Stimulation (all electrodes off), the patient exhibits pursed lips breathing consistent with his COPD[6]. When the motor thalamus is stimulated, the pursed-lips breathing disappears.

**Figure 2. Dyspnoea-12 scores at 3 days and 11 weeks.** At 3 days, the motor thalamus (VIM) abolished breathlessness and at 11 weeks, all nuclei substantially reduced breathlessness. The D12 Total score incorporates 12 items (7 physical and 5 emotional) each rated on a likert-type scale (none, mild, moderate, severe). Each item is scored 0-3 and the sum score is expressed as a percentage of the highest score possible (36). The physical and emotional scores are also expressed as a percentage of their respective maximal sub scores (21 and 15 respectively). Note that stimulation amplitude increased between visit 1 and visit 2 (see text). GPi = Globus Pallidus interna, VIM = ventral intermediate nucleus of the thalamus, PAG = periaqueductal gray, VPL = ventroposterolateral nucleus of the thalamus