The effect of neurosurgical intervention and neurological damage on the perception of dyspnoea

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Abstract

Dyspnoea is a complex and unpleasant sensation that can have a severe impact on a person's quality of life. Evidence for there being distinguishable types of breathlessness arising from distinct neural networks has been produced, and experimental models have also been produced to reproduce these sensations in healthy individuals. Current knowledge of the cerebral mechanisms has been gleaned predominantly through the use of brain imaging studies, however alternative methods also present opportunities to further elucidate the mechanisms behind intractable dyspnoea in ways that brain imaging cannot.

Aim: The ultimate purpose of this thesis was to investigate the cerebral mechanisms behind breathlessness using neurological populations. Using deep brain stimulation (DBS), it is a primary aim of this thesis to further investigate the role of different brain structures in dyspnoea perception, specifically 'air hunger' which is a particularly unpleasant form of breathlessness often experienced by those with Chronic Obstructive Pulmonary Disease (COPD). An additional aim was to investigate whether neurological damage in the form of Parkinson's disease, and glioma of the insular cortex alters the perception of breathlessness.

Methods: (i) Experimental air hunger was induced in participants with deep brain stimulation of the motor thalamus to assess whether perception of dyspnoea is changed when stimulation is turned ON compared to when it is turned OFF. Experimental air hunger was also induced in one patient with low grade glioma to explore the impact of this damage on the insular cortex. (ii) A

validated tool for measuring breathlessness called the Dyspnoea 12 questionnaire was utilised in patients who were breathless at rest and whom had DBS of the motor thalamus or the STN. This questionnaire was completed with their stimulation turned ON and turned OFF. This same questionnaire was also used to assess dyspnoea in individuals in the community with Parkinson's disease to determine the prevalence of dyspnoea in this group (iii) Local field potentials (LFPs) where recorded from the motor thalamus whilst air hunger was induced. These LFPs are signals which correlate with neural activity.

Results: (i) Participants with DBS of the motor thalamus rated air hunger significantly lower with stimulation ON in comparison to OFF by (median change 12mmVAS; range +19 to -50mmVAS). (ii) The participant with low grade glioma of the insular cortex did not rate an increase in breathlessness when air hunger was experimentally induced (increase in PCO2 of 11mmHg with VE fixed at 4.4 L/min). (iii) Participants with breathlessness at rest and DBS of the STN reported an overall increase in breathlessness when stimulation was turned on (an increase of 10% fullscale in the D12 total score). Conversely, DBS of the motor thalamus in participants with breathlessness at rest due to pre-existing COPD experienced a reduction in breathlessness with stimulation ON (-20.2% full scale for D12 total score) (iv)The prevalence of dyspnoea in individuals with Parkinson's disease was 63.6%. (v) an LFP signal was detected when air hunger was induced that was not present in other breathing conditions.

Conclusions: The motor thalamus and the STN have opposite roles in modulation of breathlessness, the mechanism of which is yet to be determined.

The prevalence of breathlessness among patients with Parkinson's disease is considerable and warrants more attention. Glioma of the insular cortex confirms the importance of this region in breathlessness perception. Study of patients with neurological interventions (Deep brain stimulation) and with neurological damage (low grade glioma or Parkinson's disease) will lead to a better understanding of the cerebral network for dyspnoea perception and ultimately to identify new treatment options for intractable dyspnoea.

Please note that this thesis was completed before the COVID-19 pandemic.

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Glossary

AH	Air hunger
COPD	Chronic obstructive pulmonary disease
D12	Dyspnoea-12 questionnaire
DBS	Deep brain stimulation
DRG	Dorsal respiratory group
DTI	Diffuse tensor imaging
EEG	Electroencephalography
FEV	Forced expiratory volume
fMRI	Functional magnetic resonance imaging
FR	Frequency rate
FVC	Forced vital capacity
LFP	Local field potential
MCID	Minimal clinically important difference
MRC	Medical Research Council
MDP	Multidimensional dyspnoea profile
MRI	Magnetic resonance imaging
Motor thalamus	A collection of neurons within the thalamus

PAG	Periaqueductal grey
PET	Positron emission topography
PAW	Airway pressure
PD	Parkinson's disease
$PETCO_2$	End-tidal carbon dioxide partial pressure
$PETO_2$	End-tidal oxygen partial pressure
PSD	Power spectral density
SpO_2	Oxygen saturation
STN	Subthalamic nucleus
TBI	Transition Dyspnoea Baseline
TMS	Transcranial magnetic stimulation
VAS	Visual analogue scale
VIM	Ventral intermediate nucleus
VOP	Ventralis oralis posterior
VT	Tidal volume
WE	Work and effort

1 Introduction

1.1 Overview of dyspnoea and this projects contribution to the field.

Dyspnoea is one of the most distressing symptoms that terminally ill patients experience, surpassing pain in unpleasantness and intensity, particularly in the palliative stages (O'Driscoll et al., 1999). Dyspnoea, defined as the "subjective experience of breathing discomfort" (Parshall et al., 2012), is the common symptom of multiple diseases including cardiopulmonary and neuromuscular disease and lung cancers, and can have a severe impact on a person's quality of life. It promotes sedentary behaviour due to the fear of worsening the sensation through movement, which in turn reduces the person's fitness levels, further enforcing their belief that exercise is a risk to their health, and is to be avoided (Spathis et al., 2017). This can contribute to the subsequent development of physical and mental health issues which can reduce quality of life further.

Dyspnoea has been reported to be multidimensional in nature, with the sensations experienced varying based on the underlying pathology. The most frequently cited forms of breathlessness are work and effort of breathing, chest tightness and air hunger. Work and effort is the uncomfortable sensation that there is increased difficulty in making the chest wall expand, and so is tiring and makes achieving adequate ventilation increasingly difficult. Chest tightness is most frequently reported in asthmatics when trying to overcome bronchiole constriction. Lastly, air hunger is the urgent and intense desire to take more air

into the lungs. This feeling of unsatisfactory respiration has been reported by patients to be the most difficult to tolerate out of the sensations that make up dyspnoea (Simon et al., 1990). It is this last sensation which is the focus of this work.

It is relevant to this thesis to define the difference between dyspnoea and the breathlessness experienced by the general population. Breathlessness as experienced after intense exercise for example, does not contain the psychological element as clinical dyspnoea. The individual is confident that they have control over how breathless they become. They are also aware that stopping the activity will cause the breathlessness to subside. In this instance, being breathless can be an annoyance, but is not likely to affect the persons mood or overall feeling of wellbeing. In stark contrast however, a person with clinical dyspnoea does not have that sense of control. The sensation can be unpredictable in its severity and duration, and the trigger for it can be seemingly random. This causes great distress both whilst the sensation is there, but also during its absence as the person is waiting for it to reappear. There has been a movement within the dyspnoea research community to identify breathlessness as a separate and distinct clinical syndrome called chronic breathlessness syndrome. This term is defined as "breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability" (Johnson et al., 2017). The intention behind this is that more recognition of this symptom is needed and achieving that recognition will lead to improved clinical care, and possibly give patients and their carers an opportunity to regain a sense of control. Having this distinct and identifiable

syndrome will also help clinicians understand their patient's concerns and hopefully manage their condition so as to limit unnecessary hospital visitations.

Suffering from intractable breathlessness can severely diminish a person's quality of life. It promotes sedentary behaviour due to fear of exacerbating one's condition, which has not only numerous physical consequences, but psychological ones as well (Janssen et al., 2015). The restriction in activity can cause increased muscle wastage and reduced cardio-vascular fitness in turn making it harder to exercise. This reduction in physical capability further reinforces the sufferer's perception that they cannot perform physical activity due to their condition (Spathis et al., 2017). Breathlessness at its worst can also make a person's daily activities such as getting dressed or climbing stairs in their home too difficult to perform without help. This loss of independence can lead to the individual suffering from emotional distress and depression, further decreasing their quality of life. The burdensome nature of breathlessness on those affected is not the only compelling reason for trying to improve our understanding of this life limiting sensation. Family members and carers often experience great emotional trauma from watching another person suffer from intractable breathlessness. Additionally, due to the chronic nature of the sensation, coupled with it being a common symptom of life-limiting diseases such as COPD and heart failure, it is one of the most frequently cited reasons for unscheduled hospital visitations (Parshall et al., 2012). This, therefore, makes the financial burden of dyspnoea on healthcare systems extremely large (Murthy and Sastry, 2005, Dalal et al., 2011).

Successfully treating dyspnoea is further complicated by the limited number of treatment options currently available to us. Furthermore, the sensation often persists once all medical options have been exhausted. It is therefore, of paramount importance that we try to develop our understanding of the cerebral mechanisms behind dyspnoea so that we are better equipped to create targeted therapeutic treatment options in the future.

Though there are several excellent reviews of breathlessness and the cerebral mechanisms behind dyspnoea available (Hayen et al., 2013, Herigstad et al., 2011), each reflects, of course, the authors' personal research interests and expertise. There have been several recent advances within the field of dyspnoea research, and as such, a truly comprehensive review is most likely impossible, and certainly beyond the scope of this thesis. The following brief review outlines the current understanding of breathlessness and the treatment options available. There is also mention of the current approaches used to study breathlessness, and the clinical significance of the presented work.

If breathlessness is to be fully understood, we must study the cerebral mechanisms which give rise to the sensation, as well as the mechanics of what is happening in the chest. The experimental approach of using neurosurgical intervention to study the regions involved in breathlessness perception is novel and gives us a unique insight into the structure-function relationship of dyspnoea which brain imaging techniques cannot. This use of virtual and permanent lesions to assess changes in breathlessness will be discussed in the main body of this thesis (chapters 3-6).

1.2 Physiology of breathing and air hunger

Changes in arterial blood PCO_2, hydrogen ions, and O_2, dictate respiration. When these ions change in concentration, peripheral and central chemoreceptors present in the carotid and aortic vessels, and the medulla respectively, are stimulated. These chemoreceptors send a message to the respiratory centres of the brainstem (notably the medulla and the Dorsal respiratory group (DRG)) demanding a change in respiration. These brain regions then send a signal to mechanoreceptors in the lungs which will promote the lungs to inflate more to accommodate the increased respiratory demand. A copy of this signal from the brainstem will also be sent to the cortical areas of the brain such as the thalamus, which gives rise to the perception of being breathless. The mechanoreceptors in the lungs will send feedback to both the brainstem and the cortical areas. If the feedback received from the mechanoreceptors compensates for the increased respiratory demand, the sensation of breathlessness will fade. This process can be affected by emotional state, memories of previous breathlessness, and associations that the individual has formed between varying stimuli and breathing (Figure 1-1).

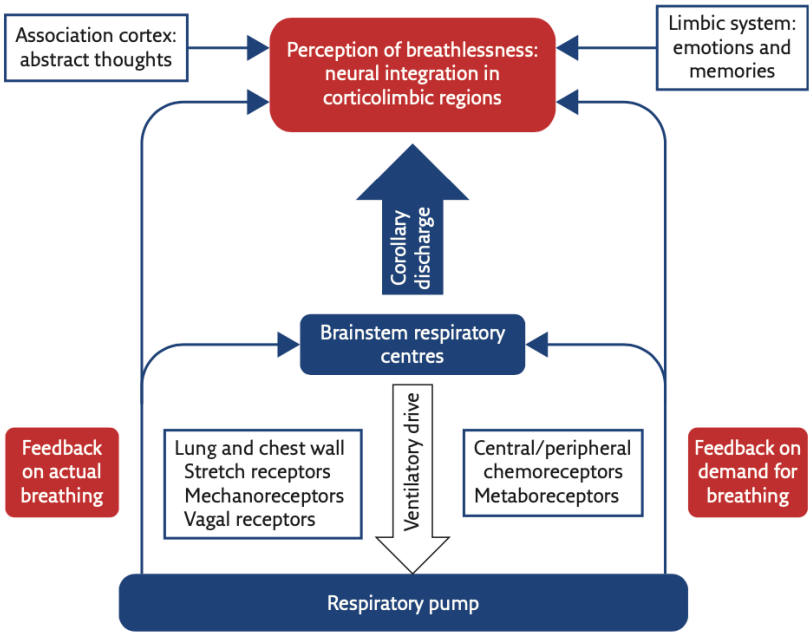


Figure 1-1 Schematic outline of the physiology of breathing

Reproduced from Booth et al., (2019).

A comprehensive understanding of the physiology of air hunger will benefit ongoing research into treatment options immensely. Early investigations into the physiological mechanisms behind air hunger focused primarily on the role of the chest wall or mechanoreceptors in breathlessness perception (Campbell et al., 1969, Killian et al., 1984).

Banzett et al., (1989) endeavoured to test this hypothesis by studying subjects whose respiratory muscles were paralysed. Inspired CO_2 was gradually elevated in 4 patients who had sensorimotor lesions affecting the chest wall. Three out of four patients identified feelings of air hunger, thus disputing the claims that paralysation of the respiratory muscles inhibits feelings of air hunger, even with increased inspired CO_2. This finding was further corroborated by Gandevia et al., (1993) which demonstrated that air hunger can remain in healthy

volunteers experiencing complete neuromuscular block and therefore, feedback from the chest wall was not necessary to experience air hunger as for the same level of CO2, the same amount of air hunger can exist irrespective of the level of chest wall feedback being received.

It is now established, therefore, that generating a feeling of air hunger is not dependent on the mechanoreceptors, but instead is caused by a complex physiological mechanism involving different receptors. Manning et al., (1992) hypothesized that changes in arterial blood PCO_2 as well as O_2 and other ions cause a demand for an increase in respiration. This demand signal is sent to the respiratory centres in the brainstem which is then forwarded to the respiratory muscles to increase respiration. A copy of this signal called the corollary discharge is sent to the forebrain which then acknowledges this experience of air hunger. The stretch receptors in the lungs will send a signal to the brainstem (which is forwarded onto the forebrain) indicating that this change in respiratory need has been met. This compensatory signal being sent back from the lungs to the brain is what resolves the feeling of air hunger. Consistent with this theory is the work conducted with paralysed polio sufferers which demonstrated it was possible to experience air hunger both when CO_2 was increased, and when ventilation was restricted, and CO_2 was fixed at a lower level. This has led to the conclusion that air hunger can not only be generated by high levels of inspired CO_2, but also by a combination of ventilation being fixed at a low level, with a moderately increased inspired CO_2. Furthermore, much evidence has been produced on the subject to suggest that air hunger is sustained when there is a mismatch between signals reporting the need to

breathe, and prevailing feedback on the current ventilation levels (Moosavi et al., 2004).

Now that the physiological mechanisms behind breathlessness have been explored, it seems logical to turn our considerations to which areas within the forebrain are responsible for receiving this corollary discharge. Based on recent imaging work a large number of brain areas have been identified as implicated in breathlessness by a number of different authors, however, the explicit role of these areas, and the network they make up, has yet to be clearly defined. Areas which are most frequently cited in the literature are the amygdala, insular cortex, anterior cingulate and periaqueductal grey (PAG) (von Leupoldt et al., 2009, von Leupoldt et al., 2008, Evans et al., 2002, Banzett et al., 2000). These areas, therefore, need to be explored further as potential members of the breathlessness neural network.

1.3 Treatment options and their limitations

Numerous treatment options; both non-pharmacological based, and pharmacological therapies have been suggested for relieving breathlessness, and it has been acknowledged within the literature that a combination of non-pharmacological and pharmacological treatments provides the best method for relief (Booth et al., 2009). With regards to breathlessness as a result of cardiorespiratory disease, in particular in the earlier stages, non-pharmacological options can prove very effective in managing breathlessness. However, as the disease becomes more advanced, pharmacological management becomes increasingly necessary (Booth et al., 2009).

1.3.1 Pharmacological options

In specific contexts, the use of pharmacological treatment can be a simple and effective solution to a person's breathlessness; however, they can also come with some very serious side effects. Opioid use for example, whilst being associated with a significant improvement in breathlessness, can cause respiratory depression if not titrated correctly, a potentially fatal side effect. It is, however, an appropriate procedure in some contexts. Within palliative care for example, patients with terminal disease in the advanced stages, using pharmacological treatments is a common solution to their discomfort. The side effects that they may experience are of limited concern in proportion to the severity of their breathlessness, and their discomfort, and long-term consequences of opioid use such as addiction are less of a concern at this stage. However, for patients with intractable breathlessness who have an expected lifespan of several years, providing them with an effective therapy that will not encroach on their quality of life in other domains becomes a challenge.

Despite these serious concerns, Opioids remain still the most commonly prescribed pharmacological treatment for dyspnoea. The use of opioids has the largest evidence base and is a very flexible approach to dyspnoea treatment in terms of changing dosage, administration type, and drug itself (Booth et al., 2009). A meta-analysis of primary studies by Jennings et al., (2002) showed a consistent, significant improvement in breathlessness for patients prescribed opioids across multiple studies. However, many of these studies were very short or only provided the patient with a single dose of medication. A long-term pharmacovigilance study on morphine treatment for chronic dyspnoea found

that after taking morphine for a period of three months, one in three patients (N=83) still maintained a benefit (Currow et al., 2011). Additionally, despite the prescription of laxatives, patients still struggled with constipation as a result of the medication. Opioid use does come with some very serious side effects and can often be the reason for the patient to discontinue with the medication (Booth et al., 2009). Respiratory depression, where breathing is slowed down to the extent where a person's oxygen and carbon dioxide levels become impaired, is a very real risk of opioid use. Drug induced respiratory depression can be fatal, and whilst some have suggested that it is possible to titrate the opioid (Currow et al., 2011), it is still dangerous.

A more recent Cochrane report (Barnes et al., 2016) on opioids for treating breathlessness at the end of life included 26 studies and found low quality evidence for oral or injected opioid drugs helping to alleviate breathlessness, and no evidence when the opioids are nebulised. Barnes et al., (2016) found that there was inconsistency in the outcome measures reported (for example, only 4 studies addressed quality of life), and the sample sizes per study were small, meaning it is not possible to be certain about the results. The report drew the tentative conclusion that there is a trend for small improvement in quality of life in the opioid group compared to the placebo group. Furthermore, short term opioid use could help to improve exercise capacity as patients who were prescribed opioid based medication performed better on a 6-minute walk test compared to a placebo group. Interestingly, a comparison study by Navigante et al., (2010), cited in the report, found that Midazolam, a benzodiazepine, improved breathlessness scores more than morphine in patients with late stage

cancer. This suggests that non-opioid based medications can be more effective and could be offered as a non-opioid alternative to patients who cannot tolerate the side effects seen with opioids, or who get little improvement to their quality of life.

A potential pharmacological alternative which has been studied at length in relation to experimentally induced breathlessness, but has failed to translate into clinical practice, is inhaled furosemide. Furosemide is known to act on the mechanoreceptors in the airways and is hypothesized to modulate feelings of air hunger. In a study comprised of healthy volunteers, dyspnoea was induced during an inhalation of either a placebo or a dose of furosemide, the finding being that furosemide greatly reduced feelings of dyspnoea (Nishino et al., 2000).

In research with individuals with respiratory conditions however, furosemide has not been shown to be effective. Wilcock et al., (2008) gave 15 patients with late stage lung cancer either inhaled saline or furosemide (in random order) for 3 consecutive days. No significant differences in outcome were reported between the placebo and drug condition. Six patients did anecdotally report that they felt less breathless with the nebulized treatment, but only one of those preferred the furosemide, three preferred saline, and two said both mists had equal effect. In contrast, however, Shimoyama and Shimoyama, (2002) found that 20mg of furosemide nebulised and inhaled 4 times per day dramatically improved dyspnoea in 3 cancer patients in the palliative stages with no reported negative side effects. This, therefore, raises questions about the appropriate dosage and frequency of use needed in order to get the desired

relief. There is also the additional question of whether furosemide, or indeed any pharmaceutical option discussed in this thesis can be seen as a drug to treat dyspnoea as an overall sensation, or instead it is more sensible to consider whether these medications can help relieve specific sensations of dyspnoea. For example, Grogono et al., (2018) presented data that inhaled furosemide was effective at relieving air hunger in 16 healthy volunteers, but did not give relief from the feeling of work and effort. Overall, it seems plausible that furosemide does have a therapeutic benefit, however the potential of this medication needs to be further investigated before it is incorporated into regular practice for dyspnoea management.

In recent years, cannabinoid-based treatments have begun to be investigated for their therapeutic properties for a host of symptoms including intractable breathlessness. Recently, a small Canadian study conducted by Abdallah et al., (2018) reported that vaporized inhaled cannabis had no beneficiary effect on exertional breathlessness and exercise stamina in patients with advanced COPD. When working with both healthy volunteers with induced air hunger and COPD patients, Pickering et al., (2011) found there to be no difference in breathlessness ratings (using a visual analogue scale) between the control drug and the cannabis extract cohorts. Pickering et al., (2011) did however note that the COPD patients were less likely to select the 'air hunger' specific descriptors after the administration of cannabis. This has led to the tentative suggestion that cannabis may decrease the unpleasantness of air hunger, but not the overall intensity of the breathlessness, hence the VAS score remaining the same. Furthermore, work by Reid et al., (2011) determined that in a comparison

between cannabis smokers and tobacco smokers from a primary respiratory disease population, cannabis smokers reported fewer incidences of breathlessness, cough and sputum. However, those who smoked cannabis did not benefit from significantly better lung function test scores and had the same air flow limitations as the regular tobacco users. This once again reinforces that the use of cannabis may reduce the unpleasantness of breathlessness experienced but does not promote any positive physiological changes.

This line of enquiry is relatively new and unexplored, and much like the use of opioid based medications, can be controversial. There is still much research that could be done before cannabinoid-based medications are definitively ruled out as an option for sufferers of breathlessness, and there is much to be learnt from research already conducted.

1.3.2 Nonpharmacological options

Pulmonary rehabilitation is one of the most recommended non-pharmacological treatments for dyspnoea (Herigstad et al., 2017). Paz-Díaz et al., (2007) found pulmonary rehabilitation over a period of 8 weeks improves patients' feelings of breathlessness during exertion and in 'activities of daily living'. Additionally, it is reported by Verrill et al., (2005) that as well as reduction in dyspnoea, patient's anxiety around exercise and feeling breathless decreases, meaning they are more comfortable with being active in their daily lives. However, the benefit seems to be relatively short term unless the program is in excess of 24 weeks (Verrill et al., 2005) and only if the patient does continues to exercise at home or participates in activities in the local community. Unfortunately, the uptake of pulmonary rehabilitation is poor and

this may be due to the vicious cycle of breathlessness and emotion as suggested by Spathis et al., (2017).

There are other alternative non-pharmacological treatments available as well, with the cheapest and most accessible being the use of a fan to blow cold air onto the face. This therapy provides a sense of self-efficacy to patients, and is internationally available, making it a popular choice (Booth et al., 2016). Research has suggested that it is useful to patients in providing relief (Galbraith et al., 2010, Johnson et al., 2016), but only whilst the patient is sitting quietly; any minimal level of exertion causes the feeling of dyspnoea to return to its baseline level (Booth et al., 2016). It is not known whether the mechanism of action is purely psychological or has a physiological basis e.g. stimulation of facial temperature receptors.

Overall, the current treatment options available to patients all have their limitations, and none are appropriate for alleviating dyspnoea in the long term. With regards to pharmacological treatments, there is a need to find both new and repurposed compounds that can be used as an alternative to opioids for people who are either unable or unwilling to tolerate them. Options such as furosemide and cannabinoid-based agents have been trialled experimentally with limited success and it is reasonable to suggest that further experimentation must be conducted before any definitive guidance can be given on the use of these drugs in dyspnoea management. Less has been produced on non-pharmacological alternatives, although pulmonary rehabilitation has recently become a promising forerunner in breathlessness therapies, and further management techniques need to be developed.

1.4 Similarities between pain and breathlessness

Two common symptoms for patients with chronic conditions are pain and dyspnoea (Banzett and Moosavi, 2001). These two sensations are similar in nature in three distinct ways; both can cause extreme discomfort, they both cause externally visible signs, and they both have a severely negative impact on the sufferer's quality of life (Gracely et al., 2007). Additionally, in both instances of intractable breathlessness and intractable pain, eliminating the symptom with current available treatment options risks harming the patient further, whilst undertreating can contribute to a reduced quality of life.

Pain research has made significant scientific advances in recent years, something which dyspnoea research can benefit from. The methods used to better map the neurological network behind pain perception can be used as a model when trying to advance our understanding of dyspnoea. It is commonly accepted in the pain speciality that the model of pain is multidimensional. This model incorporates multiple different components such as anxiety, fear, attention, and expectation. With regards to breathlessness research however, the focus has primarily been on anxiety and depression, but addressing the cognitive components of dyspnoea could be the key to developing our understanding. Indeed, the dyspnoea-12 questionnaire has incorporated affective items demonstrating a progression in how the dyspnoea community views the breathless experience.

In terms of neurological structures, there is evidence to suggest that the neural regions identified as being involved in pain, may also be involved in the perception of breathlessness. The insular cortex, anterior cingulate cortex and

the amygdala have all been found by brain imaging studies (von Leupoldt et al., 2009, Evans et al., 2002) to be involved in both pain and breathlessness modulation. These areas are implicated in conscious awareness of bodily state (Craig and Craig, 2009), cognitive and affective emotional processing (Treede et al., 1999), conditioning responses and attention (Beckmann et al., 2009). It is, therefore, theorized that these brain regions and their interactions are not only crucial to the perception of dyspnoea, but also to multiple sensory perceptions.

It appears reasonable to suggest however, that the neurophysiological mechanisms which give rise to dyspnoea are not identical to those which are the root of chronic pain. Whilst using pain research as a guide may be fruitful, it is important to also investigate what makes dyspnoea different to other sensations. By implementing unique experimental techniques with either dyspnoeic patients, or carefully induced realistic models, it will become possible to tease apart the distinct mechanisms of dyspnoea from the mechanisms behind unpleasant sensation.

1.5 Current experimental approaches

When studying intractable breathlessness, we have limited experimental approaches available to us. It is not possible to rely on animal models, as breathlessness is a subjective sensation, and so we need to be able to communicate with the subject in order to understand their breathless experience. With regards to animals therefore, we are forced to look at behavioural markers of breathlessness which come with their own, possibly incorrect assumptions. This means that fundamentally we have two potential approaches; patient centred research, and the study of induced breathlessness

in healthy volunteers. In some conditions, dyspnoea does not appear until the very advanced stages of the disease, and often, the patient's health begins to decline rapidly after this point. This makes recruitment of patients with breathlessness rather difficult, and attrition rates are often very high with patients struggling to meet the demands of the study. Furthermore, it is not possible to control a person's pre-existing breathlessness in an experimental setting, meaning that the sensation may vary in intensity and comprise of different components between patients. For these reasons therefore, a considerable portion of dyspnoea research involves experimentally inducing breathlessness in individuals without a respiratory condition.

This methodological approach raises the question of whether the breathless sensation which is induced in the lab is representative of the dyspnoea experienced by someone who has dyspnoea as a result of an underlying condition. (O'Donnell et al., 2013) compared questionnaire responses from sufferers of COPD who had dyspnoea when active and healthy volunteers with induced dyspnoea and found no significant difference between responses. An additional questionnaire also asked the cohort with COPD to compare artificially induced dyspnoea to when they experienced breathlessness during their daily lives. There was no significant difference between patient questionnaire scores in either condition. We can, therefore, be confident that inducing breathlessness in healthy volunteers is an accurate reproduction of the sensations felt by dyspnoea sufferers.

1.5.1 Neuroimaging

Increasingly, imaging work has been used in order to better establish the neural mechanisms behind breathlessness. Modern non-invasive imaging techniques have provided researchers with a tool for studying multiple different cognitive systems and the neuronal activity associated with them. This tool, however, has been underutilized by the breathlessness research community. This may be due to the difficulties in patient recruitment as previously discussed, but also problems with practicality may play a role. As neuroimaging scanners such as MRI machines are essentially giant magnets, the equipment used in order to induce dyspnoea must be non-magnetic. This can be difficult and expensive to achieve, and perhaps contributes to the limited number of studies which use this experimental approach. Furthermore, key interpretational issues can be common in neuroimaging studies, with the possible implication being that false correlations are made between neural activation and the behaviour being studied. Neuroimaging studies have been accused in the past of publishing findings with lack of critical interpretation or questioning of fMRI as an approach and of its statistical analysis.

1.5.2 Structural imaging

Structural brain imaging studies have examined differences in neuroanatomy between patients with respiratory disease, and healthy controls, as well as anatomical changes over time. Esser et al., (2016) reported there to be a decrease in grey matter density in the cingulate cortex of patients with COPD. This is an area often theorized to be involved in breathlessness perception. The outcome of this study also demonstrates the importance of not relying on

healthy volunteer studies when looking at the cerebral mechanisms of breathlessness, as anatomical changes can occur in disease populations that will not be identified if patients are not included in studies on intractable dyspnoea.

Additionally, Von Leupoldt et al., (2011) reported findings of an increase in grey matter density in the PAG of patients with mild to moderate asthma. This study, however, cannot conclude whether these structural changes caused, or were a consequence of, disease progression. In order to try and better understand this relationship, additional longitudinal studies into the same area would be required. Furthermore, follow up studies would benefit from including patients with mild to moderate as well as moderate to severe categories of asthma in order to try to establish whether this relationship between grey matter density and disease progression is mediated by disease intensity. Additional behavioural information, for example, frequency of exacerbations and times emergency treatment was necessary, would also be very helpful in better understanding the meaning of this finding.

1.5.3 Functional imaging

The first functional neuroimaging study conducted by Banzett et al., (2000) showed that the limbic system had high levels of activation during induced breathlessness and this finding has been consistent across multiple imaging studies (Evans et al., 2002, Herigstad et al., 2011). Specifically, the most common regions of activation are the insula, anterior cingulate, orbital frontal cortex, thalamus and the basal ganglia. The use of neuroimaging to identify structures involved in breathlessness is limited however, by the fact that areas within the brain will be active during scanning, but their function does not

necessarily relate to the activity the participant is performing. This limitation can be overcome to an extent as it is possible to discount certain areas, as we are confident, they are not involved in the task we are interested in- but other activation patterns are more ambiguous.

Additional limitations of this type of work include the difference between chronic breathlessness and an acute induced attack. It is difficult to experimentally induce in healthy volunteers that feeling of dread and anticipation which patients with ongoing breathlessness may experience when they have the sensation. Similarly, if the healthy volunteer has never experienced breathlessness before, that sense of uncertainty will not be present in the respiratory patient's mind. This, therefore, could mean that the findings of an imaging study using healthy volunteers and induced breathlessness may not have validity for clinical patient populations as the cognitive processing and neural activation will be different. Furthermore, it is possible that prolonged medication use designed to blunt the intensity and unpleasantness of breathlessness may change a person's perception of dyspnoea over time. This in turn could alter the neural activation patterns recorded and mean that any conclusions drawn about the structures involved in breathlessness have the caveat of only being valid for a specifically medicated population.

1.5.4 Lesion deficit approach

An alternative approach to studying the cerebral mechanisms of breathlessness is to perform a lesion-deficit study, which would establish a structure function relationship. This approach provides complimentary data to the correlative approach of fMRI. An initial study using this approach,

conducted by Schön et al., (2009) showed that patients who had suffered a stroke affecting the functioning capabilities of the right insular cortex demonstrated a reduced perceptual sensitivity to both pain and dyspnoea. The size of the cohort for this study was very small however, (N=4 per condition) and there have been some queries as to whether the sensation being induced was in fact dyspnoea. Furthermore, some of the patients tested stated that they were breathless at rest without any additional stimulus, meaning that the control cohort did not have the same experience as the patient cohort. This, therefore, makes it difficult to conclude whether there was any dampened perception of dyspnoea in the patient cohort, and further work needs to be completed to address these specific issues.

A lesion-deficit study conducted by Liaw et al., (2016) which focused on stroke patients with heart failure and exertional dyspnoea, found there to be pulmonary dysfunction in a statistically significant proportion of the patients studied. They also commented that patients reported low levels of dyspnoea at rest; however, clinicians observed signs of breathlessness at rest throughout their interviews with the patients. The authors theorized that this discordance between patient and clinician reports might be because of an impaired perception of dyspnoea due to stroke damage. It is difficult to draw a conclusion however, as the patient inclusion criteria was patients who have suffered a stroke, with no neurological location specified. The results are interesting, even if we cannot establish a definitive structure-function relationship. The data collected will offer further insight into the impact of neurological damage on cognitive functioning and be complementary to the fMRI data which is

correlative in nature. This additional data will not suffer from the same methodological problems faced study by Liaw et al., (2016) and will help to establish whether the insular cortex does play a vital role in breathlessness perception.

1.6 Aim and approach

An urgent clinical need for better treatment options will only be met if we better understand the mechanisms of dyspnoea. It is necessary to build on what we have learnt about the peripheral mechanisms by now focusing on brain networks implicated in dyspnoea perception. So far, we have primarily relied on functional brain imaging to broaden our understanding, however this approach has key interpretational and practical issues. There is a need to move away from the assumption that activation of whole brain structures is evidence of their involvement in breathlessness, and instead, an appreciation of different nuclei forming a breathlessness network needs to develop. Current neurosurgical interventions for neurological patients provide new opportunities to investigate the brain mechanisms of dyspnoea using a different approach.

1.6.1 Deep brain stimulation

Deep brain stimulation (DBS) has been shown to successfully treat symptoms of neurological disease such as tremor, freezing of gait, dystonia and epileptic seizures. Common therapeutic sites within the brain are the motor thalamus, the Globus Palladium, and the sub-thalamic nucleus. Inserting electrodes into these target nuclei and delivering high frequency electrical current has been shown to successfully relieve these treatment resistant symptoms. A currently

under-utilized resource for research, DBS provides us with a novel approach for investigating the role of specific nuclei in the generation of air hunger.

1.6.2 Surgical resection

A secondary novel approach to investigate the role of specific neuroanatomy is to assess breathlessness before and after a surgical resection of brain tissue. Working with patients who have a low grade glioma (a type of non-malignant brain tumour) involving their insular cortex (an area implicated in breathlessness through brain imaging (Evans et al., 2002)) has the potential to provide us with further insight into whether this region is imperative to being able to experience dyspnoea. The function of the insular cortex and the effect of its removal on other brain functions have been studied, however, the implications of damage to the insular cortex for breathlessness perception, are yet to be established.

1.7 Aims and hypotheses

The specific neural mechanisms behind the perception of air hunger have yet to be resolutely mapped. During dyspnoea there is an increased awareness of the respiratory system as well as a heightened emotional component. Based on this, and what we understand about the function of specific brain structures, it has been hypothesized in the literature that the neural basis of dyspnoea involves the cortex and the limbic system. The predominant body of research on this subject has used brain imaging methods such as fMRI. However; no study to date has used a phantom lesion deficit approach involving multiple patient populations with different neurological damage, to try to decipher which neuroanatomy is responsible for breathlessness. I, therefore, aim to identify,

using this unique approach, the cerebral structures and connectivity involved in the perception of breathlessness. Elucidation of this cerebral mechanism will allow for us to identify potential therapeutic targets for intractable breathlessness, as well as gain insight into whether neurological patients are at risk of developing an abnormal dyspnoea perception.

1.8 The organisation of this thesis

Chapter 1

Chapter 1 provides a general introduction to the thesis. The focus of this chapter is the current understanding of breathlessness, and the treatment options available. There is also mention of the current approaches used to study breathlessness, and the clinical significance of the presented work.

Chapter 2

Chapter 2 reports the general methodology used for the experiments throughout this thesis. It outlines the physiological and neurological techniques that were applied, and describes the tools used to capture the participant's subjective experience of breathlessness.

Chapter 3

Chapter 3 details a study involving participants with DBS of the motor thalamus for disordered movement. Anecdotal evidence from neurosurgeons, combined with pilot data, suggested that patients with DBS of the motor thalamus experienced a change in breathlessness perception when stimulation was

turned ON. The main aim of this chapter was to explore whether DBS of this brain region reduces the perception of experimentally induced dyspnoea.

Chapter 4

Chapter 4 is split into 2 sections.

Section 4.1: There is preliminary evidence that stimulation of the sub thalamic nucleus (STN) can contribute to the sensation of breathlessness (Chalif et al., 2014). Chapter 4 uses the D12 questionnaire to assess whether stimulation of the STN modulates dyspnoea perception in patients who have breathlessness at rest.

Section 4.2: Non-motor symptoms of Parkinson's disease (PD) are less well quantified than their motor counterparts. When asked in a clinical environment if they have experienced feelings of breathlessness in the past month, 39% of patients with PD answered positively (Baille et al., 2019). Building on this, the second study presented in chapter 4 uses the D12 questionnaire to quantify whether individuals with Parkinson's disease in the community experience breathlessness experience breathlessness in their daily life.

Chapter 5

In addition to studying a neurological population with dyspnoea experimentally induced, as is done in chapter 3, it is also important to work with a population who have a respiratory disease. Chapter 5 outlines a study involving patients with both DBS of the motor thalamus, and with a pre-existing respiratory disease. Here, participants used questionnaires to record their breathlessness with stimulation turned ON and OFF.

Chapter 6

The final experimental chapter in this thesis is dedicated to novel explorative approaches to better elucidating the mechanisms of air hunger and comprises of 2 case reports.

Section 6.1 reports a study of experimentally induced breathlessness in a patient with simultaneous recording of neural signals from electrodes implanted for DBS of the ventral intermediate nucleus (VIM). This was in an effort to capture a distinct signal within the thalamus that is only produced during air hunger.

Section 6.2 reports a study of experimentally induced breathlessness in a patient with tissue damage to the insular cortex resulting from low-grade glioma. This was in an effort to explore whether tissue damage can cause a change in perception of air hunger.

2 General methods

The following methodologies will be discussed in this chapter:

1) Experimentally induced air hunger
2) Subjective measurements of dyspnoea
3) Neurological recording from and stimulation of the cortical & subcortical brain areas

2.1 Attributions

The following individuals assisted with the methods discussed below:

Dr Yongzhi Huang assisted with the collection and provided expertise with analysis of Local Field Potential data.

Claire Fletcher, Beth Farrow, and Laura Bacchini assisted with participant recruitment across all studies.

Elizabeth Coney assisted with data collection of 1 participant and performed preliminary analysis of air hunger and CO_2 steady state data for 3 participants.

Ross McLean assisted with the data collection of 3 participants.

Cathal Gates assisted with data entry and preliminary analysis of the postal survey.

2.2 Experimentally induced dyspnoea

2.2.1 Evidence for distinguishable components of dyspnoea

Evidence suggests that air hunger, work and effort, and chest tightness are all distinct components of breathlessness, which arise from separate neural pathways (Banzett et al., 2008). The separation between air hunger and work and effort has been through work performed with participants who were

partially paralysed (Moosavi et al., 2000). Participants were temporarily partially paralysed during 2 breathing conditions (i) hypercapnia with fixed breathing and (ii) hyperpnoea with normocapnia. During both of the conditions, decline of vital capacity was matched and ventilation was constant. The sense of effort increased with partial paralysis and the voluntary breathing, as well as during partial paralysis with hypercapnia and fixed breathing. However, a sensation of air hunger, as rated by participants during the study, only significantly increased during the condition with increased CO_2. This suggests therefore, that the neural pathways between air hunger and work and effort are separate and distinct.

Additional evidence for the separation of these cerebral pathways comes from (Binks et al., 2002) who demonstrated that the sensations of chest tightness and work and effort can be separated. Participants were given methacholine to induce chest tightness whilst ventilated. Even when their breathing was fully relaxed, participants did not get relief from the tightness elicited by the methacholine. Once again this provides evidence to suggest that different facets of breathlessness arise from separate neural pathways.

2.2.2 Utility of experimentally induced dyspnoea

The method of experimentally inducing air hunger through hypercapnia with constrained ventilation is used within this thesis. Using experimentally induced air hunger as oppose to working with patients who have idiopathic breathlessness is preferable for multiple reasons. In some conditions, dyspnoea does not appear until the very advanced stages of the disease, and often, the patient's health begins to decline rapidly after this point. This makes

recruitment of patients with breathlessness rather difficult, and attrition rates are often very high with patients struggling to meet the demands of the study. Furthermore, it is not possible to control a person's pre-existing breathlessness in an experimental setting, meaning that the sensation may vary in intensity and comprise of different components between patients. Experimental air hunger presents the opportunity to study a specific facet of this sensation in a controlled setting where we can be confident that our protocol is valid as it produces the same sensation on repeated occasions (e.g. before and after interventions).

2.2.3 Experimental model of air hunger

Hypercapnia with constrained ventilation

To create a consistent feeling of air hunger, ventilation is restricted to the individual's baseline levels, and inspired CO2 is increased. This is a validated method of achieving air hunger with minimal sensation of work and effort and is used in multiple different labs (Moosavi et al., 2004)(Figure 2-1). Constrained ventilation was achieved by using a frequency of 12 breaths pre minute which is a level that would be comfortable for most individuals. A set flow of fresh air supplied an inspiratory reservoir which resulted in targeted ventilation that matched their baseline free breathing. It would be preferable to match the baseline breathing pattern rather than the baseline ventilation but the length of testing sessions that patients could commit to was limited and this would have added time and complexity to the protocol. Furthermore, there is data within the Moosavi lab showing that breathing pattern does not make a difference to air hunger for a given stimulus, instead it is overall ventilation

target that determines the amount of air hunger for a given CO_2 (Delisle et al., 2008).

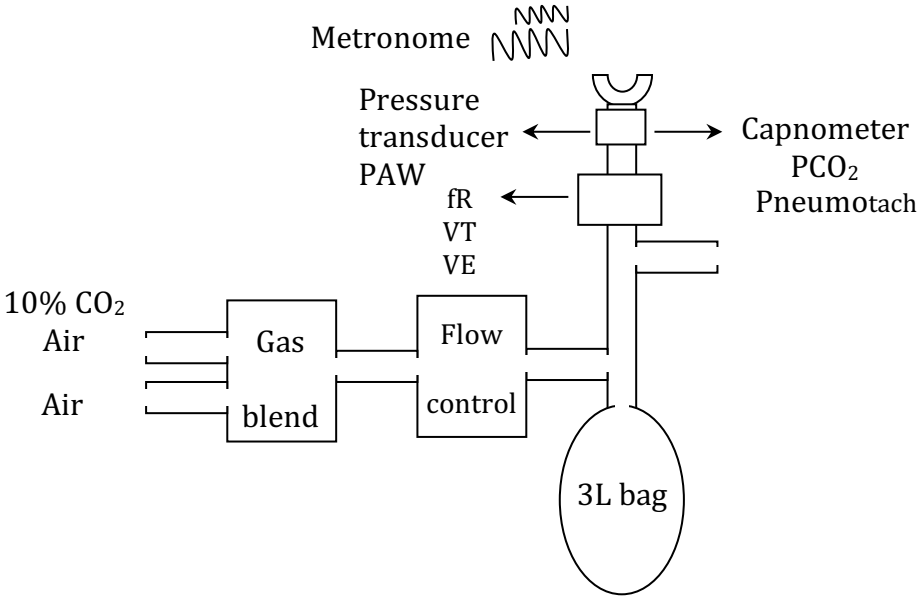


Figure 2-1 Breathing circuit

Participants breathed through a mouthpiece connected to a filter and rehumidifier rebreathing valves system. AH was generated by adding CO2 to the flow of medical air into the bag and this flow was fixed at baseline ventilation.

Raising inspired CO_2 levels can cause side effects such as an increase in heart rate and blood pressure. However, there is unpublished data within the Moosavi lab showing that these effects are only evident above 50mmHg and most healthy individuals will rate the maximal level of air hunger they are willing to tolerate before then (Figure 2-2; Banzett et al., 1996) . For the work conducted for this thesis, the upper limit of end tidal PCO_2 was set at 65mmHg (approximately 25mmHg above normocapnia). This is because levels above

65mmHg of inspired CO_2 can start to have an anaesthetic effect and can become toxic at very high levels.

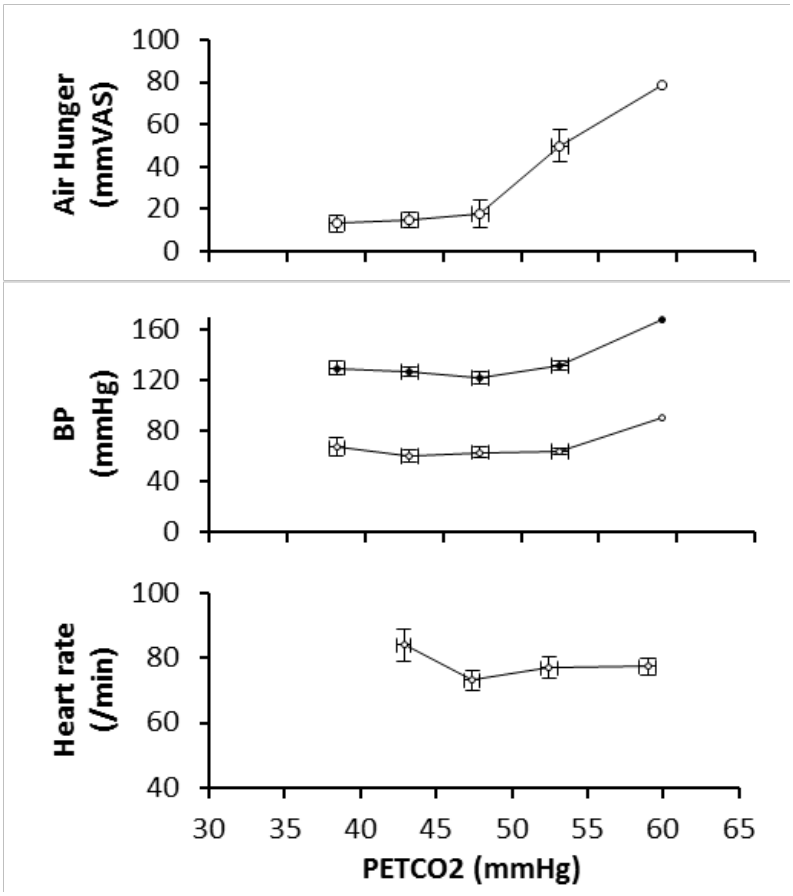


Figure 2-2 Effect of increasing PETCO2 on blood pressure and heart rate

Two air hunger protocols were performed:

Incremental/ramp air hunger test:

During the ramp air hunger test, participant's ventilation was measured at its resting baseline and the target flow was fixed at this level for the duration of the 10-minute trial. Inspired carbon dioxide was increased in steps of 1.3% every

60 seconds either until the participant rated air hunger to be 'extreme' (equivalent to 100mmVAS) or the ethical limit of 65mmHg end-tidal CO_2 was reached; all participants rated top of the VAS scale well before the 65mmHg end-tidal CO_2 limit was reached (Figure 2-3).

Steady state air hunger test:

Inspired CO_2 was set to match that which evoked a 50%mmVAS rating in the incremental air hunger test. Ventilation was set at the same baseline level as decided at the start of the incremental test. Following one minute of 'normal' breathing, CO_2 was set to the pre-determined level, and was fixed for at least 4 minutes to make sure that the CO_2 stimulus and VAS ratings reach steady state. An example of the physiological trace produced from using this method is shown in Figure 2-3.

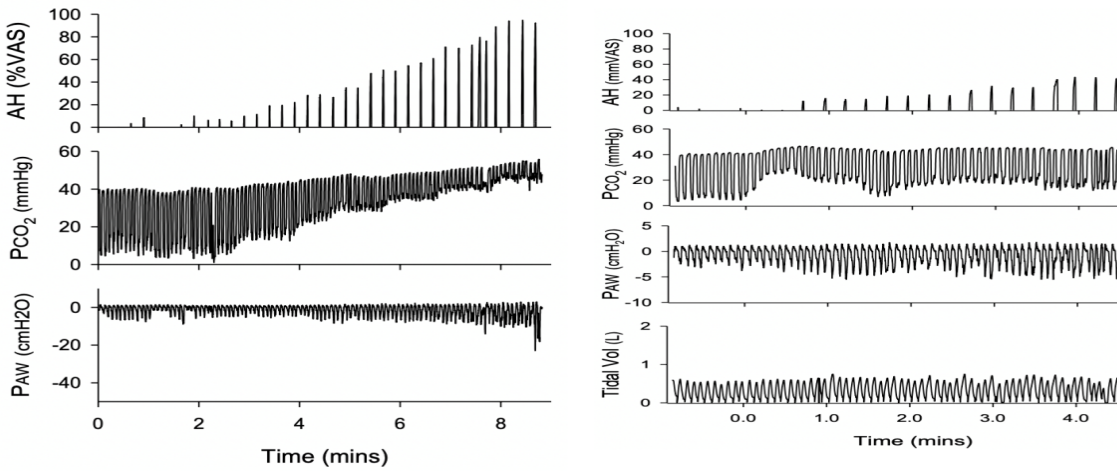


Figure 2-3 Standard incremental air hunger test and steady state test in one participant (P023)

Left panel: Typical raw data set for the air hunger test including VAS ratings of air hunger (air hunger) provided at 15 second intervals cued by an LED (top panel), continuous PCO_2 (second panel), and airway pressure (PAW; third panel). Tidal volume was recorded but is not shown here. The trial was terminated early if participants either rated extreme air hunger at the top of the VAS or removed their mouthpiece due to air hunger. Right panel: VAS ratings of air hunger (air hunger) provided at 15 second intervals (top panel), continuous PCO_2 (second panel), airway pressure (PAW; third panel) and tidal volume (VT; bottom panel) in one individual (P23) during the steady-state air hunger test with stimulation OFF (left panels) and ON (right panels. Ventilation was constrained at the resting baseline level by breathing in time with a metronome and from a bag with fixed rate of fresh gas flow.

2.2.4 Control conditions

Hypercapnic ventilatory response

For the patient with low grade glioma of the insula, an additional breathing test was conducted. This involved testing whether the innate reaction to take in larger breaths when inspired CO_2 is raised, was intact. This ensures that the brainstem mediated chemosensory reflex ventilator drive is unaffected.

A steady state method was applied with inspired CO_2 level set a level which would be expected to produce a 50% increase in VAS ratings of air hunger. This was based on the response of the participant in their incremental air hunger tests. As opposed to the steady state trial using hypercapnic with constrained ventilation, this trial allowed ventilation to change freely. All other aspects of this condition were the same as for the air hunger test. This protocol was therefore a control condition in which CO_2 stimulus was matched to that of the air hunger test, but ventilation was allowed to change –hence was expected to elicit a lesser air hunger response because of increased inhibitory vagal afferent feedback from the lungs.

Voluntary Hyperpnoea with normocapnia

For the patient with externalised electrodes, a second control condition was also imposed. The final breathing trial was a control test in which no changes were made to the inspired CO_2. Patients targeted the same levels of ventilation as in the trial with increased CO_2 and unrestricted ventilation. End-tidal PCO_2 was kept at the normal level of approximately 38mmHg by administering CO_2 gas as required. No air hunger was expected to be elicited by this control condition because air hunger generating afferents (corollary discharge of brainstem motor drive to breathe) would be absent while air hunger mitigating vagal afferents from the lungs would be maximised.

2.3 Physiological measurements and recordings

A mixture of medical air and CO_2 from two medical gas cylinders was blended using an air-oxygen mixer and the blended output was heated and humidified before feeding an inspiratory reservoir (3 litre anaesthetic bag). To record airway pressure a sampling line was inserted into the participants' mouthpiece to provide a continuous recording of airway pressure (PAW) relative to atmosphere via a differential pressure transducer (Validyne, ±50cmH_2O). Respiratory airflow was measured at the mouth using an in-line pneumotachometer with pressure lines connected to a second pressure transducer (Validyne, ± 2cmH_2O). PCO_2 was monitored continuously via a second sampling line inserted in the mouthpiece feeding a fast responding infra-red capnometer (ADinstruments gas analyser, Oxford, UK). End-tidal PCO_2 was determined from the plateau in the expired PCO_2 levels. Analogue signals were converted into digital form using an A-D converter (micro1401, Cambridge Electronic Design, Cambridge, UK) at a sample rate of 20Hz. Safety monitoring included; non-invasive blood pressure via a cuff inflated around the upper arm every 2.5 minutes, continuous 3-lead ECG from which heart rate was derived, continuous arterial oxygen saturation levels using a pulse oximeter via a finger transducer (Datex, cardiocap). A rise in inspired CO_2 can lead to changes in blood pressure and heart rate. Experiments were stopped if SPO_2 fell below 95% or if heart rate exceeded 150 beats per min. One participant with thalamic electrodes was excluded due to their SPO_2 falling without explanation (P27).

2.3.1 Validity, reliability of these tests

There is discussion within the literature regarding whether the sensation created through hypercapnia with constrained ventilation is the same as what is felt by people with organic lung disease. In a comparison between questionnaire responses from sufferers of COPD who had dyspnoea when active, and healthy volunteers during induced dyspnoea, no significant difference was found between responses. Additionally, when comparing induced dyspnoea with dyspnoea occurring in daily life, individuals with COPD recorded no difference between sensations (O'Donnell et al., (2013). The method of inducing air hunger, as described and used in this thesis, can therefore, be used with confidence.

In this model of experimentally induced air hunger, in which bag limited breathing is used to constrain ventilation, the air hunger response appears to mirror the rise in negative airway pressure as the subject continues to inspire after the bag collapses. Thus, it would be reasonable to posit that the negative airway pressure is the cause of the air hunger response via changes in afferent information from airway mechanoreceptors. However, work conducted within this lab has demonstrated that removing the negative pressure by constraining the ventilation through voluntarily targeted breathing (and not limited air supply) still generates air hunger (Figure 2-4; Delisle et al., 2008).

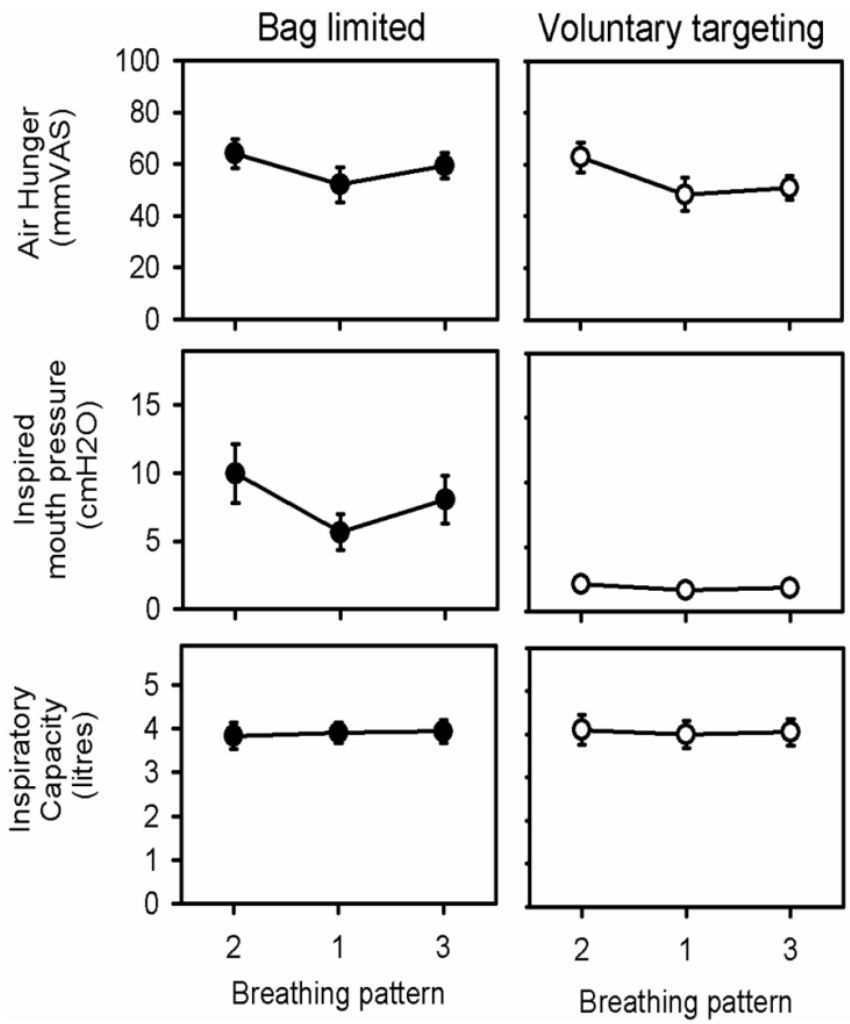


Figure 2-4 Air hunger ratings during bag limited breathing versus voluntary targeted breathing

During different breathing patterns, bag limited and voluntary targeted breathing created similar amounts of air hunger.

If we are to conclude that these tests cause a rise in arterial $PaCO_2$ which promotes a signal delivered to the forebrain and the ultimate feeling of air hunger to arise, the assumption must be made that $PETCO_2$ is used as an indicator of arterial $PaCO_2$. In chapters 3, 6 and 7 this assumption can be made because no participant had a history of lung disease, and there are no reports within the literature of movement disorders having an effect on gas exchange.

This assumption is irrelevant for participants in chapter 4 and 5 as they had a dyspnoea at rest and so did not partake in the protocol involving the circuit.

At the start of each testing session the equipment was calibrated. The capnograph was calibrated prior to each testing session using a gas with a known concentration of CO_2. The circuit was checked for leaks visually (looking for cracks in the tubing) and also by using a 3-litre syringe attached to the mouthpiece whilst the gas supply was turned off. This was done to ensure no air could be pulled into the circuit by the participant sucking hard on the empty bag. After each visit the breathing circuit was dismantled and soaked in an antiseptic solution for 10 minutes.

Due to working with a vulnerable patient population the amount of time available to complete each testing session was set at a maximum of two hours. This meant that it was not feasible to include practice tests for the participants in the studies with induced air hunger. After the initial incremental air hunger test (see above for more detail) participants completed a debrief questionnaire which asked them to tick relevant statements about the respiratory sensations felt and it was anticipated that they would choose the 'air hunger' descriptors. Examples of the air hunger descriptors are 'I felt a hunger for more air' and 'I felt starved for air'. This was used to ensure that air hunger was being induced successfully. This step in the protocol was important as it confirms the validity of the data collected.

2.4 Measurements of dyspnoea

Multiple, and varied measures of dyspnoea are used across the clinical and the research domain. Where the work within this thesis involves the use of experimentally induced dyspnoea two measures of breathlessness were utilised; the visual analogue scale and the Dyspnoea 12 questionnaire (D12), as well as an in-house debrief form (Figure 2-5). In instances where the participant had existing breathlessness, for example in chapter 5 where the effect of STN stimulation on existing dyspnoea was investigated, the D12 was used in isolation

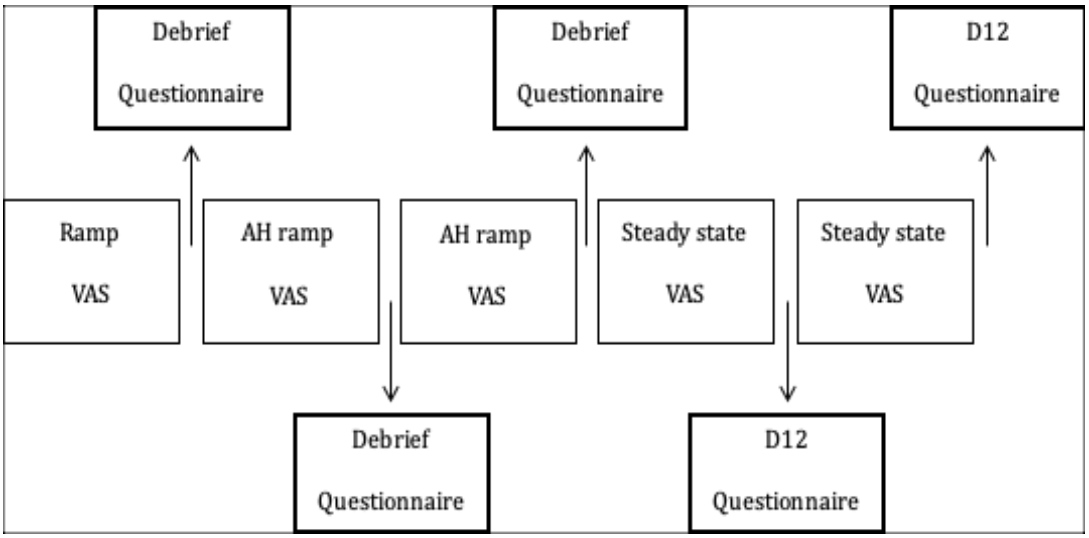


Figure 2-5 Protocol for experimentally induced air hunger protocol

Schematic of protocol followed for study titled 'the effect of thalamic DBS on breathlessness perception'.

2.4.1 Visual analogue scale

The main measure of dyspnoea that was used to assess experimentally induced breathlessness in patients with thalamic DBS and glioma was the visual analogue scale. The visual analogue scale is 100mm in length with the lower and upper limits of the scale labelled 'none' and 'extreme' respectively, with

'moderate' and 'severe' anchored in between at equidistant locations alongside the scale. Participants were prompted to rate their breathlessness using this scale every 15 seconds by a LED light attached to the scale turning on. If participants failed to make ratings, they were prompted by an experimenter. After each rating participants returned the sliding VAS indicator to the bottom of the scale. Rating 'extreme' caused an alarm to sound and in this instance the stimulus was immediately reduced.

There has been some discussion within pain literature as to whether the VAS is an adequate measure of subjective sensation. Some have cited that patients find it difficult to judge where their pain is on the VAS line and find that they resort to guess work (Jackson et al., 2006). However, others (Price et al., 2012) contest that any confusion experienced by the patient is a result of poor instruction on the part of the researcher. In a time constrained setting, where changes are made to see their effect on dyspnoea in the short term, the large range that the VAS provides may be preferable to the fixed 4- or 5-point scales such as the Medical Research Council's (MRC) dyspnoea profile. This is because the limited grades may not be able to capture the sudden shift (Ambrosino and Scano, 2001).

Additionally, ease of use has been reported to be a feature of the electronic VAS in multiple studies (Price and Harkins, 1987, Jamison et al., 2002, Price et al., 2008). It also has the capacity to incorporate multiple dimensions of a sensation (Price and Harkins, 1987) which is important when studying dyspnoea, a sensation thought to have a physical and emotional component (Lansing et al., 2009).

2.4.2 Dyspnoea 12 questionnaire

Following each steady state breathing trial in both the thalamic DBS (chapter 1) and glioma (chapter 3) studies, the Dyspnoea-12 questionnaire (D12) was administered. The D12 was also used as the primary measure of breathlessness in the community-based study focused on breathlessness in individuals with Parkinson's, and for the patients with idiopathic breathlessness (chapter 4) and co-respiratory disease (chapter 5).

The D12 is a published and validated measure of breathlessness. This is a 12-item questionnaire with a 4-point response scale ranging from 'none' (0) to 'severe' (3). The total possible score is 36 with higher scores indicating a higher degree of breathlessness. A total of seven items from the questionnaire assess the physical symptoms of dyspnoea and five measure the emotional content. This inclusion of both the somatic and sensory domain is important as it means that this tool is an accurate measure of overall breathlessness severity. It also uses descriptors that encompass the different aspects of the breathlessness experience, as opposed to a single measurement score, such as the modified Borg scale which cannot capture the complexity of dyspnoea sufficiently. The D12 has been shown to have good internal reliability, correlates well with measures of anxiety and depression (Yorke et al., 2010).

The D12 questionnaire is one of multiple options when trying to gauge a person's breathlessness, a popular alternative to the D12 is the Multidimensional Dyspnoea Profile or MDP. The MDP is a longer, less user-friendly questionnaire than the D12, and as such takes longer for the participant to complete (Banzett and Moosavi, 2017). There are also other validated

options such as the MRC's dyspnoea profile, or international measures such as the Transition Dyspnoea Baseline (TBI). In the research setting where the participants involved do not have pre-existing respiratory disease (chapters 3, 4 and 6) questionnaires such as the MRC's dyspnoea profile, and the TBI are not appropriate. These questionnaires use the participant's previous experience of breathlessness as the baseline and ask them to score the experimentally induced breathlessness in comparison. If the participant has never before experienced intense breathlessness, they are most likely to always rate the experimentally induced dyspnoea as the worst ever experienced. This means that if the participants did feel a change in sensation between the different trials, it would not be captured.

The instructions used in the thalamic DBS and glioma studies were "Rate how your breathlessness felt at the end of the breathing test you just completed when you were rating high on the VAS scale". This questionnaire has been shown to be flexible enough to capture experimentally induced breathlessness in the present (Williams et al., 2016).

The instructions for people in the community study where they were completing the D12 questionnaire in their own home were "Circle the number that best describes how you feel at this moment". The participant was instructed to complete one D12 questionnaire after having sat quietly at rest for at least 5 minutes and once after immediately having walked up a flight of stairs or 50 yards. This process was to be repeated 3 times a day; morning, noon and evening. Eighteen questionnaires were completed in total per person.

The participants in the 'breathlessness in individuals with PD in the community' received copies of the information sheet, consent form and 18 copies of the D12 (with items randomized on each) in the post (Table 2-1). Limited research has been conducted on the effect of mailing physical copies of the questionnaire to the participant on the quality of the data. In populations where internet access is very prevalent it is worth considering whether an online questionnaire is more sensible as it can lead to a greater response rate. An additional advantage of having an online questionnaire is that it is possible to prompt participants to complete any prompts that they have missed such as questions asking for their demographical information, or an item on the questionnaire itself. For this study however, participants were expected to be of an older generation and there were concerns that hosting the survey on an online platform would hinder recruitment. In a written communication from a research participate lead at Parkinson's UK, the decision to use a postal survey was acknowledged as an approach that was inclusive and sensitive to people's needs.

Table 2-1 Sample D12 questionnaire

Participants completing the questionnaire in their own home were instructed to complete the questionnaire after having rested for at least 5 minutes and again immediately after having either climbed one flight of stairs or walked 50 yards.

Item	None	Mild	Moderate	Severe
My breath does not go in all the way	0	1	2	3
My breathing requires more work	0	1	2	3
I feel short of breath	0	1	2	3
I have difficulty catching my breath	0	1	2	3
I cannot get enough air	0	1	2	3
My breathing is uncomfortable	0	1	2	3
My breathing is exhausting	0	1	2	3
My breathing makes me feel depressed	0	1	2	3
My breathing makes me feel miserable	0	1	2	3
My breathing is distressing	0	1	2	3
My breathing makes me agitated	0	1	2	3
My breathing is irritating	0	1	2	3

2.4.3 Other debrief questionnaires

In addition to the D12, two in-house questionnaires were used in the studies where experimental dyspnoea was induced; a background information questionnaire and a debrief questionnaire (Table 2-2). These have been used in previous published studies (Banzett et al., 1989, Grogono et al., 2018). The debrief questionnaire included an open question asking participants to describe the respiratory sensations felt when they rated high on the VAS. This questionnaire also contains a list of statements, some of which refer to air

hunger and others to the sensation of work and effort. Participants were instructed to read through the items and to tick all that were applicable to how they felt towards the end of the initial breathing trial. Participants are then asked to rank the items they selected as first second and third, based on how well the items fit the overall sensation they had experienced.

This additional step in protocol provided opportunity to ensure that the participant experienced air hunger when the air hunger stimulus (hypercapnia with constrained ventilation) was applied. Once established, participants were instructed to only rate 'air hunger' specifically as identified by them, for all subsequent breathing trials.

Certain patients found it uncomfortable to read and write due to the nature of their condition. In this scenario, an experimenter acted as reader and scribe. Experimenters did not engage, however, in discussion of the question items or potential answers to them.

Participants were also provided a list of other non-respiratory sensations and were asked to report if they had experienced them at any point during the breathing trial. These sensations included known side-effects of CO_2 such as headaches, dizziness and visual disturbances.

Table 2-2 Debrief descriptors

Participants were presented with this list at the end of the first trial and asked to tick all that apply. They were then instructed to rank the top 3 descriptors they experienced. Participants did this by putting a 1,2, or 3 next to the relevant statement.

	Tick
Size of breaths feels about right	
Breathing requires more work	
Breathing is comfortable	
Feel starved for air	
Feel short of breath	
Feels like heavy exercise	
Feel a hunger for more air	
Breathing requires more effort	
Size of breaths feels too large	
Feel an urge to breathe more	
Feel a tightness or constriction in chest	
Breaths feel too small	

2.5 Analysis of physiological and questionnaire data

2.5.1 Hypercapnia with constrained ventilation

For the ramp air hunger test, a 60 second boxcar average was performed on the end tidal PCO_2 data. This is because evidence suggests that there is a thresholding effect where the CO_2 concentration detected by chemoreceptors must rise by a certain amount before the air hunger signal is created and copied upwards to the thalamus and midbrain. This means that the VAS ratings given may not correspond to the PCO_2 measured at that moment in time. (Banzett et al., 1996) determined that a boxcar average of 60 seconds was sufficient in order to realign the delayed air hunger response to the PCO_2 stimulus it represents.

With regards to the steady state, the end tidal PCO_2 and VAS ratings from the last minute of each air hunger test were averaged for each condition of all participants. It was ensured that, within participants, each condition was well matched in terms of ventilation and end tidal PCO_2. A two-tailed paired t-test was conducted to compare steady state VAS ratings between the DBS ON and DBS OFF conditions; significance was set at the 5% level of probability.

2.5.2 Dyspnoea 12 questionnaire

Each questionnaire item has a score ranging from 0 to 3 and each item's score is added together to create a total for that individual questionnaire. This raw score is turned into a percentage total of the full scale which is 36 points. This is the combination of the emotional and physical question items. These two domains can also be separated. There are a total of 5 items that are within the emotional domain, and 7 within the physical.

2.6 Neurological approaches

2.6.1 Deep brain simulation

Deep brain stimulation (DBS) involves surgically inserting electrodes into target brain structures and providing those areas with therapeutic, electrical stimulation. This stimulation helps to disrupt abnormal firing of neurons which are giving rise to a variety of symptoms of disease such as tremor and freezing of gait in Parkinson's disease and chronic pain (Vitek, 2008, Boccard et al., 2012). The DBS hardware consists of (i) the electrode that is placed in the cortical structure, (ii) an implantable pulse generator (IPG) that is most

commonly positioned under the skin in the chest, and (iii) a cable that connects the IPG to the electrodes (Amon and Alesch, 2017).

The clinical relevance of this is that DBS can be used as a therapy to help control multiple different symptoms depending on which brain region is stimulated. This therapy has been used to treat conditions such as movement disorders, as well as psychological conditions such as anorexia nervosa and obsessive-compulsive disorder. Participants involved in the studies contained within this thesis were all diagnosed with a movement disorder which was the reason for their DBS therapy.

The surgical procedure for implanting DBS electrodes is of little relevance to the research within this thesis, and as such, shall not be discussed in depth. The neurosurgeons based at the John Radcliffe hospital gave assurances that all participants had working hardware (spoken communication). The research team is not aware of any participant having any surgical complication which affected the success of the procedure. All participants within this thesis who had DBS had electrodes located in either the STN or the motor thalamus. Two participants tested had electrodes in additional brain regions but the effect of stimulation of those areas on dyspnoea perception was not part of the protocol adopted, and they were not turned ON at any point during the testing session. Patients can have either bilateral or unilateral stimulation, with the former being more common. All participants who completed the study focused on the effect of thalamic stimulation (chapter 3) or STN stimulation (chapter 4) on breathlessness had bilateral stimulation bar one who only had electrodes implanted in the left hemisphere. All participants who completed the local field

potential protocol (chapter 6) had bilateral electrodes implanted but had only one electrode cable exposed at the time of testing.

2.6.2 Stimulation parameters

One of the benefits of DBS is its flexibility, meaning that therapy can be adjusted in multiple ways for each individual in order to provide maximum symptom relief, with minimal side effects (Amon and Alesch, 2017, Evans et al., 2002). The electrical signal that is delivered to the target area of the brain is made up of the stimulation rate, pulse width, and stimulation amplitude. The stimulation rate is the number of electrical pulses delivered per second and the length of each of those pulses is the pulse width. The stimulation amplitude is also commonly known as the voltage and represents the strength of the electrical signal being administered. The stimulation amplitude and stimulation rate are what is most commonly adjusted in order to achieve the best therapeutic result possible for the patient (Vitek, 2008). Each participant with DBS presented in this thesis had their own therapeutic settings which are reported in the relevant chapters.

2.6.3 Lesion deficit

A secondary novel approach to investigate the role of specific neuroanatomy in dyspnoea perception is to assess breathlessness before and after a surgical resection of brain tissue. Working with patients who have a low grade glioma (a type of non-malignant brain tumour) involving their insular cortex (an area implicated in breathlessness through brain imaging (Moro et al., 2002)) has the potential to provide us with further insight into whether this region is imperative to being able to experience dyspnoea. The function of the insular

cortex and the effect of its removal on other brain functions have been studied, however, the implications of damage to the insular cortex for breathlessness perception, are yet to be established.

2.6.4 Local field recording

Local field potential recording involves using the DBS device to record the neural activity from the site of the electrodes implanted into the brain tissue. This is made possible by the externalisation of both the wires connecting the electrodes to the IPG device, and the IPG device itself. This is done for clinical purposes but can be taken advantage of in the research setting. It is the common consensus that the frequency and amplitude that a neuron oscillates at, changes based on the input being received. The data collected from this method makes it possible to see the power spectral density (PSD) of the neural signal at different frequencies. Using this approach, it is the aim within this thesis to establish whether evoking air hunger will also cause a change in frequency and/or power in comparison to two control conditions: (i) increased CO_2 with free breathing, and (ii) fixed CO_2 and free breathing.

2.7 Conclusion

This thesis makes novel use of a neurological population to assess the mechanisms behind dyspnoea. Safe and reliable methods of experimentally inducing air hunger have been utilized in chapters 3 with patients with DBS and without respiratory disease, and chapter 7 in two case reports, one involving an individual with a low-grade insular glioma, and another with externalised electrode wires. As well as using this approach of artificially inducing air hunger, this thesis also makes novel use of a population whom have DBS and a

pre-existing respiratory condition. A variety of subjective ratings have been collected across these studies including simple measures such as the VAS, and measures that give us further insight into the physical and emotional domains of breathlessness such as the D12. The opportunity was also taken to work with individuals with Parkinson's disease to try to quantify the amount and the intensity of breathlessness they experience in their daily lives in a community setting. This is the first example of using the D12 questionnaire for neurological patients in a community setting.

3 The role of the thalamus in breathlessness perception

Dyspnoea is one of the most distressing symptoms that terminally ill patients experience, particularly in the palliative stages. Patients in Intensive Care Units were found to be as least as likely to report dyspnoea as they did pain, and in some instances, dyspnoea is reported by patients to surpass pain in unpleasantness and intensity (O'Driscoll et al., 1999). Dyspnoea, defined as the "subjective experience of breathing discomfort" (Parshall et al., 2012) is a common symptom of multiple diseases including cardiopulmonary and neuromuscular disease and lung cancers, and can have a severe impact on a person's quality of life. It promotes sedentary behaviour due to the fear of worsening the sensation through movement, which in turn reduces the person's fitness levels further enforcing their belief that exercise is a risk to their health, and is to be avoided (Spathis et al., 2017). This can contribute to the subsequent development of health issues such as muscle wastage and obesity which can reduce the quality of life further (Spathis et al., 2017). Pharmacological and non-medication-based treatments are both available but have been limited in their effectiveness, with the sensation often persisting once all options have been exhausted (Booth et al., 2009).

A comprehensive understanding of the central neurophysiology of air hunger will benefit ongoing research into treatment options as a more complete

knowledge would leave us better equipped to create targeted therapeutic treatment options.

There have been several recent advances within the field of dyspnoea research, of which air hunger is a particularly unpleasant form (Banzett et al., 2008). Distinct sensations of breathlessness have been characterized (Banzett et al., 2008) and it is popular consensus that it is different peripheral mechanisms that give rise to these components (O'Donnell et al., 2007). Reliable, safe, and effective methods have also been produced that can isolate specific sensations of breathlessness in an experimental setting (Moosavi et al., 2004). Furthermore, patients with COPD have confirmed that experimentally induced hypercapnic air hunger feels the same as pathological breathlessness. Air hunger has also been identified as the most unpleasant to experience by patients (O'Donnell et al., 2013). These developments in the field place us in a better position to advance our understanding of the cerebral mechanisms that give rise to dyspnoea. Thus far, study of the cerebral mechanisms of breathlessness has relied primarily on brain imaging studies in healthy individuals, in whom dyspnoea has been induced experimentally. The first neuroimaging study focused on air hunger used Positron Emission Tomography (PET) (Banzett et al., 2000) and found evidence for the involvement of the insular cortex in air hunger perception. fMRI studies have corroborated this, and have found other areas activated during air hunger such as anterior cingulate, orbital frontal cortex, thalamus, amygdala and the basal ganglia (Evans et al., 2002, Herigstad et al., 2011, von Leupoldt et al., 2009).

Recent medical technology advances have also seen DBS become an established therapy for multiple neurological conditions including Parkinson's disease (PD) and chronic pain. This therapy involves surgically inserting electrodes into target nuclei and providing that area with high frequency electrical stimulation. Common therapeutic sites within the brain are the motor thalamus, the Globus Palladium, and the sub-thalamic nucleus (STN). The therapy is primarily designed to combat motor symptoms such as tremor, rigidity and freezing of gait and has been shown to be very successful in helping patients control their disordered movements and regain some confidence and independence in their daily life (Lagrange et al., 2002). Overall, this surgical intervention, whilst only a few decades old, has shown to greatly improve patients' quality of life across the biopsychosocial domains. Research has also shown that DBS is a potential viable treatment for non-motor outcomes as well. It is an emerging therapy for the management of intractable chronic pain Boccard et al., (2012).

The study within this chapter takes advantage of the new and reliable techniques to induce the separate components of breathlessness, and also makes novel use of neurological patients who have no respiratory disease. Air hunger is the focus of this study as it appears to be the most unpleasant to experience by respiratory patients Banzett et al., (2008).

This study was first conceived when a patient receiving bilateral DBS of the motor thalamus for movement disorder complained of intractable breathlessness when stimulation was turned ON. This led to the hypothesis that DBS of the motor thalamus would increase sensitivity to experimentally induced air hunger. However, unpublished pilot data within this lab is

contradictory of this, with the data showing that 4 out of 5 participants experienced a decrease in experimentally induced breathlessness when motor thalamic stimulation is turned ON. The present study, therefore, serves as the first definitive and appropriately powered study to investigate the effect of motor thalamic stimulation on breathlessness perception.

Expanding our understanding on the relationship between breathlessness and DBS is vital. Motor thalamic DBS improves quality of life in terms of motor dysfunction but may lead patients to ignore breathlessness.

The aim of this study was to explore whether DBS of the motor thalamus reduces the perception of experimentally induced dyspnoea.

3.1 Methods

3.1.1 Participants

Sixteen participants were recruited and studied over a 5-year period from the Clinical Neurosciences unit based at the John Radcliffe Hospital in Oxford. All had bilateral electrodes implanted into the motor thalamus to treat tremor associated with movement disorders. All participants provided written informed consent with the knowledge that they were participating in a study investigating breathlessness. The exclusion criteria consisted of patients who had documented cognitive impairment or confusion which would likely impair their ability to understand the protocol and questions being asked. Patients were also not recruited if they had a documented need for a translator. No participant had any history of respiratory disease. Ethics approval was

provided by South Central Oxford Research ethics committee (REC: 11/SC/0229).

3.1.2 Sample size

A study in healthy volunteers estimated the slope of the visual analogue scale plotted against rising $PETCO_2$ and determined the effect size to be 6.7±2.4 mmVAS per mmHg $PETCO_2$ (Banzett et al., 1996). Using this information it was determined that to be able to reject the null hypothesis for mean difference in VAS score between thalamic stimulation ON and OFF with a power of 0.8 and a Type 1 error probability of 0.05 it would be necessary to study 16 patients. PS Power and Sample Calculations software V3.0 January 2009 was used for this calculation.

3.1.3 Protocol

Recruitment started in September 2016 and patients who were eligible were first approached by a member of the clinical neurosciences team. If interested in participating, patients were then contacted by a member of the research team to book in a time for testing to take place. All patients attended the laboratory within the Clinical Neurosciences department in the John Radcliffe Hospital. Participants visited the laboratory on one occasion for up to two hours.

Ten-minute maximum incremental air hunger tests (Figure 3-1) and 5-minute steady state air hunger tests (Figure 3-2) were performed sequentially. Each test was performed with DBS ON and OFF in random order (Figure 3-3). Test levels of hypercapnia for steady state tests were the same for ON and OFF (mean±sd end-tidal PCO_2 42±3mmHg). Patients rated air hunger on a 100mm visual analogue scale (VAS) every 15s.

After each of the 5 trials, participants were invited to give comments and were asked to choose respiratory descriptors from a pre-set list. The list of respiratory descriptors included those commonly used to describe air hunger and others to describe sense of breathing work and effort. Participants were asked to rank the items they selected as first second and third, based on how well the items fit the overall sensation they had experienced. This is in line with the debriefing method described by (Lansing et al., 2009). The rationale behind completing this questionnaire is that it opens up a dialogue about the different sensations of air hunger between the participant and the experimenter. It is a useful reference for the researcher when asking participants to only rate sensations of air hunger in the subsequent breathing trials.

Participants completed a D12 questionnaire after each steady state. The instructions to the patient were to rate their dyspnoea during the experimental trial that had just taken place. The 12 items were presented in a randomized order on each questionnaire.

3.1.4 Statistical analysis

Ramp air hunger test

A 60 second boxcar average was performed on the end-tidal PCO_2 data. This is to overcome the fact that due to the CO_2 concentration needing to rise by a certain amount before the signal is created, the VAS ratings given may not correspond to the PCO_2 measured at that moment in time. Experimental work (Banzett et al., 1996) has determined that a boxcar average of 60 seconds was sufficient in order to realign the delayed air hunger response to the PCO_2 stimulus it represents. The VAS ratings were then plotted against the corrected end tidal PCO_2 data. Two individual plots were created for each participant (ON and OFF stimulation) and the air hunger threshold was determined by using a liner regression. The threshold PCO_2 for air hunger onset and the slope of air hunger/PCO_2 relationship were compared ON and OFF. R^2 values were computed for each plot and only participants with a R^2 value above 0.7 were included in the statistical analysis.

Steady state air hunger tests

All participants completed at least 4 minutes of steady state air hunger. Air hunger ratings, airway pressure, tidal volume, and breath-by-breath end-tidal PCO_2 in the last minute of the four-minute period were averaged for each condition. The group mean for each of these variables within the ON and OFF conditions were compared using a paired t-test.

D12 questionnaire

The D12 questionnaire was completed by participants after each steady state condition took place. The items on the D12 were randomized for each condition

and for each participant. The total, physical and emotional scores for the D12 were expressed as a % of the maximum possible scores. A paired t-test was used to compare the D12 total, physical, and emotional scores for ON and OFF states. A Bonferroni correction was applied to the D12 as multiple comparisons were being performed on the same dependent variable.

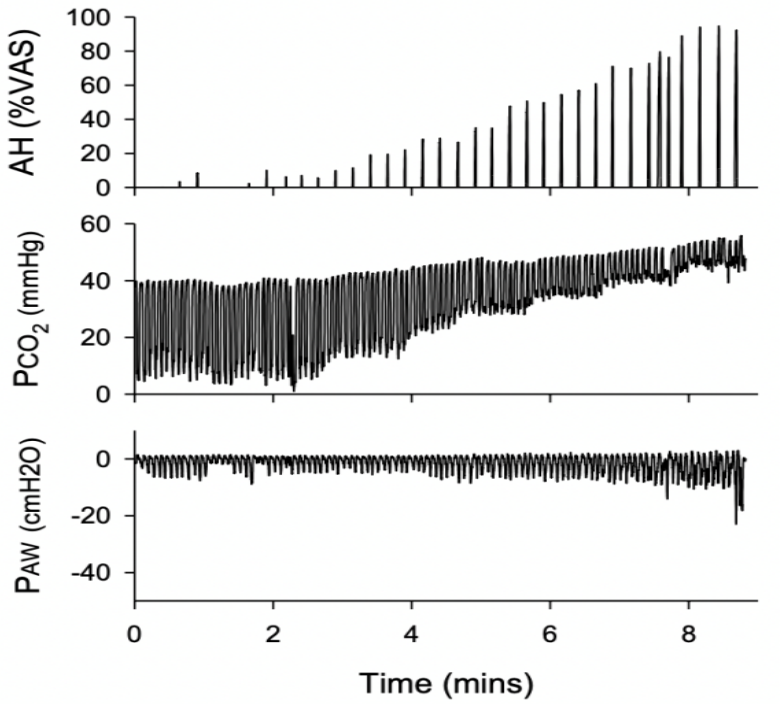


Figure 3-1 Standard incremental air hunger test in one participant (P023)

Typical raw data set for the air hunger test including VAS ratings of air hunger (AH) provided at 15 second intervals cued by an LED (top panel), continuous PCO2 (second panel), and airway pressure (PAW; third panel). Tidal volume was recorded but is not shown here as upon analysis there was a drift in the data attributed to our collection device not resetting itself at the end of each exhalation. Inspired co2 was increased by 1.3% every minute for a maximum of 10 minutes. The trial was terminated early if participants either rated AH as 100/100 in the VAS or removed their mouthpiece due to air hunger. Ventilation was constrained at the resting baseline level by breathing in time with a metronome and from a bag with flow of fresh gas fixed at their resting ventilation level.

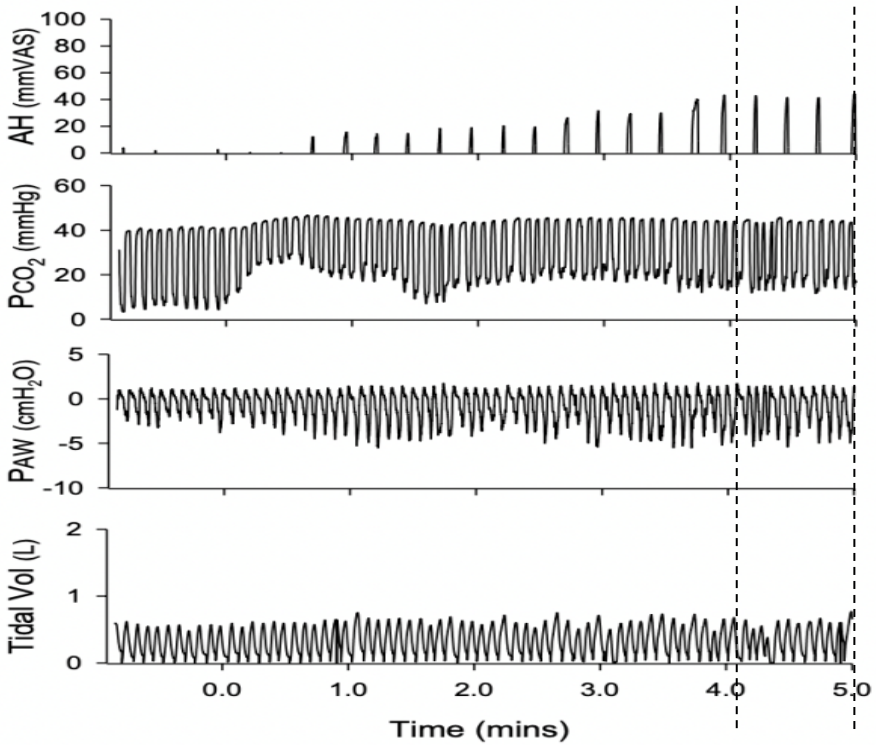


Figure 3-2 Steady state air hunger in one individual (P023)

VAS ratings of air hunger (AH) provided at 15 second intervals in response to a LED cue (top panel), continuous PCO_2 (second panel), airway pressure (PAW; third panel) and tidal volume (VT; bottom panel) in one individual during the steady state air hunger condition. Ventilation was constrained at the resting baseline level by breathing in time with a metronome and from a bag with flow of fresh gas fixed at their resting ventilation level. CO_2 level was chosen to match what had elicited 50% VAS ratings in incremental ramp trials. Tidal volume (VT), continuous airway pressure (PAW) measured at the mouth. Vertical dashed line indicates the 60 seconds of steady state data used in analysis.

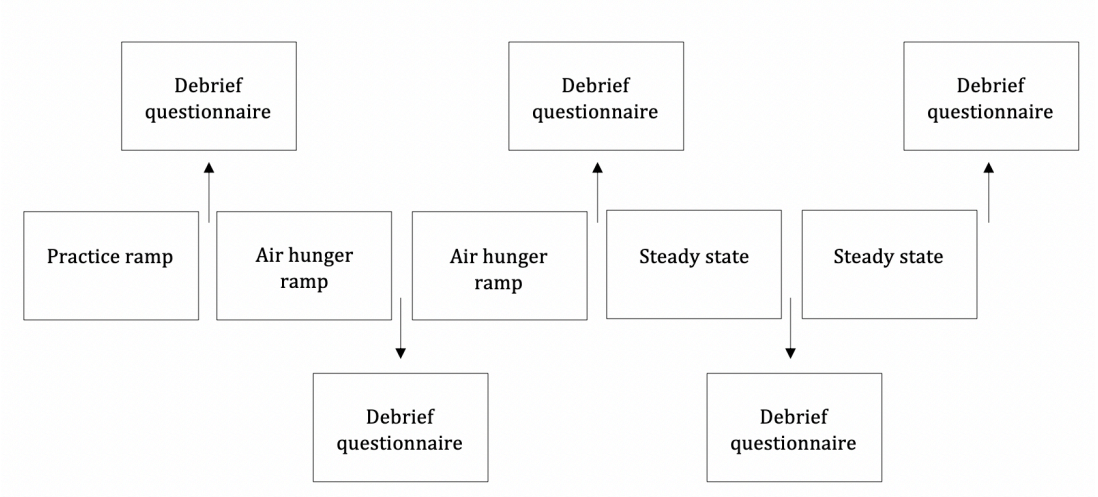


Figure 3-3 Schematic of protocol for testing session

Example of protocol used for study looking at the effect of DBS of the motor thalamus on breathlessness perception. Each air hunger test was repeated twice; once with stimulation ON and once with it OFF. The order of this was randomized for each patient. The ramp was always conducted first as the amount of CO2 administered in the steady state is dictated by what level elicited a 50% response on the VAS during the incremental test.

3.2 Results

Participants

A total of 16 people (15 male) were recruited and participated in this study (mean±SD age of 67±10years; Table 3-1). Sixteen participants completed the entire protocol and are therefore, included in the subsequent analysis. One participant did not complete the complete protocol due to faulty equipment.

Table 3-1 Demographical data for participants (n=16)

All participants were right-handed.

participants	age	gender	race	Height (cm)	Weight (lbs)	Frequency of right electrode	Frequency of left electrode
2	73	Male	WB	183	158	3.1	3.1
3	69	Male	WB	183	158	2.5	2.5
6	73	Male	WB	170	207	2.1	2.1
7	69	Male	WB	164	171	2.6	2.6
13	40	Male	WB	169	165	1.5	1.4
15	63	Male	WB	182	189	3.6	3.6
18	53	Female	WB	169	168	2.6	2
20	76	Male	WB	175	200	3.15	3.15
21	72	Male	WB	172	165	1.9	3.5
22	61	Male	Irish	172	189	1	3.2
23	75	Male	WB	180	169	2.3	2.3
26	75	Male	WB	187	174	1.9	3.8
25	72	Male	WB	180	160	1.9	3.6
29	70	Male	WB	172	213	4	4.4
31	70	Male	WB	176	206	1	2.25

Incremental air hunger test

The data from the incremental air hunger test was only included if the R^2 value for ON and OFF condition exceeded 0.7. This means that the data from 6 participants were included in the subsequent analysis. To assess the difference in PCO_2 for air hunger onset and the slope of air hunger/PCO_2 relationship between ON and OFF stimulation paired t-tests was conducted and the results were insignificant. A Bonferroni correction was used (P=0.016). A paired t-test was also performed to establish that there was no significant difference between R^2 values for ON versus OFF stimulation (P>0.016).

Individual data

Three out of six participants had a decreased slope with stimulation ON in comparison to with stimulation turned OFF (Table 3-2).

Four out of six participants experienced a rightward shift in air hunger threshold with stimulation was ON compared to OFF (Figure 3-4). The two remaining participants experienced no change in air hunger threshold between the two stimulation conditions.

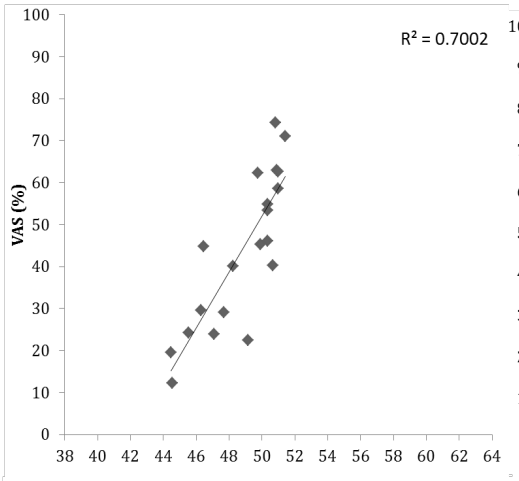
Participant 23 experienced the most dramatic change as a result of thalamic stimulation during the incremental air hunger test. Air hunger sensitivity to increasing CO_2 remains unchanged whether stimulation was ON or OFF (slope = 6.11 and 6.37mmVAS/mmHg respectively; Figure 3-4). However, onset of air hunger is at a much higher level of hypercapnia when stimulation is ON (threshold end-tidal PCO_2 = 49 versus 41mmHg respectively (Table 3-2).

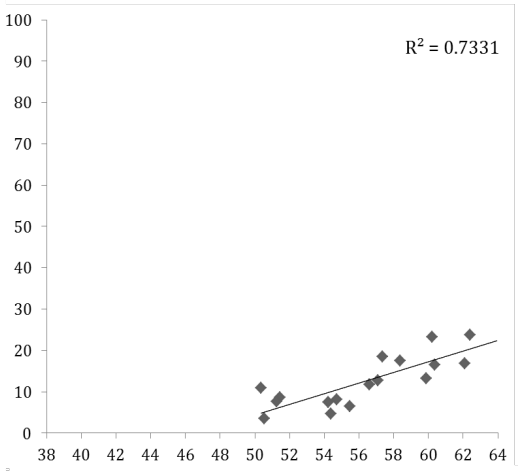
Table 3-2 Participant data for incremental air hunger

Average±SD threshold for air hunger onset is higher with thalamic stimulation than without. Average±SD slope for DBS ON is steeper than the DBS OFF slope.

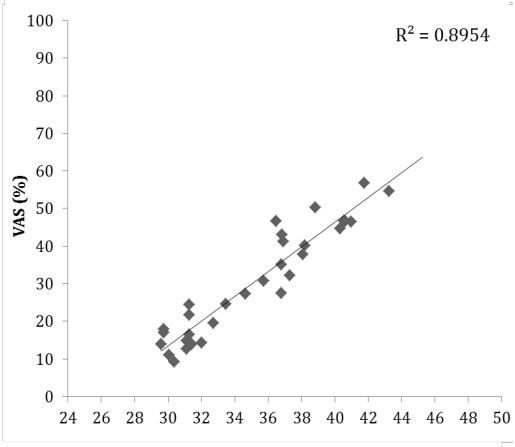
	Slope (b)		Threshold	
Patient	ON	OFF	ON	OFF
P2	1.29	6.66	53.00	44.00
P6	6.89	3.29	32.00	31.00
p21	12.89	12.78	43.00	43.00
p22	3.30	5.75	34.00	32.00
p23	6.11	6.37	49.00	41.00
p30	14.24	9.72	41.00	41.00
Mean	7.14	5.78	42.00	38.67
SD	4.75	2.98	8.20	5.68

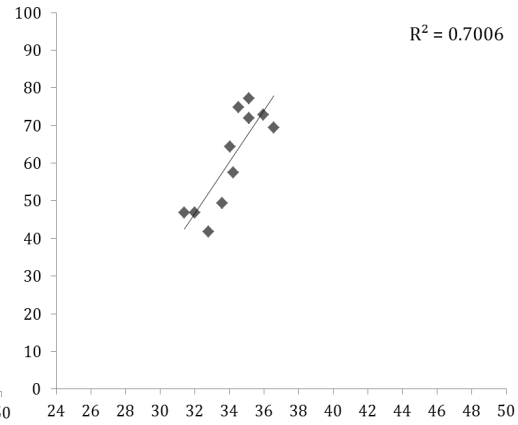
P02


R² = 0.7002
VAS (%)

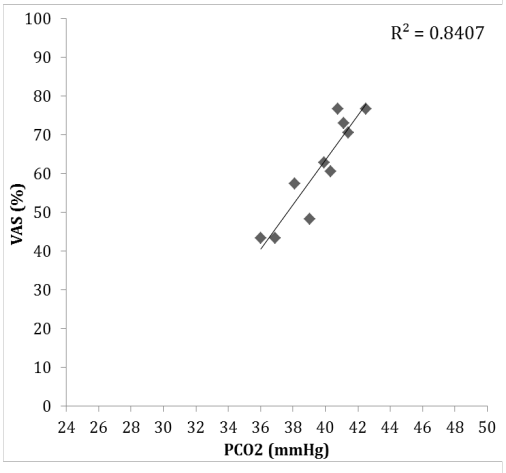

R² = 0.7331

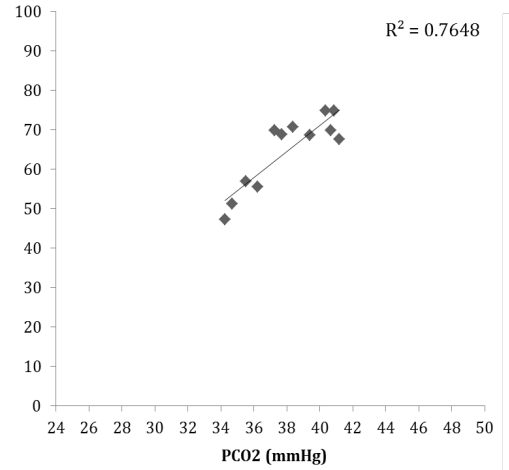
P06


R² = 0.8954
VAS (%)


R² = 0.7006

P22


R² = 0.8407
VAS (%)
PCO2 (mmHg)


R² = 0.7648
PCO2 (mmHg)

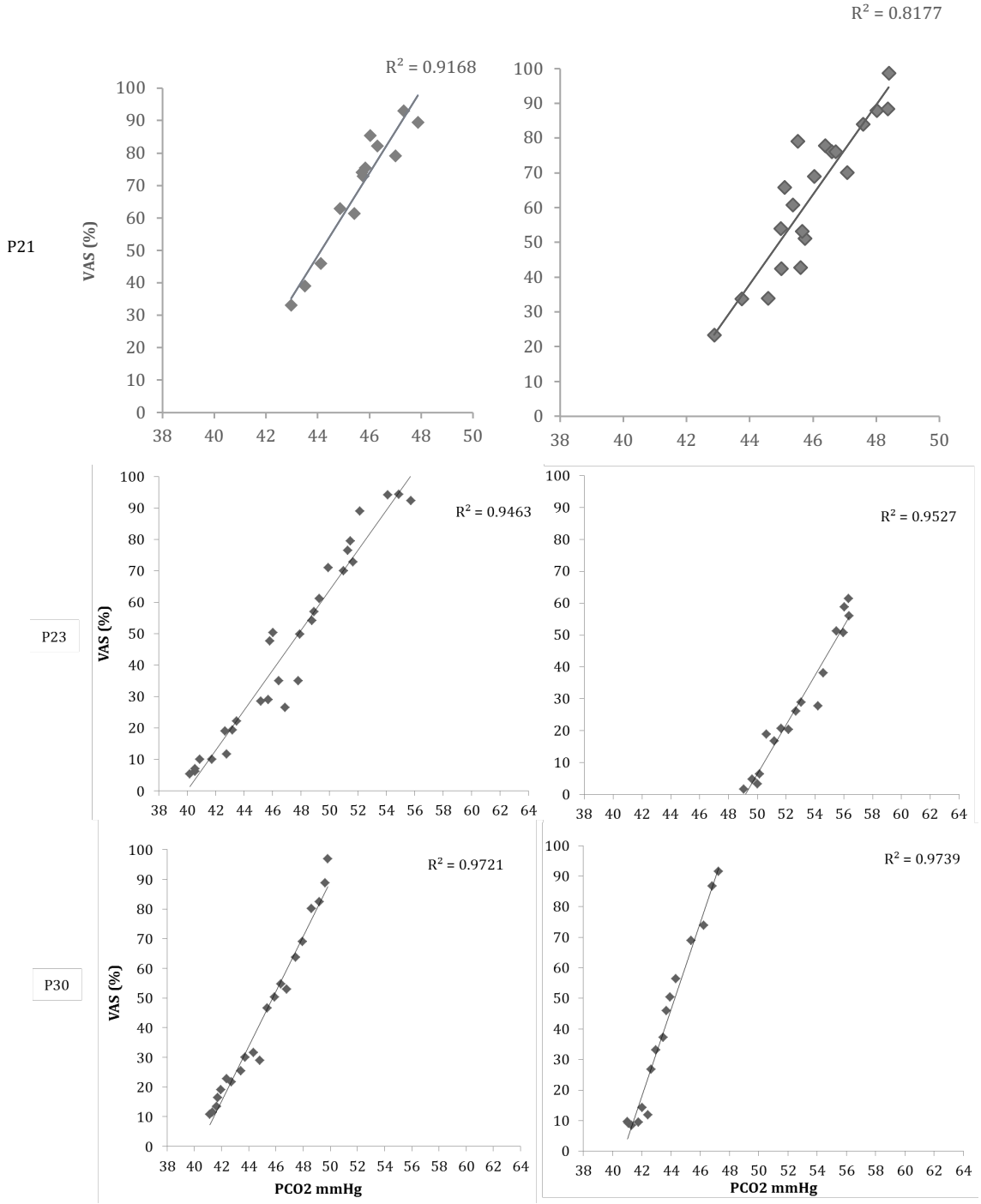


Figure 3-4 Stimulus response slopes for 6 participants

Relationship between VAS ratings of air hunger and increasing end-tidal CO_2 in 6 patients with electrodes located in the motor-thalamus.

Steady state air hunger test

DBS of the motor thalamus was shown to have an effect on breathlessness perception in 15 out of 16 patients during the steady state protocol. Sixty seconds of the physiological recording was used, and this was the fourth minute after CO_2 had been introduced. This was to ensure that the participant was experiencing a consistent level of increased CO_2 and that their VAS ratings were reliable.

Stimulation of the motor thalamus produced a median reduction in air hunger of 12mmVAS (range +19 to -50mmVAS) for the same level of hypercapnic stimulation as given when stimulation was turned OFF. This difference exceeds the minimally clinically important difference (MCID) of 10mm VAS. Overall mean steady state air hunger was significantly different (P = 0.008; paired t-test) with 44±22 mmVAS for the ON state and 65±22mmVAS for the OFF state.

D12 Questionnaire data

D12 questionnaire scores were lower when participants completed the steady state air hunger test with stimulation ON, compared to when turned OFF. The average±SD total score (%) for breathlessness with stimulation ON and OFF was 33±30 and 45±29 respectively. This difference surpasses the minimally clinically relevant difference of 9.7% as established by Johnson et al., (2013). With stimulation ON, 6 participants reported their breathlessness to be at a mild level (>33%), 3 reported it to be at a moderate level (33%> ≤66%), and 1 at a severe level (>66%). When stimulation was turned OFF, 4 participants reported their breathlessness to be mild, 3 moderate, and 3 severe. A paired t-test was conducted with a 3-way Bonferroni correction at a 0.02 significance

level. The difference was found to be statistically significant (P =0.018) (Figure 3-5).

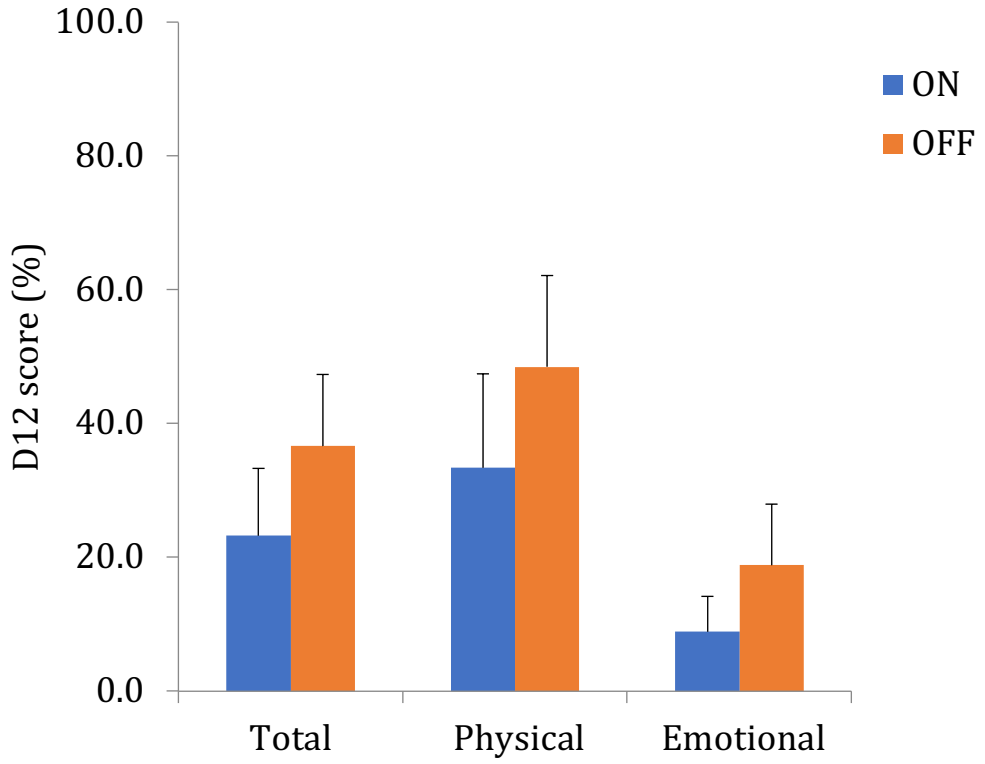


Figure 3-5 Dyspnoea 12 questionnaire averaged score ±SEM for ON versus OFF stimulation

Averaged ±SEM total, physical, and emotional score for 9 participants with DBS of the motor thalamus who completed steady state air hunger trials ON and OFF therapeutic stimulation. Not all participants completed the D12 due to time constraints.

In-house debrief data

Ten participants chose the descriptor "felt an urge to breath more" when completing the in house debrief questionnaire after incremental air hunger tests (Figure 3-6). Eight out of ten participants also chose the air hunger descriptors "felt short of breath" and "felt an urge to breathe more". Participants less frequently selected descriptors relating to work/effort, and those unrelated to breathlessness.

When participants were given opportunity to describe the sensation they experienced on the top of the scale in their own words they used language similar to that of the air hunger descriptors Table 3-3.

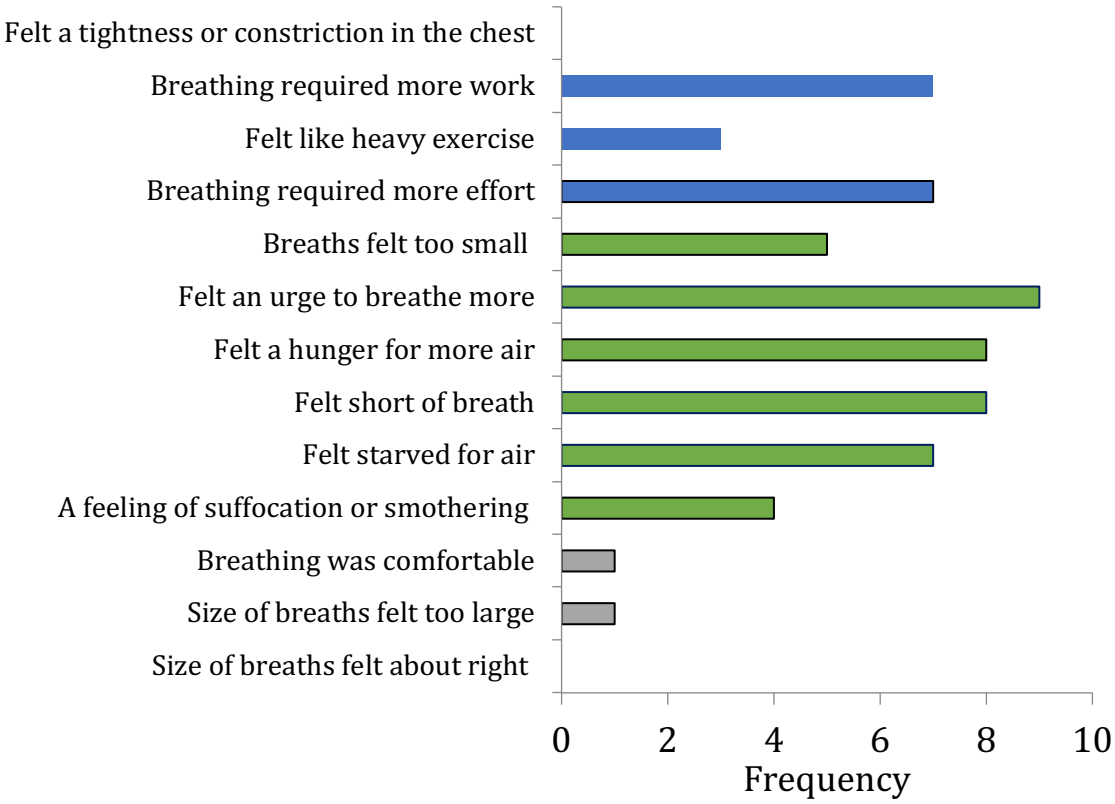


Figure 3-6 Averaged frequency descriptors after incremental air hunger tests

Participants consistently chose statements that describe air hunger as oppose to other facets of breathlessness. This provides further evidence that the experimental protocol used was creating the sensation of air hunger.

Table 3-3 Verbatim comments after experiencing hypercapnic induced air hunger in ramp form for the first time

All comments were volunteered by participants during the course of the debrief questionnaires and recorded verbatim by the experimenter. Participants were not coached in their language style or word choice.

Participant	Comment
P013	[Felt a] shortness of breath.
P015	No oxygen there.
P020	Can't get enough air. Shortness of breath. A starvation.
P021	[It] felt like I wasn't taking in any air. Felt like the tubing was blocked and there was nothing useful.
P023	[Felt like] being starved
P032	[It] feels like the tubing is blocked. Suddenly there is nothing there to take in.

3.3 Discussion

3.3.1 Key results

The work presented in this chapter is the first demonstration of dyspnoea relief by DBS of specific nuclei within the diencephalon.

During the incremental air hunger test, four out of six participants experienced a rightward shift in air hunger onset when stimulation was turned ON, in comparison to when it was turned OFF. This trend with just 6 participants is suggestive that with more participants included in the analysis, a significant difference in threshold between ON and OFF stimulation would be identified. In one participant, the shift in threshold occurred independently to sensitivity to CO_2 which remained unaltered. This preservation of sensitivity to CO_2 was not replicated in other participants. This may be because this patient had previously participated in a separate study discussed in chapter 7 that used the

same breathing circuit and also involved experimentally induced breathlessness. Therefore, he had practiced giving ratings and breathing in time to the metronome, improving the quality of his data.

Participants also gave lower VAS air hunger ratings when motor thalamic stimulation was turned ON in comparison to when it was turned OFF for the same given level of CO_2. This difference in air hunger rating exceeds the minimally clinically important difference of 10mm VAS (Johnson et al., 2013). This indicates that a patient with intractable breathlessness would detect noticeable relief from their symptoms with stimulation of the motor thalamus, and would therefore, experience a benefit from having DBS therapy.

Complimentary to the VAS ratings participants provided, Dyspnoea 12 questionnaire data collected at the end of each steady state trial also demonstrated that participants felt a significant decrease in breathlessness with stimulation turned ON in comparison to stimulation turned OFF. This statistically significant difference was found despite the number of completed D12 questionnaires available for analysis being less (n=9) than the number of participants needed for this study to be sufficiently powered (n=16).

3.3.2 Importance of these findings

The study presented here provides evidence that DBS of the motor thalamus may provide relief from experimentally induced air hunger by blocking the ascending breathlessness signal through the thalamus on its way to the cortex. Early investigations into the physiological mechanisms behind air hunger focused primarily on the role of the chest wall or mechanoreceptors in breathlessness perception (Campbell et al., 1969, Killian et al., 1984). Later

work established that feelings of air hunger can persist even in instances of chest wall paralysis, indicating that dyspnoea is not generated by mechanoreceptors alone, and is instead a result of several signals from receptors combined. This demand signal is sent to respiratory centres in the brainstem to increase respiration, and a copy of this signal is sent to the forebrain which acknowledges the experience of dyspnoea (Manning et al., 1992). The stretch receptors in the lungs will send a signal to the brainstem and forebrain reporting that the change in respiratory need has been met. Further evidence has been produced through the use of functional brain imaging which suggests that dyspnoea is sustained when there is a mismatch between the reporting need to breathe, and the prevailing feedback on the current ventilation levels (Moosavi et al., 2004). It is proposed here therefore, that the motor thalamus has a previously undefined role which is sensory in nature, and the stimulation of this tissue blocks the ascending afferent signals that report the need to breathe.

This study makes novel use of a neurological population in order to assess the role of the motor thalamus in breathlessness perception. The study of the cerebral mechanisms of breathlessness thus far, has relied primarily on healthy volunteer brain imaging studies in which dyspnoea have been induced experimentally. These brain imaging studies have been able to identify which areas are active during air hunger such as the insular cortex, anterior cingulate, orbital frontal cortex, thalamus and amygdala (O'Donnell et al., 2007, Banzett et al., 2000, Evans et al., 2002) . However, the way in which these different areas connect to form a network for dyspnoea perception is yet to be discovered. The

approach as aforementioned in this study, allows us to gain insight into such mechanisms through the study of specific nuclei, and the role they play in breathlessness perception. Functional brain imaging studies have their merit, however, these alone cannot reveal the neurophysiological pathways and may miss putative targets for dyspnoea relief. This study uses a different approach which is complimentary to brain imaging, and which makes it possible to marry structure with function.

In light of this finding, it is important to consider whether DBS of the motor thalamus may lead patients to ignore breathlessness. If this is the case, this patient population may be at an increased risk of respiratory issues such as pneumonia or aspiration due to their dampened perception of breathlessness. This study therefore, has clinical importance as clinicians need to be aware of these potential complications so they can monitor for any change in dyspnoea sensitivity following the onset of DBS therapy. The monitoring of pain perception is performed routinely at the beside in patients who have a neurosurgical intervention or suffer neurological trauma. A simple protocol such as a timed breath hold could also take place during the same assessment to check for a dampened breathlessness response.

3.3.3 Critiques and future directions

Participants all had electrodes positioned within the motor thalamus however, the specific nuclei targeted varied marginally between individuals (15 ventral intermediate thalamus (VIM); 1 ventralis oralis posterior (VOP)). Unpublished pilot data within this lab shows that stimulation of the VOP at varying percentages of full therapeutic power (25%, 50%, and 75%) has a dose effect of

air hunger, whereas the same protocol with stimulation of the VIM does not. A future project therefore, could be a definitive study involving equal numbers of patients with these two regions. The focus of this work could be examining whether lower amplitude stimulation causes air hunger response, or if the amplitude which best controls the patient's motor symptoms is the amplitude necessary to alter air hunger perception.

This being an appropriately powered study instils confidence that the difference seen between air hunger perceptions with motor thalamic stimulation turned on in comparison to off is a real and clinically relevant phenomena. In chapter 5 a similar study is outlined using patients with VIM DBS and co-existing respiratory disease, meaning that dyspnoea does not need to be induced in this population. The result of this work is preliminary, yet complimentary to the results outlined here. This provides additional support to the hypothesis that the motor thalamus plays a role in breathlessness perception in an experimental setting and in instances of idiopathic lung disease.

When participants selected statements that described the respiratory sensation they experienced during the first incremental air hunger test, 9 participants selected the descriptor 'felt an urge to breathe more', and participants most frequently chose items related to air hunger rather than descriptors relating to work and effort. This therefore, provides reassurance that the method used here to experimentally induce air hunger is reliable and consistent.

Previous work has shown that participants need to have at least 3 practice sessions before they begin to produce reliable air hunger ratings. Within this

study no practice session was possible due to time constraints. The lack of familiarity with the sensation of air hunger and the equipment itself could therefore contribute to some participants struggling to provide consistent air hunger ratings. One participant had experience with the breathing circuit and VAS rating system (P023) and demonstrated a clear rightward shift in air hunger when stimulation was turned ON, without any compromise on the R^2 value or slope.

3.3.4 Conclusion

This study has shown that DBS of the motor thalamic region is associated with a significant relief of experimentally-induced hypercapnic air hunger in patients with disordered movement. This relief has been quantified using two different measures; (i) a visual analogue scale, and (ii) a dyspnoea focused questionnaire. The possible mechanism of relief by stimulation of the motor thalamus is not yet defined. We propose that DBS causes a virtual lesion that blocks the ascending air hunger signal in the thalamus. The thalamus is recognised as a relay station for ascending sensory and descending motor information between the brainstem and the cortex, and so this conclusion would seem plausible. The outcome of this study has clinical relevance as it raises the question of whether DBS of the motor thalamus, whilst improving quality of life in the motor domain, may be having an unforeseen impact on breathlessness perception. This may lead individual's with DBS to ignore breathlessness, resulting in additional health complications. This warrants further investigation.

4 The effect of Parkinson's disease and sub thalamic stimulation on dyspnoea perception

Deep brain stimulation (DBS) of the STN is an accepted therapy for Parkinson's Disease motor symptoms. There is evidence to suggest that stimulation of the STN can contribute to dysautonomia, such as excessive sweating, bowl and bladder control, and changes in pain perception. Work focused on the effect of STN stimulation on breathlessness perception, however, has thus far been limited. Chalif et al., (2014) concluded that stimulation of the STN can contribute to the onset of dyspnoea. However, the study by Chalif et al (2014) was initiated because patients with PD anecdotally mentioned experiencing dyspnoea after surgery. Therefore, the focus was on a comparison between pre-operative and post-operative breathlessness. In the Chalif et al (2014) paper, comparison of ON versus OFF states was not the primary aim. Two studies are presented in the current chapter which follow up on the initial studies by Chalif et al (2014).

Section 4.1 reports the effect of DBS of the STN on breathlessness in patients with Parkinson's disease who have had electrodes implanted in the STN for tremor relief. This was to independently verify that stimulation of the STN causes the onset of breathlessness (Chalif et al., 2014). This was of particular interest because the STN is a region that is relatively close to the VIM and yet DBS of the STN may have an opposite effect on dyspnoea to that of VIM DBS (previous chapter). In order to contextualise the effect of STN stimulation on breathlessness perception it is also important to examine whether dyspnoea is

a non-motor symptom of Parkinson's disease. Dyspnoea as a symptom of PD is poorly understood and under-recorded. This is surprising considering that the original description of Parkinson's disease in 1817 by James Parkinson specifically mentioned breathing problems (see Baille et al., 2016). Thus the second study reported in this chapter (section 4.2) reports the results of a postal survey of dyspnoea in patients with Parkinson's disease in their daily lives.

Both studies reported in this chapter utilised the dyspnoea-12 questionnaire (D12), a multi-dimensional tool incorporating physical and emotional aspects of dyspnoea and providing one global score of severity. An advantage of this questionnaire over other measures of dyspnoea is that it was synthesized from the language used by breathless patients themselves and irrespective of the underlying pathologies. It is comprised of a core set of 12 descriptors which any patient, suffering from any quality of dyspnoea, would recognise as part of their breathing experience (Yorke et al., 2010). The D12 was used in the STN DBS study to capture the individual's prevailing breathlessness with DBS of the STN turned ON and OFF. For the postal survey study however, the questionnaire was used to capture the variation of dyspnoea over different times of the day (morning, afternoon and evening), and over 3 days. The D12 has been shown to be flexible enough to capture breathlessness in an experimental setting, as well in an environment where breathlessness is not being induced (Williams et al., 2017).

4.1 STUDY 1: Does DBS of the STN generate dyspnoea in patients with Parkinson's disease?

The suggestion in Chalif et al., (2014) that STN DBS generates breathlessness was supported by anecdotal evidence from individuals undergoing DBS of the STN who complained of new breathlessness when DBS was ON and that changing stimulation parameters either improved or worsened this sensation. This study, therefore, recruited patients who had self-reported feelings of breathlessness in order to try to understand whether their stimulation was modulating these feelings of dyspnoea, and if different stimulation conditions would cause this sensation to change. The specific aim of this study was to assess whether DBS of the STN promotes breathlessness as this would be the opposite to what was found with DBS of the VIM in chapter 3.

4.1.1 Methods

Sample size

The recruitment of this study was constrained by the number of patients with STN DBS who reported post-operative breathlessness and were under the care of the John Radcliffe Hospital neuromodulation team. Recruitment ran from October 2017 to June 2019 in which time 9 patients were identified by the neuromodulation team within the clinical neuroscience division. With patient consent, contact details were shared between the clinical team and the research team. A member of the research team then approached the patient about participating.

Participants

Five of the 9 potential participants were studied. Two of the remaining 4 declined to participate, one was excluded because his medical status deteriorated and one remained undecided about enrolling in the study. Inclusion criteria consisted of having DBS electrodes implanted in the STN to control movement symptoms of Parkinson's disease, as well as having reported to be experiencing breathlessness post-operatively once DBS was switched on. Patients had to be a minimum of 18 years old with no upper age limit. Individuals could not participate if they had a documented history of dementia or confusion as this would likely have impaired their ability to reliably complete the D12 questionnaire.

Full ethical approval was obtained from the NHS Health Research Authority (REC: 11/SC/0229, Study Title: Non-invasive Cerebral Blood Flow Monitoring in Patients with Deep Brain and Occipital Nerve Stimulators; PI: Alex Green) with the University of Oxford acting as research sponsor.

4.1.2 Protocol

Patients were asked to complete a D12 questionnaire when stimulation was turned ON, OFF and with unilateral stimulation of each hemisphere (Figure 4-1). Prior to completing each questionnaire patients sat quietly at rest for 10 minutes. The instructions to participants were to rate their dyspnoea at that moment in time. Changes in stimulation setting were performed in a random order for each patient. Items on each D12 questionnaire were listed in a random order. Chapter 2 provides more information about the questionnaire items

included in the D12 and the validity of using the D12 questionnaire in a research setting.

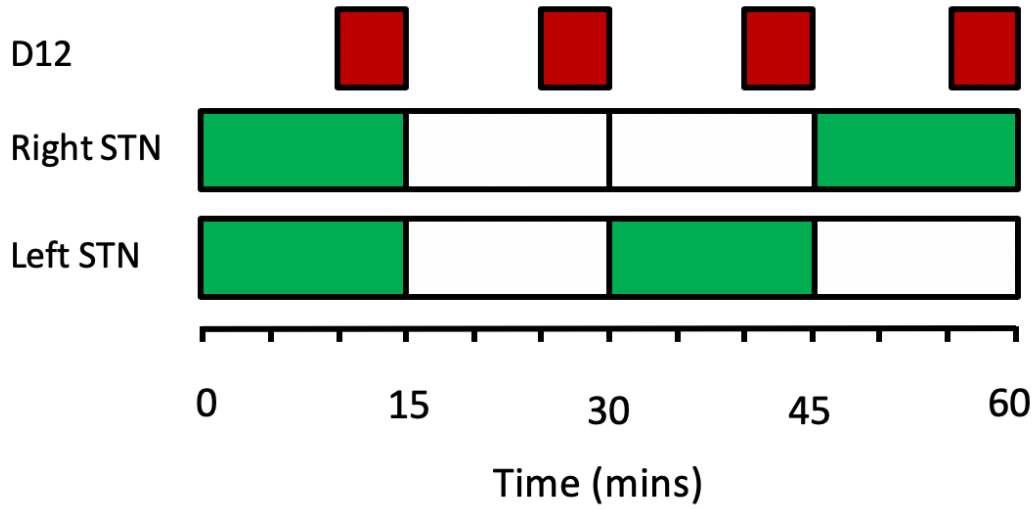


Figure 4-1 Protocol for the effect of DBS STN breathlessness perception

Five participants completed a D12 questionnaire to assess breathlessness with all electrodes ON at their normal therapeutic level, and then 10 minutes after each change to the stimulation setting. The order of the stimulation changes was randomized for each patient. Red represents the period of time the participant spent filling out the D12 questionnaire. Green represents the period of time that the patient had altered DBS settings.

Data processing and Statistical analysis

Raw questionnaire scores for each condition were converted into percentages of the full scale for the total, physical and emotional components of the D12. A repeated measures ANOVA was conducted to compare the difference in D12 score between each stimulation condition (ON and OFF in both hemispheres, and with unilateral stimulation in the left and right hemisphere independently).

Paired t-tests were conducted to compare the difference in D12 score between ON and OFF stimulation with both hemispheres, and ON versus OFF with unilateral stimulation. A paired t-test was also conducted to look at the

difference in D12 score between the left hemisphere and right hemisphere with stimulation ON.

4.1.3 Results

Demographic and clinical details of the participants

Five participants (3 male) with STN stimulation participated (mean age±SD 62±5 years) participated (Table 4-1).

Table 4-1 Demographics for those who completed the study protocol

Age, race, weight, height for all participants. Electrode parameters are also included. All participants had a diagnosis of Parkinson's disease and were under the ongoing care of a neurologist based at the John Radcliffe hospital.

Patient ID	right electrode frequency (Hz)	Left electrode frequency (Hz)	age	Race	Weight (lbs)	Height (cm)	Sex	Handedness
4	3.2	3.3	60	white British	257	179	M	Right
5	1.3	1.8	64	white British	178	173	F	Right
6	1	3.2	70	white British	213	173	M	Right
7	4	4.4	60	white British	224	182	M	Left
8	1.7	0.9	57	white British	106	169	F	Right

The individual scores for the total, emotional and physical domains of the D12 (expressed as % full scale) with stimulation OFF, bilateral stimulation and unilateral stimulation are shown in Table 4-2.

Table 4-2 Individual D12 scores for participants with and without DBS
The raw, mean, SD and SEM scores for total, emotional and physical domains of dyspnoea expressed as a % full scale for DBS off (ALL OFF) all DBS ON (BILATERAL ON), and unilateral DBS (UNILATERAL LEFT ON or UNILATERAL RIGHT ON) in individuals with STN stimulation.

DBS	Participant ID	D12 Total (%fullscale)	D12 Emotional (%fullscale)	D12 Physical (%fullscale)
ALL OFF	4	0	0	0
	5	8.3	0	14.2
	6	63.8	76	47
	7	19.4	24	13
	8	16.6	13	19
	Mean	21.6	22.6	18.6
	SD	24.8	31.5	17.3
	SEM	11.1	14.1	7.8
BILATERAL ON	4	11	0	19
	5	0	0	0
	6	94	95	93
	7	41.6	48	33
	8	13	0	23.8
	Mean	31.9	28.6	33.8
	SD	38.0	42.5	35.2
	SEM	17.0	19.0	15.8
UNILATERAL (LEFT ON)	4	50	47	52
	5	5.6	0	9.5
	6	86.1	86	87
	7	53	0	0
	8	8	0	14.3
	Mean	40.5	26.6	32.6
	SD	33.9	38.9	36.3
	SEM	15.2	17.4	16.2
UNILATERAL (RIGHT ON)	4	36	20	48
	5	5.6	6.7	4.8
	6	86.1	0	0
	7	52.7	62	40
	8	11	0	19
	Mean	38.3	17.7	22.4
	SD	32.8	26.1	21.1
	SEM	14.7	11.7	9.5

The mean D12 total score increased from baseline with unilateral or bilateral stimulation (Figure 4-2; left panel). The biggest change in total D12 score

appears to be from bilateral OFF to Left stimulation ON (Figure 4-2; right panel). This difference in D12 scores between OFF and ON conditions for both bilateral and unilateral stimulation was not found to be statistically significant ($p>0.0125$ with Bonferroni correction).

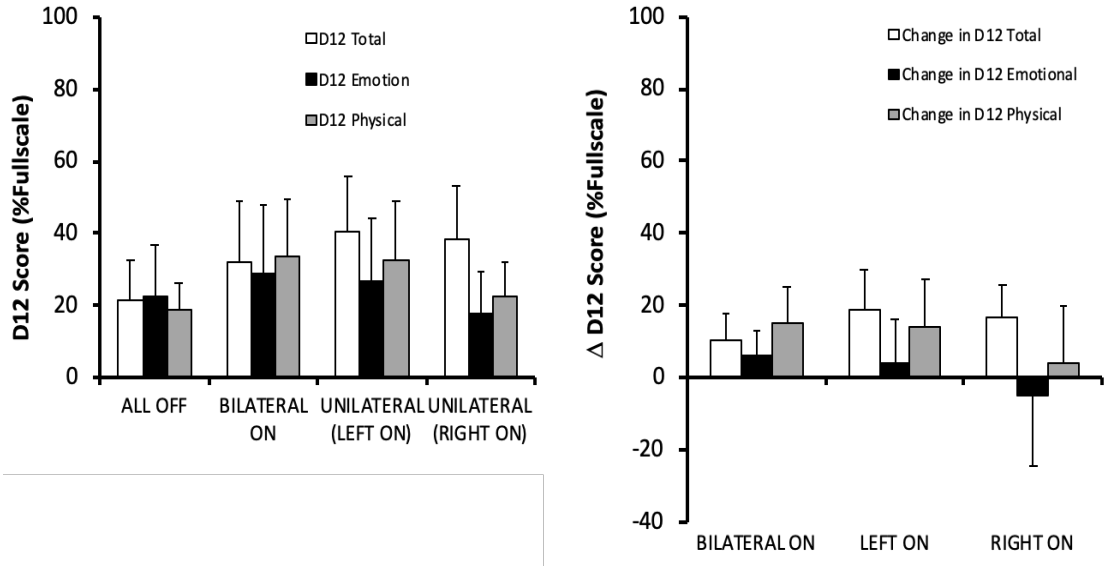


Figure 4-2 Average D12 scores with bilateral, unilateral or no stimulation of the STN

Left panel: Mean +/- SEM D12 total score (open bars), D12 emotion score (black bars) and D12 physical score (grey bars) with stimulation off (ALL OFF), bilateral stimulation (BILATERAL ON) and unilateral stimulation (UNILATERAL LEFT ON and UNILATERAL RIGHT ON) in 5 individuals with stimulation of the STN. Right panel: Same data expressed as the difference between the baseline OFF and bilateral and unilateral stimulation.

4.1.4 Discussion

Key results

The overall trend in this study is an increase in total D12 score with bilateral or unilateral stimulation of the sub thalamic nucleus (STN) compared to when stimulation is turned OFF. Overall, it appears that the biggest change in total D12 score is between OFF stimulation and with stimulation unilaterally in the left hemisphere. The physical component of the D12 score follows the same pattern. The average D12 score for the emotional domain was highest when both electrodes were turned on.

Interestingly, unilateral stimulation of the right hemisphere produces the smallest change in total, emotional, and physical D12 score from OFF stimulation compared to both bilateral and left hemisphere stimulation. With the small number of participants it is not possible to pick up clear trends in unilateral response differences in relation to left and right-handedness (only 1 patient was left-handed)

Wider impact

The average increase in total D12 score for OFF compared to bilateral ON or unilateral stimulation of either hemisphere exceeds the minimally clinically important difference of 9.7% (Johnson et al., 2013). This suggests that this change in D12 total score is sufficient that it would have a noticeable effect on a person's quality of life. This is an important finding in the context that patients are having STN DBS fitted to alleviate chronic symptoms that have diminished their quality of life for potentially a long period of time. It is, therefore,

important to consider this potential contraindication for offering DBS of STN for Parkinson's disease.

Furthermore, as reported in the second study in this chapter (section 4.2), dyspnoea is an under studied non-motor symptom of Parkinson's disease, and one that has been shown to affect multiple people with Parkinson's on a daily basis. As evidence is emerging that respiratory dysfunction is a symptom of Parkinson's disease (Baille et al., 2016) it is worthy of consideration to check for dyspnoea in patients with Parkinson's who are eligible for DBS of the STN.

Critiques and limitations

This study did not reach statistical significance which is unsurprising when considering the small number of participants – it was underpowered for a definitive conclusion. The number of prospective participants is dependent on multiple factors including how many people with STN DBS and Parkinson's disease present to the clinic during the time of recruitment. However, the trend picked up in this study, albeit with only 5 patients is consistently suggesting that DBS of the STN generates breathlessness which is in stark contrast to the finding in the previous chapter which showed that DBS of the VIM consistently produces a reduction in dyspnoea. This raises a strong contention that these regions have different modulatory roles or connect with different regions of the brain that are involved in breathlessness perception.

The study as described here, focused on the difference between D12 questionnaire scores between OFF and ON stimulation at the participants normal therapeutic level for controlling their motor symptoms. This is a valid approach when investigating the impact that STN stimulation has on

breathlessness for that individual. An interesting addition to the protocol would be adjusting the power of the stimulation to different levels which does not presume that the therapeutic level for motor symptoms would be the same for dyspnoea generation. This addition would be sensitive to a dose response which may be present and would show the minimum threshold that still causes the breathlessness.

Future studies, as well as generating more data would benefit from paying attention to hemispheric dominance as there may be a difference in the response in individuals with left or right dominance. Indeed functional brain imaging studies have implicated the right insular cortex in breathlessness perception more than the left (Banzett et al., 2000).

4.2 STUDY 2: The prevalence of breathlessness in individuals with PD in their daily lives

Studies in a hospital setting have shown that 39.2% PD sufferers responded positively to the question: "Have you experienced breathlessness in the past month"? (Baille et al., 2016). Other studies have also demonstrated that individuals with PD have a blunted perception of dyspnoea and a subnormal hypoxic ventilatory response (Onodera et al., 2000). However, these studies do not address breathlessness as a symptom of PD in daily life in the community, and how it affects PD sufferers in both the physical and emotional domain. Gaining a better understanding of the prevalence of dyspnoea in patients with PD may allow symptoms to become better recognised and managed by PD clinical teams improving the sufferer's quality of life. The specific aim of this

study was to assess the prevalence of dyspnoea at rest and after physical activity in individuals with PD within the community.

4.2.1 Method

Participants

Participants were recruited through a national advert place on the website of the Parkinson's UK online research hub. A presentation was made at the local Parkinson's support group to foster interest. The inclusion criteria consisted of a diagnosis of Parkinson's disease (PD) and no indication of dementia or confusion as it could hinder their ability to understand the study and record their questionnaire responses. Participants had to be a minimum of 18 years old with no upper age limit. Full ethical approval was obtained from the research ethics committee at Oxford Brookes University (UREC: 171148). Oxford Brookes University acted as research sponsor.

4.2.2 Protocol

Recruitment began in January 2019. Participants who expressed an interest (N=51) in participating were sent a questionnaire pack. Each questionnaire packet contained a letter inviting them to participant, a participant information sheet, a consent form and a questionnaire booklet containing 18 D12 questionnaires with items listed in different randomized order on each. A D12 questionnaire needed to be completed 6 times each day for 3 alternating days. On each of these days, participants completed a questionnaire immediately after a 10min period of rest and then again immediately after performing mild physical activity (climbing a set of stairs or walking 50 yards if they did not have access to stairs); this was repeated in the morning, afternoon, and evening.

The instructions provided were to rate their dyspnoea at that moment in time and to return the questionnaires and consent form in the prepaid envelope. Any returned packets that were returned blank or not returned at all were interpreted as them having declined to participate.

Data processing and Statistical analysis

All analyses were performed using the D12 total score and the separate D12 physical and emotional scores expressed as % of the full scale. A repeated measures analysis of variance (ANOVA) with 3 within factors: time of the day (3 levels, morning, afternoon, evening), day of participation (3 levels, day 1, 2, and 3) and exertion level (2 levels, at rest, after physical activity) was conducted. A further analysis was performed with the addition of 3 between factors; age, sex, and history of cardio-respiratory disease. Age was defined as 'under 50 years' (n=2) which is considered early onset PD and '50 years or over' (n=19) which is considered either later onset or longer duration of diagnosis of Parkinson's disease.

Percentage change in breathlessness score between at rest and following exertion was calculated for all participants. Two paired t-tests were performed to compare the difference in percentage change between (i) cardiorespiratory and non-cardiorespiratory disease and ii) sex. A Bonferroni correction was applied to these tests making the threshold for significance at a p value <0.025.

4.2.3 Results

Overall prevalence of dyspnoea

A total of 51 individuals expressed an interest in receiving a participant pack (25 males). Out of those who requested an information pack, 17 chose not to participate, and 33 returned completed questionnaires and consent forms (M = 15, 45% F = 18, 55% Mean age±SD = 66±9.4). This gives an overall response rate of 67%.

Out of those who responded, 21 individuals (M=10, F=11, 63.6% mean age±SD= 67±8.4) stated that they experienced dyspnoea whilst at rest on at least one occasion during the three-day trial. Twelve participants did not report experiencing dyspnoea at rest. Within those who experienced a level of dyspnoea at rest at some point in the study, 10 (48%) participants reached a maximal level of mild, 9 (43%) experienced moderate at maximum, and 2 (9%) experienced a severe amount at least once over the course of the study.

For those who experienced dyspnoea at rest (n=21) the overall mean±SD (%) total, physical and emotional D12 scores were 8.2±2.9, 10.1±3.5 and 3.5±7.3 respectively. For those who experienced dyspnoea after exertion (n=28) the total D12 mean±SD (%) score was 15.7±17.2, the physical mean±SD (%) score was 19.6±20.1, and the emotional D12 mean±SD (%) score was 10.3±17.5.

Figure 4-3 shows the overall levels of dyspnoea during rest and after exercise irrespective of day or time of day, showing a clear increase with physical activity. A repeated measures ANOVA did not detect any main effect of time of day, day of participation, or exertion level on D12 total, physical or emotional scores (all $p>0.05$).

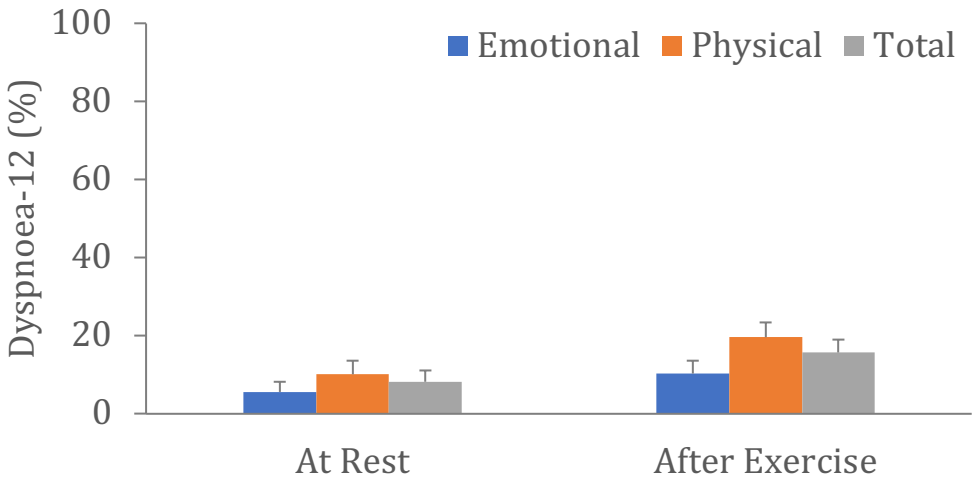


Figure 4-3 Averaged Dyspnoea-12 scores (%) at rest versus exercise

Mean±SEM total scores for dyspnoea across all days both upon rest and after performing exercise.

Day to day variation in dyspnoea

Averaged D12 scores (%) remained consistent across the days of the study,

both at rest and after exertion (Figure 4-4).

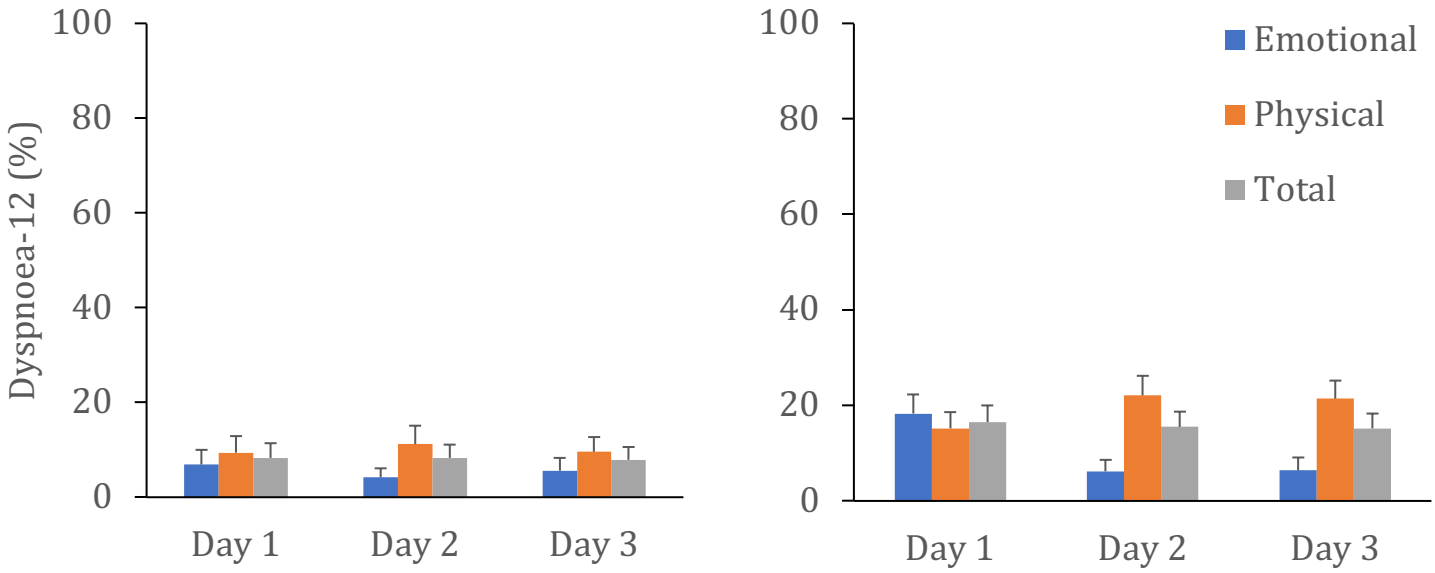


Figure 4-4 Averaged D12 scores (%) for each day of the study during rest and after exercise

Mean±SEM emotional, physical and total scores for dyspnoea expressed as % of full scale. Scores were recorded after sitting at rest for 10 minutes (left panel) and after walking 50 yards or climbing a flight of stairs (right panel) over 3 alternating days.

Within day variation

There is a visible trend over the course of the day for the total D12 score during rest to decline, with it becoming lowest in the evening. This trend is also observed in the physical component of the D12 questionnaire, but not in the emotional (Figure 4-5). No significant difference was found between D12 questionnaire scores recorded at different time points after exercise.

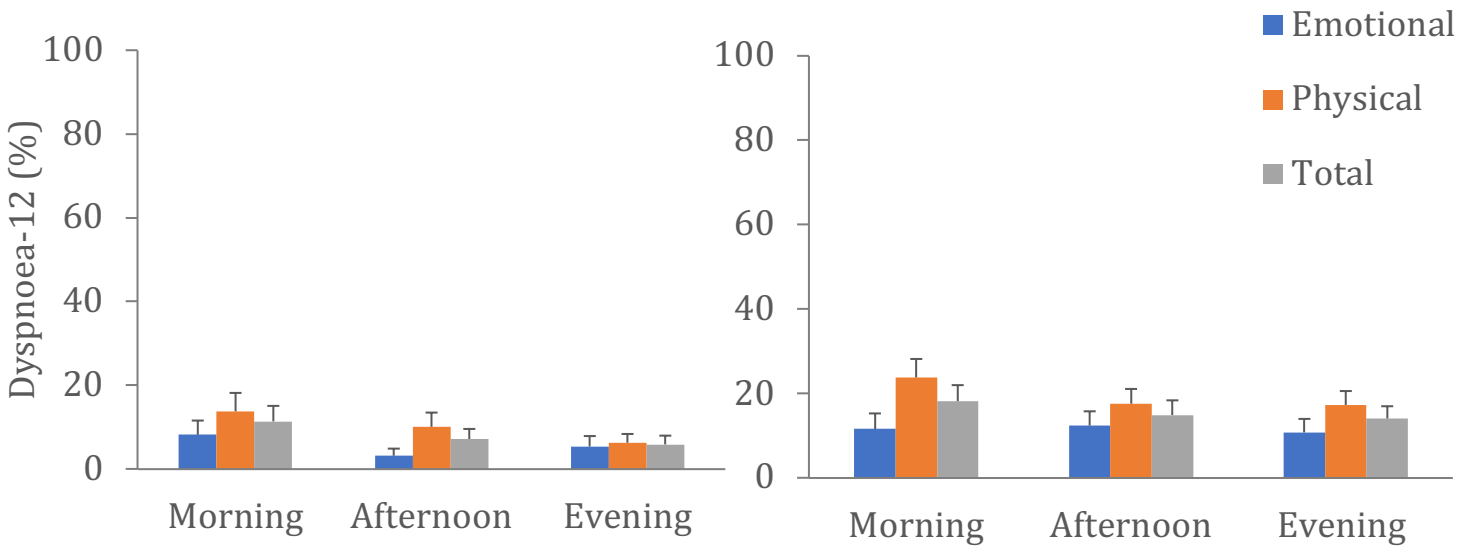


Figure 4-5 Effect of time of day and physical activity on D12 scores

Left panel: The Mean± SEM emotional, physical and total scores for dyspnoea at rest expressed as % maximum recorded at morning, noon and evening over 3 alternating days. Each measurement was taken after 10-minute rest. Right panel: The same data collected after physical activity involving climbing a flight of stairs or walking 50 yards.

Effect of between factors

Sex appeared to not have any effect on participant's total, emotional, or physical D12 scores (%) either at rest or after exercise (M=10, F=11). From within the total cohort 24% reported a history of heart or lung disease (cardiac n= 8, lung disease n=1). A repeated measures ANOVA showed no main effect of the of presence of cardio-respiratory disease (Table 4-2).

Table 4-2 Effect of presence of cardiorespiratory disease history

History of cardio-respiratory disease	% change in total D12 score
Yes (n=9)	5.0
No (n=23)	9.7

4.2.4 Discussion

This study has found that individuals with Parkinson's disease in the community report a low level of dyspnoea at rest (8.2%±2.9 full scale for D12 total). The prevalence however was almost double what has previously been reported; 63.6% versus 39.2% reported by Baille et al., (2016). Currow et al., (2013) reported that from a sample size of 755,729 patients, 0.96% reported breathlessness as the reason for their consultation. This shows that the breathlessness being reported in the PD community within this study far exceeds what exists within the general population.

Variation between time of day or day of participation (scores were collected over a 3-day period) was minimal but there was a suggestion that mornings

may yield the highest D12 scores. No relationship was found between sex and dyspnoea score, or age and dyspnoea score but it is likely that this study is underpowered for this level of stratification. This study supports the view that breathlessness is an important non-motor symptom of Parkinson's disease, thereby building for the case that greater clinical attention should be paid to this (Baille et al., 2019, Witjas., 2002).

4.2.5 Wider impact of findings

Interestingly, the data shows a trend for participants to experience the most breathlessness in the morning, with it gradually reducing across the day. Within the field of COPD, multiple studies have reported that respiratory symptoms are at the most severe in the mornings (Partridge et al., 2009, Kessler et al., 2010). It is not clear why participants within this study would mirror the same pattern as those with chronic respiratory disease.

The key message from this study is that neurodegeneration of the sub-thalamic region as a result of Parkinson's disease is directly linked to the motor and non-motor symptoms experienced by Parkinson's sufferers (Halliday 2009). This contrasts sharply with the previous chapter which shows definitively that DBS (as a virtual lesion) of the motor thalamus mitigates breathlessness perception. Alternatively, reduced strength in inspiratory muscles has been reported in early stage Parkinson's disease (Baille et al., 2018). The implication of this muscle weakness is that it could contribute to a feeling of increased work and effort when breathing (a form of dyspnoea (Lansing et al., 2000)).

4.2.6 Critiques and limitations

The proportion of participants who report experiencing dyspnoea ranges between studies. Here, it is reported that 63.6% of participants recorded an experience of dyspnoea at least once over the study. In contrast, Baille et al., (2019) showed that 39% of 159 patients with Parkinson's disease gave a positive answer to the question "in the past month, have you suffered from breathlessness?". Lastly, a study by Witjas et al., (2002) reported that 80% of patients interviewed (n = 50) confirmed that they experience dyspnoea. A possible explanation for this variability is the methodology used by each study to capture the patient's experience with breathlessness. Using the phrase 'in the past month' relies on the participant being able to recall their non-motor symptoms over a significant period of time with a great accuracy. This can lead to under reporting if individuals do not have good recall. With regards to Witjas' et al., (2002) study, asking the participant if they have ever experienced breathlessness could cause participants to over report breathlessness. The majority of individuals will experience breathlessness in their adult lives, and therefore, it is not possible to attribute all participants reports of breathlessness to their diagnosis of Parkinson's disease. The properties of the D12 (i.e. derived from the language breathless patients use irrespective of underlying pathology) suggests that the participants may have related better to the items in the list. Using the D12 questionnaire is also a good opportunity to gain an understanding into the daily challenges that individuals with Parkinson's disease face with regards to non-motor symptoms.

Parkinson's disease is characterized by progressive neurodegeneration. Therefore, for future studies in this area, it would be of interest to collect data over a longer time period to assess whether feelings of dyspnoea increase as their disease progresses. Asking a participant to complete the questionnaire on alternating days for any lengthy period of time would not be viable, however, it would be possible to ask a participant to complete the questionnaires on 3 alternating days at start of the study, and again in 2 years' time, for example. This would give additional insight into whether the dyspnoea experienced was stable after onset, or if it increases at the same rate as other symptoms of the disease progress. An alternative approach would be to separate participants into different cohorts based on the stage of their disease, or the degree of disability that their condition causes them. Braak's staging is used within the field of Parkinson's research to quantify the stage that the patient's disease has reached using neural pathology. An alternative that is also used in the research community to quantify Parkinson's disease is the Movement Disorder Society – Unified Parkinson's Disease Rating Scale. It provides a score between 0 (meaning no disability) and 100 (the most severe disability). However, a disadvantage of both of these measures is that it would require significant clinician input as these measures require specialist staff to administer them correctly. This would change the study from something the participant can do independently in their own home to something that they would need to visit a professional to complete.

4.2.7 Conclusion

In conclusion, this postal survey has demonstrated that breathlessness is a non-motor symptom of Parkinson's disease. This study is novel in the use of the D12 questionnaire in order to quantify the level of breathlessness that individuals with Parkinson's disease experience in their daily lives and it could argued provides a more reliable estimate of prevalence. Parkinson's research has a large focus on the motor symptoms of the disease, but it is also important to gain an appreciation for the non-motor symptoms as they also have a significant impact on the individual's quality of life.

5 The effect of deep brain stimulation on the dyspnoea of respiratory disease

5.1 Introduction

An aging population means that the prevalence of chronic obstructive pulmonary disease (COPD) is expected to increase, with it being one of the leading causes of death by 2020. COPD is defined as progressive lung disease involving chronic airflow obstruction (Global Initiative 2018). It is not one disease, but a collection of lung conditions including chronic bronchitis, emphysema, and chronic asthmatic bronchitis with common symptoms being wheeze, tightness in the chest, frequent coughing and dyspnoea.

Dyspnoea upon exertion in particular, is an exceedingly common complaint in the cardio-respiratory population. A telephone-based questionnaire of individuals with COPD living in North America and Europe found that 70% of respondents were breathless when walking up a flight of stairs (Paladini et al., 2010). This is a clear problem for people trying to maintain their independence as it promotes fear and anxiety and will cause people to shy away from exercise which further promotes an isolating and sedentary lifestyle (Spathis et al., 2017).

COPD is only partially reversible with bronchodilators and the effectiveness of this and other inhaled therapy targeting the pathophysiology will diminish with severity. For symptomatic treatment on the other hand, there is currently no option that is both successful in relieving symptom burden long term and has

limited side effects. The preferred solution for dyspnoea relief would be to treat the underlying pathology responsible for the breathlessness itself, but this is not always possible as in the case of chronic obstructive pulmonary disease (COPD). The current most successful symptomatic treatment options include; (i) pulmonary rehabilitation, although uptake of this is poor among COPD sufferers and the effects are not long lasting (Booth et al., 2009), (ii) use of opioids (Banzett et al., 2011, Currow et al., 2011), but this is beset with serious side effects and a lack of research into long term effects and its addictive qualities (Grogono et al., 2019). These options may not be appropriate in instances where the individual is not at the end stage of a disease.

A further complication of COPD is its effect on the risk of contracting other diseases. A systemic review found that stroke is more common in COPD sufferers compared to the general population (Morgan et al., 2017). Data also suggests that patients with COPD have an increased risk of haemorrhagic stroke as oppose to an ischaemic stroke. This has the implication that hypoxia and oxidative stress which are prevalent in COPD, have a role to play in multi-morbidity including neurological consequences from the onset of bleeding within the brain (Austin et al., 2016).

A cursory search of the literature with keywords “Neurology” or “Neurological” and “Respiratory” or “Breathing” showed that currently, little attention is paid to the respiratory symptoms by neurologists in their management of patients with pre-existing respiratory conditions. A recent anecdotal report (Green et al., 2019) showed that a patient who had undergone Deep Brain Stimulation (DBS) for the relief of post-stroke pain, tremor, and dystonia also experienced a

substantial relief of their breathlessness associated with their pre-existing COPD. An additional unexpected finding was that the DBS resulted in elimination of the pre-surgery pursed lips breathing, a common feature of breathlessness in COPD patients. This patient had multiple electrodes implanted unilaterally for the DBS, and the ventral intermediate nucleus (VIM) of the motor thalamus was identified as the site of stimulation that appeared to have the biggest impact on breathlessness (Green et al., 2019).

The anecdotal report discussed above raises the possibility that DBS may also benefit patients with respiratory conditions. Given the need for better treatment options for intractable breathlessness, the current chapter aimed to investigate whether DBS could provide a viable therapeutic option for breathlessness relief. DBS is an established therapy that has been successful in providing relief from drug resistant chronic pain (Boccard et al., 2012) which shares common features with cerebral mechanisms of dyspnoea (Banzett and Moosavi, 2001). In chapter 3 an experimentally induced model of dyspnoea had to be used to assess the effect of DBS. In the current study, the opportunity presented itself to test the effect of DBS of the same area on pre-existing clinical dyspnoea, foregoing the need for experimentally induced dyspnoea. Furthermore, the recent development of multi-dimensional dyspnoea tools lends itself to this study. Thus, dyspnoea is quantified in the current chapter using the same tool used in the postal survey reported in the previous chapter.

The current study is also novel in the use of neurological patients and their management in better understanding of the cerebral mechanisms of dyspnoea. The latter has thus far depended almost entirely on functional brain imaging

studies which have been useful in identifying putative regions of interest in the brain (Banzett et al., 2000, Evans et al., 2002). However, functional brain imaging studies are beset by assumptions and have had limited success in establishing the precise role and connectivity of the regions of interest in relation to dyspnoea.

Thus, the two specific aims of the study reported in this chapter were:

(i) Use the D12 multi-dimensional dyspnoea tool to quantify resting breathlessness with and without DBS of the motor thalamus in patients with pre-existing respiratory disease. The hypothesis being that DBS of the motor thalamus, at the threshold level for tremor relief, will also relieve the dyspnoea of pre-existing COPD.

(ii) Provide new data to improve understanding of the cerebral mechanisms of dyspnoea.

5.2 Methods

5.2.1 Participants

Eight patients were identified by the neuromodulation nurses within the clinical neuroscience division at John Radcliffe over a period of 1 year. The inclusion criteria consisted of diagnoses of movement disorder which is controlled through DBS of the thalamic ventral intermediate nucleus, and a co-existing respiratory condition. Participants had to be a minimum of 18 years old with no documented dementia or need for a translator. This is because cognitive impairment or lack of proficiency in English is likely to affect the participants' ability to reliably complete the D12 questionnaire.

Ethics approval for this study was granted as a substantial amendment to an existing wider investigation from the NHS Health Research Authority (REC: 11/SC/0229, Study Title: Non-invasive Cerebral Blood Flow Monitoring in Patients with Deep Brain and Occipital Nerve Stimulators; PI: Alex Green) with the University of Oxford acting as research sponsor.

5.2.2 Sample size

This study was an entirely novel prospective study and as such no prior sample size estimation was conducted. The number of patients with VIM DBS and co-respiratory disease registered under the neuromodulation team at the John Radcliffe dictated recruitment rates.

Recruitment ran from October 2018 to May 2019 in which time 8 patients were identified and 7 consented to participating. Initial identification of eligible patients was performed by specialist neuromodulation nurses. With patient consent, contact details were then shared with a member of the research team to discuss the study further and schedule an appointment. Of the 7 who initially consented, 4 went on to complete the protocol. Testing was scheduled for the same day as a clinical appointment to minimise travel time and expenses for the patient. Withdrawal for each of the 3 remaining patients was due to their clinical appointment taking longer than originally foreseen and them being unable to commit the extra time to the study.

1.1.1. Protocol

Patients were asked to complete a D12 questionnaire when stimulation was turned ON, OFF and with unilateral stimulation of each hemisphere (Figure 5-1). Prior to completing each questionnaire patients sat quietly at rest for 10

minutes. The instructions to participants were to rate their dyspnoea at that moment in time. A minority of participants also completed the questionnaires after a brisk walk. This was not possible for all participants due to issues with mobility and the results are not reported here. Changes in stimulation setting were performed in a random order for each patient.. Please see chapter 2 for details about the questionnaire items, and the validity of using the D12 questionnaire in a research setting.

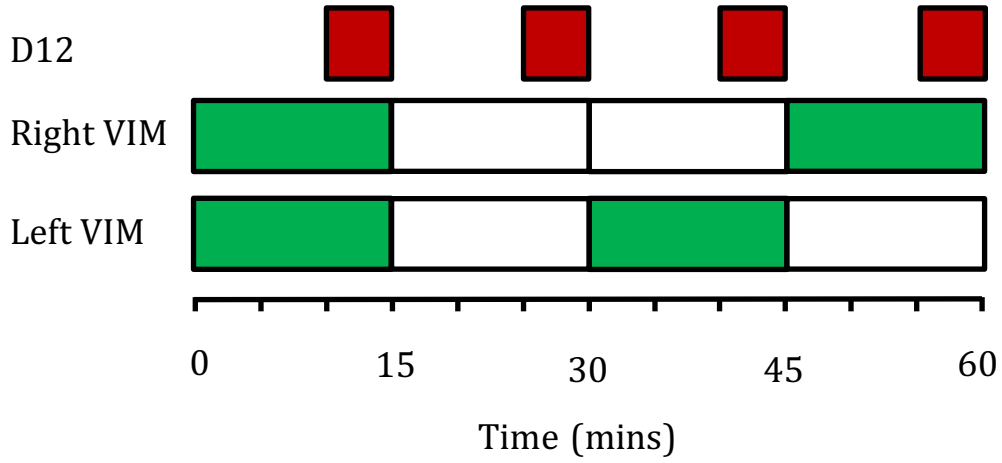


Figure 5-1: Protocol for the effect of DBS on dyspnoea in patients with COPD

Participants completed a D12 questionnaire to assess breathlessness with all electrodes ON at their normal therapeutic level, and then 10 minutes after each change to the stimulation setting. The order of the stimulation changes were randomized for each patient but every patient apart from one (N=4) completed all conditions. Items on each D12 questionnaire were presented in a random order. DBS ON is indicated by green bars and completion of D12 is indicated by the red boxes.

5.2.3 Statistical analysis

Percentages of the full scale for the total, physical and emotional components of the D12 were calculated. For statistical analysis, paired t-tests were conducted to compare the difference in D12 score between ON and OFF stimulation with

both hemispheres, and ON versus OFF with unilateral stimulation. A paired t-test was also conducted to look at the difference in D12 score between the left hemisphere and right hemisphere with stimulation ON. A paired t-test with Bonferroni correction was applied.

5.3 Results

5.3.1 Demographic and clinical details of the participants

Four males (mean age±SD 69±5 years) with pre-existing COPD participated (Table 5-1). All participants confirmed they had diagnosed COPD and were under the ongoing care of a GP.

Table 5-1 Demographics for all participants who completed the study protocol

Age, race, weight, height and diagnoses for all participants. Electrode frequency parameters are also included. All participants were male and right-handed.

Participant	Age	Left electrode frequency (Hz)	Right electrode frequency (Hz)	Race	Weight (lbs)	Height (cm)	Reason for DBS	Lung condition
01	67	1.3	1.3	White British	183	170	Post-stroke tremor and pain	COPD
03	69	1.6	2	White British	137	160	Essential tremor	COPD
27	62	3.2	3.3	White British	252	178	Essential tremor	COPD
31	65	7	7	White British	214	173	Essential tremor	COPD

5.3.2 Group results

All reported experiencing dyspnoea at some point throughout the testing session. One participant experienced no change in their breathlessness. The individual scores for the total, emotional and physical domains of the D12 (expressed as % full scale) with stimulation OFF, bilateral stimulation and

unilateral stimulation are shown in Table 5-2. Mean overall change in breathlessness score was 26.4%.

Table 5-2 Averaged D12 scores for participants with and without DBS

The raw, mean, SD and SEM scores for total, emotional and physical domains of dyspnoea expressed as a % full scale for no DBS (ALL OFF), bilateral DBS (ALL ON), and unilateral DBS (Left VIM ON or Right VIM ON) of the VIM in individuals with pre-existing lung disease.

DBS	Participant ID	D12 (Total) (%fullscale)	D12 (Emotional) (%fullscale)	D12 (Physical) (%fullscale)
ALL OFF	1	25	60	43
	3	0	0	0
	27	64	67	62
	31	67	67	67
	Mean	39.0	48.5	43.0
	SD	32	33	30
	SEM	16	16	15
All ON	1	3	7	5
	3	11	0	19
	27	53	60	48
	31	8	0	0
	Mean	18.8	16.8	18.0
	SD	23	29	22
	SEM	12	15	11
Left VIM ON	1	-	-	-
	3	0	0	0
	27	64	10	62
	31	0	0	0
	Mean	21.3	3.3	20.7
	SD	37	6	36
	SEM	21	3	21
Right VIM ON	1	-	-	-
	3	0	0	0
	27	61	60	62
	31	0	0	0
	Mean	20.3	20	20.7
	SD	35	35	36
	SEM	20	20	21

The mean D12 total score fell from a mean value of 39+/-32 to just over half this value with bilateral or unilateral stimulation (Figure 5-2; left panel). The greatest reductions appeared to be for the 'emotion' domain of the D12 with a suggestion that stimulation of the left VIM produces the biggest relieve (Figure 5-2; right panel). None of the changes in D12 score (%) from the OFF condition achieved statistical significance.

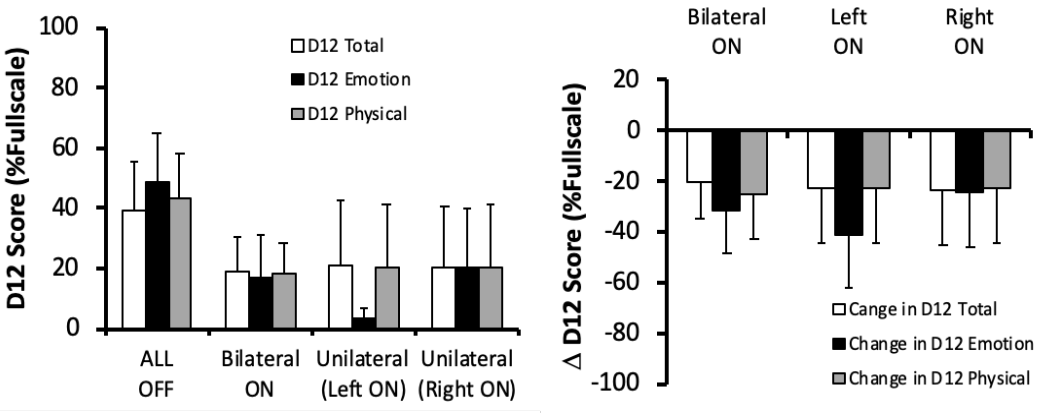


Figure 5-2: Average D12 scores with bilateral, unilateral or no stimulation of the VIM

Left panel: Mean+/- SEM D12 total score (open bars), D12 emotion score (black bars) and D12 physical score (grey bars) with stimulation off (ALL OFF), bilateral stimulation (Bilateral ON) and unilaterally stimulation (Unilateral Left ON and Unilateral Right ON) in 4 individuals with pre-existing COPD. Right panel: Same data expressed as the difference between the baseline OFF and bilateral and unilateral stimulation.

Paired t-test showed no significant difference between total D12 score (%) for ON versus OFF stimulation at the $p>0.0125$ significance level. No significant difference was also found between emotional D12 score (%) for ON versus OFF, or between physical D12 score (%) when using a paired t-test.

5.3.3 Individual results

The individual responses to DBS are shown in Figure 5-3. One individual scored higher breathlessness and this was only for bilateral stimulation. This individual had the lowest baseline breathlessness. The other three individuals

experienced varying degrees of relief of their breathlessness with bilateral DBS. Two of these three individuals felt relief with unilateral stimulation, one (P27) with preference for left VIM DBS and the other PS31) with equal relief with both left and right DBS.

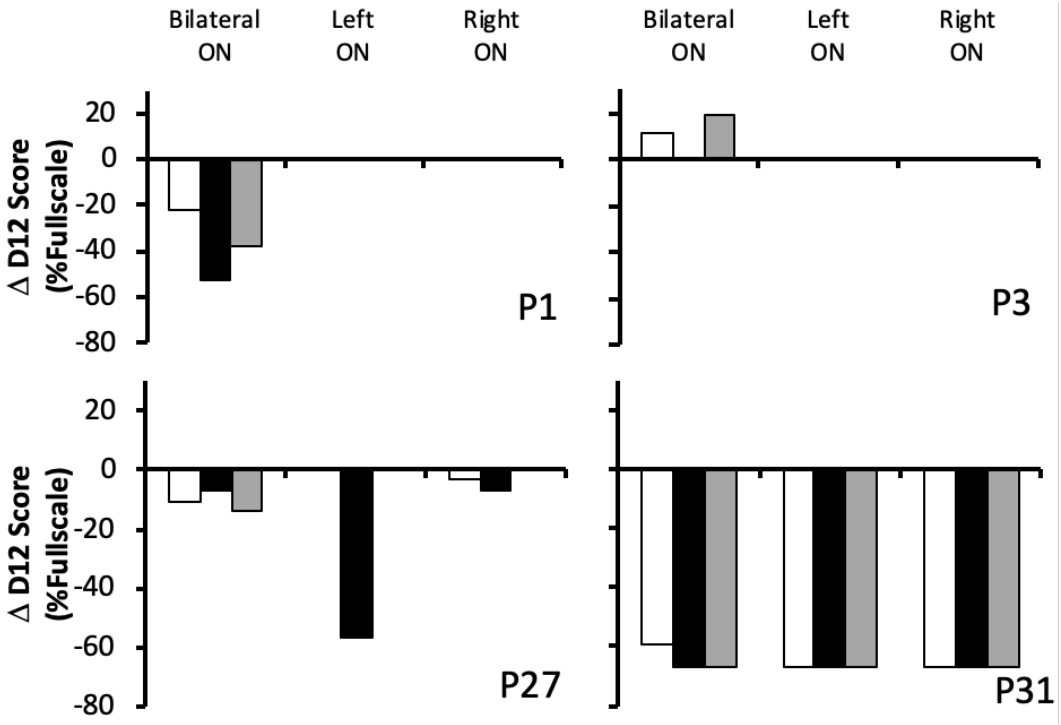


Figure 5-3 Individual responses to bilateral and unilateral DBS of the VIM

Change in D12 Total (open bars), D12 Emotion (black bars) and D12 Physical (grey bars) with bilateral DBS (Bilateral ON) and unilateral DBS (Left ON, Right ON) expressed as a % of the full scale, in 4 individuals with pre-existing COPD.

5.4 Discussion

5.4.1 Key results

The overall trend is a decrease in breathlessness with bilateral thalamic stimulation and with unilateral stimulation of either hemisphere. All the participants detected a difference in their breathlessness between stimulation conditions that exceed the minimally relevant significant difference of 9.7% of

the full scale (Johnson et al., 2013); however, 3 experienced a decrease in breathlessness and 1 an increase upon stimulation. This minimum % of the scale was proposed to be the minimal amount of difference needed for a patient with breathlessness to notice the change and to have their quality of life impacted by it (Johnson et al., 2013).

Participant 27 reported a decrease in breathlessness with bilateral stimulation of the thalamus in comparison to unilateral stimulation of either hemisphere, or with bilateral stimulation turned OFF. There is a marked reduction in the breathlessness scores in the emotional domain when the left hemisphere is stimulated in comparison to any other stimulation condition. The scores for the physical domain remain unchanged between all conditions. This shift in emotional score is not replicated in any other patient.

Participant 31 reported severe breathlessness when their stimulation was turned OFF which was reduced to mild levels when stimulation was ON. Participant 1 did not complete the entire protocol due to time constraints but demonstrates a decrease in breathlessness with thalamic stimulation compared to the OFF state.

Participant 3 experienced an overall increase in breathlessness with bilateral stimulation that was exclusively in the physical domain. With unilateral stimulation, and with bilateral stimulation turned OFF, they reported zero breathlessness.

When focusing on the affective items within the D12 questionnaire there are identifiable differences between the effects of laterality on breathlessness

perception. Figure 5-2 shows a clear difference in breathlessness score when stimulating the left hemisphere compared to with stimulation turned OFF in both hemispheres. The affective breathlessness score upon stimulation of the left hemisphere is also lower than the equivalent score produced by stimulation of the right, or both hemispheres Figure 5-2. The physical aspect of breathlessness is also lesser with bilateral stimulation of the VIM compared to stimulation turned OFF, as is shown in Figure 5-2 The breathlessness score within the physical domain does not appear to change between stimulation of the hemispheres independently.

Overall, a trend of reduced breathlessness perception with bilateral thalamic stimulation can be observed. From the cohort of 4 patients, 3 experienced a decrease in breathlessness when bilateral stimulation was turned ON in comparison to when it was turned OFF. Additionally, one patient experienced an increase in breathlessness with bilateral stimulation. This finding is complimentary to (Green et al., 2019) case study which reported that a patient with COPD and VIM DBS to control post tremor and pain, experienced an eradication of breathlessness upon stimulation. However, within this study's cohort, one participant experienced a mild increase in total breathlessness score when stimulation was turned ON in comparison to when it was turned OFF. These changes in breathlessness were represented in D12 scores.

Interestingly, one participant experienced a mild decrease in breathlessness overall between the ON and OFF condition, but a dramatic decrease in D12 emotional score when only the left hemisphere was stimulated. This finding was not replicated within the other participants. This large shift in response

raises the interesting questions about the differences between the left and right motor thalamus and their differing roles in perception and emotional state.

Statistical tests do not find a significant difference in D12 score between ON and OFF conditions or between unilateral stimulation and bilateral stimulation. However, with a limited sample size it is encouraging that a general trend in the data can still be observed and is suggestive of a significant finding in the future with a larger sample size.

5.4.2 Critiques and future directions

This is a pilot study making it difficult to draw conclusions based on the data collected. This novel study, however, does contribute to the important discussion about both the management of dyspnoea caused by respiratory disease, and the need for neurologists to take into consideration the interaction that may exist between respiratory and neurological conditions. There is now preliminary evidence that stimulation of the motor thalamus can dampen the perception of experimentally induced breathlessness as demonstrated in chapter 3 of this thesis, but the study as outlined here, shows that it may also alleviate breathlessness in patients with respiratory disease. Furthermore, it can be suggested that a proportion of patients would experience relief from breathlessness through thalamic stimulation at a clinically relevant level.

There is experimental evidence to support the equivalence of experimentally induced dyspnoea in healthy individuals and clinical dyspnoea in patients with COPD (O'Donnell et al., 2013). However, we cannot discount the possibility of differences associated with anxiety and lack of control in patients. A strength of this study therefore, is its novel use of patients with pre-existing respiratory

disease. This approach of using a patient population means that we can be confident that our findings have a real-world application. This is to say, that the assumption can be made that the differences found in the experimental setting in chapter 3, would also be found in the rest of the patient population.

5.4.3 Variability

Whilst there was a trend observed in the data, the magnitude of the change in breathlessness experienced varied between participants. Furthermore, the physical and emotional domain appeared to be affected differently by the changes in stimulation. These differences in response to stimulation of the VIM raises an important question about what factors influence an individual's response to breathlessness upon stimulation of the VIM.

The first possible contributing factor is electrode placement. All participants had electrodes located in the VIM, however, electrode location does vary marginally between each patient. This small amount of variability may account for the range in response seen in this study. Additionally, the thalamus has been known to change in morphology with age (Hughes et al., 2012), a factor which could have an impact on long term clinical outcomes in patients with DBS (Martinez-Ramirez et al., 2014). The implication being that an individual's response to therapy can change over time, both in terms of management of symptoms, and development of side effects (Martinez-Ramirez et al., 2014). The potential for changes in morphology therefore, combined with the individual differences in electrode placement between all patients may explain the varied response seen in this study.

In addition, it is possible that the variation in breathlessness response upon stimulation is a result of individuals having different morphology. Disease duration in COPD has been shown to negatively correlate with grey matter density in the thalamus (Esser et al., 2016), meaning that as the disease progresses, the thalamus may atrophy and the electrodes positions may shift. This hypothesis cannot be proven by this study but is a point of consideration for future works.

An additional point of consideration is how dyspnoea can change both over time and in different environments, meaning that the scores given by participants may not be representative of their breathlessness in a community setting. Russel et al., (2016) found that when respiratory patients were presented with two versions of the D12, one which asked for them to report breathlessness 'these days' and the other 'today', they consistently rated their breathlessness worse over the greater time period. It is possible therefore, that participants gave responses in the research setting which do not accurately represent the effects that VIM DBS has on their breathlessness in daily life. This could be due to the psychological effect of being in a hospital with clinicians present which may lower the affective component as they feel safer than at home unsupervised.

In this study, time of day and day of the week were not controlled for, which may have contributed to the range of results as COPD has been documented (Roche et al., 2013) to be worse at different points during the day, with sufferers reporting that shortness of breath in particular is the most severe in the mornings. Variability in symptoms over the course of a week has also been

shown to occur, with individuals becoming more tired and less able to cope as the week progresses. Furthermore, COPD is an umbrella term for a collection of symptoms, and so future work would benefit from having separate cohorts with one specific symptom such as emphysema or bronchitis. This could enable us to draw more well-informed conclusions as to the effect of VIM stimulation, and who specifically the therapy could benefit.

5.4.4 Wider impact

DBS of the motor thalamus has been established to improve quality of life in terms of motor dysfunction, but there is emerging evidence that this therapy has the potential to help other patient populations, including those with intractable breathlessness. A criticism of proposing DBS as a therapy for intractable breathlessness is that it is a procedure that does carry some risk. The most serious risk is having a haemorrhagic stroke, an occurrence that happens in less than 1 percent of patients who have the procedure. There is also a 10 percent risk of having a less serious complication such as infection (1 in 20) or malfunction of the hardware. These potential complications however, are within the acceptable threshold for surgical risk (Fenoy and Simpson, 2014). In addition to the statistical argument, it is also important to consider the evidence for quality of life improvement in patients who have this therapy for other conditions. A condition which is similar in multiple ways to dyspnoea is intractable pain. Both share a similar neurological pathway (Banzett and Moosavi, 2001), and are similar in intensity and unpleasantness. Furthermore, patients in the palliative stages have consistently reported dyspnoea to have a an equally large impact on quality of life as pain (O'Driscoll et al., 1999).

Therefore, it is appropriate to also suggest DBS as an appropriate therapy for patients with respiratory disease who suffer with severe intractable breathlessness.

It is worthy of note that in the recruitment period of 1 year, 8 patients out of an estimated 20 were identified as having both respiratory disease, and DBS of the motor thalamus for movement disorder. This high prevalence of patients with disordered movement and respiratory disease (~40% of patients undergoing VIM DBS in one year) suggests that this is a neglected area that requires more attention by both clinicians and researchers. It is important to consider the possible interaction between respiratory disease and neurological disorders as I have demonstrated that the therapy provided for one can influence the symptoms of the other, and ultimately impact the patient's quality of life.

5.4.5 Conclusions

In conclusion, this study has raised some interesting questions about the role of the VIM in the modulation of breathlessness in respiratory disease. At a group level there was no significant difference between total, emotional or physical % D12 scores with stimulation compared to without stimulation. When looking at individual data it became apparent that there was an interesting trend towards breathlessness perception being dampened by bilateral stimulation of the motor thalamus. There was also one individual patient who experienced an overall increase in breathlessness with stimulation turned ON (compared to OFF). With this small sample size it is difficult to draw definitive conclusions, however, this work is complimentary to that outlined in Chapter 3. In the previous chapter, experimentally induced breathlessness was relieved by motor

thalamic stimulation in non-respiratory patients. This study has the novel use of patients with respiratory disease, and again shows that with stimulation ON, breathlessness is scored lower compared to stimulation turned OFF.

6 Explorative studies of other novel approaches

Chapters 3-5 have focused on the novel use of deep brain stimulation (DBS) to better understand the brain structures involved in dyspnoea perception. Another approach, not previously attempted, is to record neural signals directly from brain structures of interest via the electrodes implanted for DBS. In addition to this there has been limited attempts to explore deficits in breathlessness perception resulting from brain lesions. The latter has focused entirely on lesions (Schön et al., 2009), no previous studies have explored the effect on breathlessness arising from the impact of tumours on target brain regions identified from the function brain imaging studies. The current chapter presents two case reports that provide pilot data generated using the additional approaches described above.

Section 6.1 reports a study of experimentally induced breathlessness in a patient with simultaneous recording of neural signals from electrodes implanted for DBS of the ventral intermediate nucleus (VIM). The recording of Local Field Potentials (LFPs) in patients with DBS has become more frequent but has never before been utilized to study breathlessness. A patient with DBS of the VIM was chosen for this pilot study on the basis that DBS of the motor thalamus significantly relieved experimentally induced air hunger (reported in chapter 3). The current study was designed to tease apart the mechanism of air hunger detection that occurs within the VIM. The specific aim was to search for a unique neural signature from the motor-thalamus which correlates to breathlessness.

Section 6.3 reports a study of experimentally induced breathlessness in a patient with tissue damage to the insular cortex resulting from low-grade glioma.

6.1 Case study 1: Local field potentials (LFPs) from VIM DBS

6.1.1 Methods

Clinical details of the patient

Ethics approval was obtained from South Central Oxford Research ethics committee (REC: 11/SC/0229 Study Title: Non-invasive Cerebral Blood Flow Monitoring in Patients with Deep Brain and Occipital Nerve Stimulators; PI: Alex Green) with Oxford University acting as research sponsor.

This patient was a right-handed 38-year-old female (Height 161cm; Weight 49kg) with a diagnosis of multiple sclerosis. She was not on any medication at the time of the experiment. She was fitted with bilateral electrodes in the VIM nucleus. She had no history of respiratory disease and was a non-smoker.

The participant provided written informed consent with the knowledge that they were participating in a study investigating breathlessness. They attended the laboratory at the John Radcliffe hospital for 2 hours. It was confirmed by the participant's clinical team that they possessed the cognitive and verbal abilities to understand the nature of the test. A physician was present for the duration of testing and no adverse events occurred.

6.1.2 Protocol

The patient initially completed an incremental air hunger test lasting 10 minutes. Following this, they completed 3 different breathing conditions:

Experimentally induced air hunger

This involved increasing inspired CO_2 to a level that targeted an end tidal PCO_2 that would generate air hunger rated at approximately 50mm of the VAS scale, while keeping ventilation constrained to the resting baseline level. The target level of inspired CO_2 was chosen from the results of the incremental ramp test conducted immediately prior to this test and the stimulus was maintained for 4 minutes to ensure that a steady state was established in the last minute. The details of this test are identical to those reported in previous chapters involving a standard test of air hunger.

Hypercapnia with unrestricted ventilation

For this control condition, the same level of inspired CO_2 was imposed as for the air hunger test above, but this time ventilation was unrestricted. The stimulus was maintained for 4 minutes as above.

Normocapnic hyperpnoea

For this control condition, the inspired CO_2 was adjusted to maintain normocapnia while the patient was coached to target their ventilation at the steady state level seen in the prior condition (Hypercapnia with unrestricted ventilation).

The differences between these three test conditions and the hypothesized LFP responses are shown in Table 6-1 .

Table 6-1 Predicted changes in LFPs and air hunger in response to tests

(i) Increased CO_2 with fixed breathing (ii) Increased CO_2 with free breathing (iii) increased breathing with fixed CO_2. The size and direction of arrows indicate the change in amount and the direction of change predicted for each variable.

	CO_2 levels	Breathing levels	'Air hunger'	Our predicted LFP changes
(i) Hypercapnia + fixed breathing	↑↑↑↑	↔	↑↑↑↑	↑↑↑↑
(ii) Hypercapnia + free breathing	↑↑↑↑	↑↑↑↑	↑↑↑↑	↑↑↑↑
(iii) Hyperpnoea + fixed CO_2	↔	↑↑↑↑	↔	↔

The patient rated air hunger every 15 seconds throughout each condition using the visual analogue scale (VAS). At the end of each condition they completed an in-house debrief questionnaire which invited volunteered comments followed by a forced choice of respiratory descriptors from a pre-set list. The list of respiratory descriptors included those commonly used to describe air hunger and others to describe sense of breathing work and effort. The patient selected the items that they felt fit the overall sensation they had experienced. This is in line with the debriefing method described by Lansing et al., (2009 review).

6.1.3 Data processing and statistical analysis

LFP data

Data was transformed from bipolar to unipolar before being imported into MATLAB for analysis. Pre-processing occurred where a filter was applied to remove any power at 50Hz. This is due to the electronic equipment used during recording operating at that frequency meaning that there would have been a

large artefact at that frequency band. A low pass and a high pass filter are applied to remove noise at very low and very high frequencies. Although the patient had electrodes implanted bilaterally, it was only possible to record relatively noise-free LFP signals from the left VIM. The overall power content of this signal was compared graphically as a function of frequency content between steady state periods of each breathing condition.

Physiological data

All steady state conditions were at least 4 minutes in length. Air hunger ratings, airway pressure, tidal volume, and breath-by-breath end-tidal PCO_2 in the last minute of the four-minute period were averaged for each condition. These averages and graphical presentation of the breath by breath data were inspected to see how well the target conditions were implemented.

6.1.4 Results

Differences in physiology between breathing conditions

Figure 6-1 shows the raw data signals recorded in the last minute of steady state for each condition. As expected, air hunger was only generated by condition 1 (hypercapnia with constrained ventilation) (Figure 6-1, top row) and this condition generated the greatest airway pressure fluctuations due to the urge to overcome the ventilatory constraint (Figure 6-1; 3rd row). The amount of additional inspired CO_2 provided in condition 2 (hypercapnia with free breathing) ensured that end tidal PCO_2 matched that seen for condition 1 (hypercapnia with constrained breathing) (Figure 6-1; 2nd row). Likewise, tidal volume targeted through verbal coaching in condition 3 (hyperpnoea with

normocapnia) matched the tidal volume in condition 2 (hypercapnia with free breathing) (Figure 6-1; 4th row).

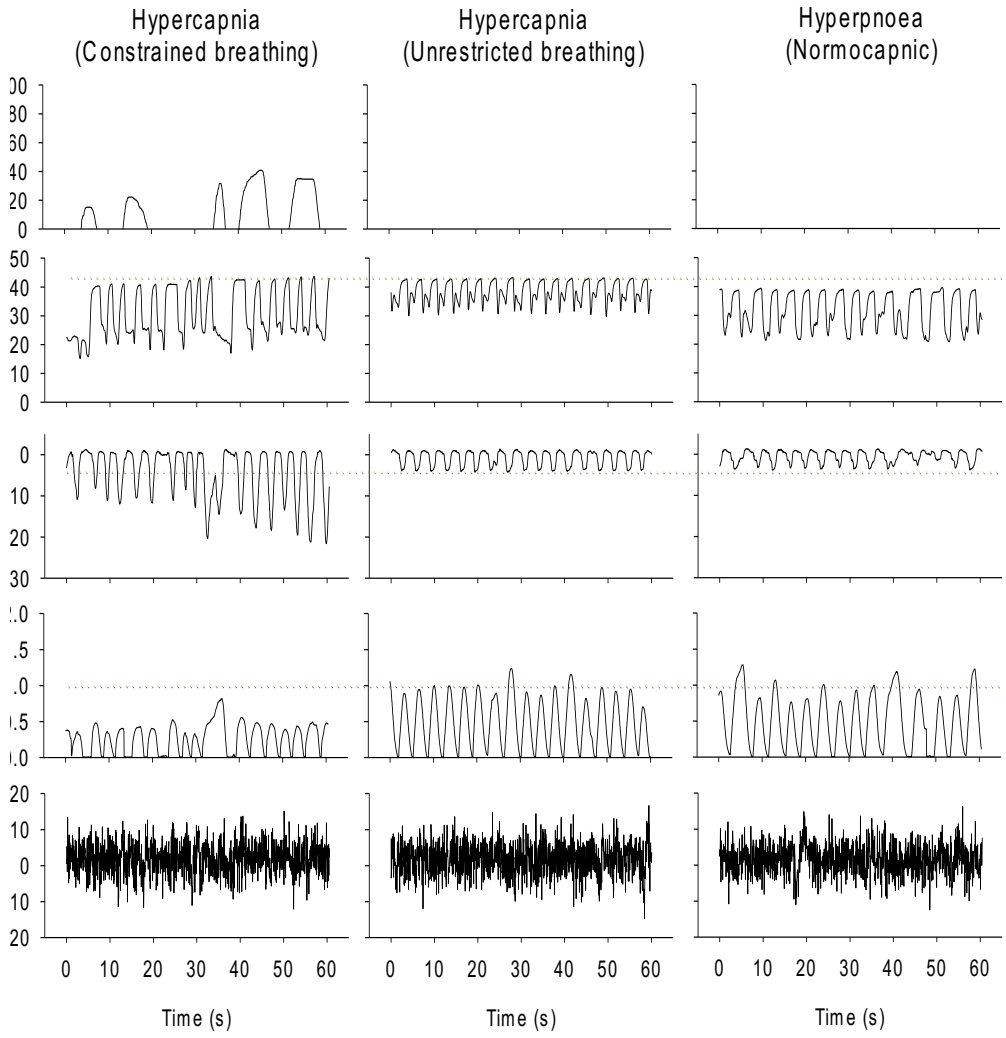


Figure 6-1 LFPs and physiological variables in the last min of each steady state.

Subjective ratings of air hunger on a 100mm visual analog scale (top row), breath-by-breath PCO_2 (second row), airway pressure (PAW; third row), and tidal volume (fourth row) in the last minute of the 4 minute steady state during Hypercapnia with constrained breathing (left column), hypercapnia with free breathing (middle column) and hyperpnoea with normocapnia (right column). The corresponding raw LFP signal recorded during this period for each condition is shown in the bottom row of panels.

The overall ventilation during the condition 3 (hyperpnoea with hypercapnia) was slightly lower than that during condition 2 (hypercapnia with free breathing) largely due to a lower breathing frequency adopted in condition 3.

However, the ventilation in both of these control conditions was substantially higher than the constrained ventilation in condition 1 (hypercapnic air hunger) Table 6-2.

Table 6-2 Average steady state levels of physiological variables during each condition

The average levels of end-tidal PCO_2 ($PETCO_2$), tidal volume, respiratory frequency (fR), overall ventilation (VE), air hunger ratings and airway pressure (PAW) in the last minute of the 4-minute steady states of each breathing condition (conditions 1 to 3). Note the degree to which the $PETCO_2$ was matched between conditions 1+2, and the degree to which ventilator variables were matched between conditions 2+3).

Condition	$PETCO_2$ (mmHg)	Tidal Volume (L)	fR /min	VE (L/min)	Air Hunger (mmVAS)	PAW (cmH_2O)
1) Hypercapnia + fixed breathing	42.7	0.44	17	7.48	26	-14.4
2) Hypercapnia + free breathing	43.0	0.97	17	16.5	0	-3.7
3) Hyperpnoea + fixed CO_2	39.4	0.92	14.7	13.5	0	-3.7

Effect of breathing conditions on LFP signal

A difference in local field potential power content was detected within the left ventral intermediate thalamus when experiencing air hunger (Figure 6-2) in comparison to the other two control breathing conditions.

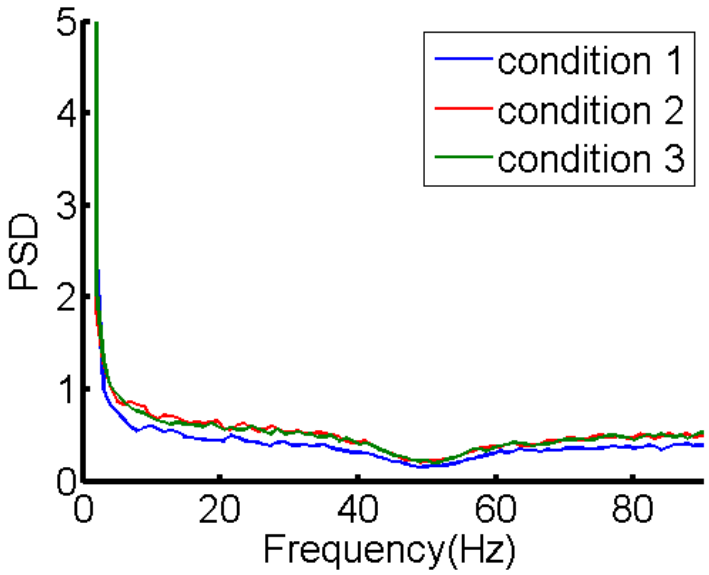


Figure 6-2 Power spectral density (PSD) of neural signal across frequencies

Condition 1, the air hunger condition, is slightly lower in power across the frequencies in comparison to condition 2 (increased CO_2 free breathing) and condition 3 (Fixed CO_2 and free breathing).

6.1.5 Discussion

6.1.6 Key results

The reduction in power across the frequencies in LFP recordings is linked to a change in neural activity around the site of the electrode. This preliminary data suggests that a reduced power of the LFP is only apparent when there is appreciable air hunger, and is not related to hypercapnia or hyperpnoea per se. This case report, therefore, has shown for the first time that a distinct neural signal from the VIM can be detected when air hunger is experienced.

Furthermore, complimentary physiological data is suggestive that the patient did experience the 3 different breathing conditions as anticipated; most notably the negative airway pressure and increased VAS rating in the air hunger condition (condition 1), in comparison to the VAS and negative airway pressure in conditions 2 and 3.

6.1.7 Wider impact

The work presented within this thesis chapter provides evidence that the VIM is directly involved in the modulation of air hunger perception. The present study shows that DBS and LFP recordings are useful and novel tools in breathlessness research and offer us additional opportunities to expand our understanding of breathlessness. Previous studies into the cerebral mechanisms of breathlessness (Banzett et al., 2000, Evans et al., 2002) have been able to comment on what neurological structures are perhaps implicated in dyspnoea. The work presented here has shown the potential for new ways to target specific nuclei within the brain. This is a move away from studying the role of whole neural structures, and instead focuses on the involvement of select nuclei.

Furthermore, as discussed at length in chapter 3, it is important to consider, in light of evidence that the VIM is an area that is implicated in breathlessness modulation, whether patients with DBS may be at an increased risk of respiratory issues due to a blunted perception of breathlessness associated with their electrode placement. Conversely, as discussed in chapter 5, this therapy may be suitable for an individual with intractable, treatment resistant breathlessness such as severe COPD.

This study is a good demonstration of using a novel approach to investigate the cerebral mechanisms of dyspnoea in a non-respiratory population. Recording neural signals in human participants was initially made possible with the development of technology such as electroencephalography (EEG) which involves the non-invasive application of electrodes to the scalp to record

electrical activity. This approach, however, has its limitations. Namely, that it is difficult to isolate where the electrical activity is coming from within the brain with any great specificity. This is due to the fact that the electrical field detected at the scalp could have come from numerous different configurations of brain activity. Furthermore, the skull being a good insulator means that the signal spreads out, making it difficult to find its centre of origin. A newer, alternative method to recording brain activity is the use of singular, or arrays of, implanted electrodes to record the activity in the extracellular space around neurons. This method has the advantage over EEG that it targets one specific cluster of nuclei, establishing a confidence in the electrical signal recorded having come from the region of interest. It does however, come with the drawback of being very invasive, as microelectrodes need to be fitted in the cortex or the nervous tissue being studied. The result of this being that this approach has not been commonly used in the research setting. With the development of DBS, recording neural patterns in human participants has become more accessible. Individuals who undergo DBS therapy often have two separate operations: (i) to implant the electrodes into the brain and attach the wires to the electrodes (ii) to secure the wires to the battery box that provides the electrical stimulation and insert said battery under the skin. During the period of time between these two operations (often several days) the wires connected to the electrodes are externalized and can be used to record local field potentials (LFPs) in the extracellular tissues, a signifier of neural activity. Involving these patients in research makes studying brain regions deep within the cortex vastly less expensive and invasive due to the electrodes already having been implanted for clinical reasons.

6.1.8 Critiques and limitations

A clear limitation of this study is that it is a case report. Recruitment can be challenging in clinical studies such as these when the pool of potential participants is low due to specific criteria needing to be met. However, it is very encouraging that the data collected in this study shows evidence for there being a distinct air hunger signal that can be recorded. For the study that was presented in chapter 3, it was calculated that 16 patients, acting as their own controls, were required in order to be able to draw definitive conclusions.

Therefore, if the findings reported here can be confirmed with a larger cohort study of n=16, this would be a fresh insight into the specific nuclei within those brain regions implicated in modulating dyspnoea.

6.1.9 Conclusion

This is the first pilot study to use VIM DBS electrodes and LFPs to investigate the neural mechanisms responsible for the modulation of air hunger perception. Results from this study are not conclusive as the study suffered from low recruitment rates, however, it has provided a possible insight into the specific cortical nuclei involved in breathlessness perception.

6.2 Case study 2: Lesion deficit approach

The insular cortex is a region of the brain that has been implicated in breathlessness in healthy volunteers by multiple neuroimaging studies (Evans et al., 2002, Banzett et al., 2000). This activation in these areas could reflect increased neuronal activity as a result of feeling breathless, however, areas essential for functional dyspnoea perception may in fact be in a different location not contained within the imaging signal. The activation in the insular cortex as captured by these imaging studies could be co-incidental rather than essential for the perception of dyspnoea. An interesting alternative method of studying the role of the insular cortex on breathlessness perception is to use the lesion deficit approach. This is to say, that patients with damage to areas activated in the imaging studies provide a clinical model with which to distinguish essential, from co-incidental, activations. These lesions can come in multiple different forms including tumours, non-malignant growths, and tissue resection, however, it is stroke studies that have seemed to focus on the insula and its association with breathlessness.

Work conducted with patients with heart failure and exertional dyspnoea who had suffered a stroke affecting the insular cortex found that despite a statistically significant portion of the cohort having pulmonary dysfunction, a minority of participants reported dyspnoea at rest (Liaw et al., 2016). However, the clinical investigators observed consistent signs of breathlessness throughout patient interviews and as a result, have hypothesized that this discordance between patient and clinician reports might be because of an impaired perception of dyspnoea due to stroke damage. Furthermore, central periodic breathing during sleep, which is when clusters of breaths are

separated by intervals of not breathing, have been reported in patients with unilateral stroke affecting the left insular cortex.

A challenge with studies that focus on stroke however, is that stroke damage tends to not be localised to one specific area, and as a result of this, it remains difficult to tease apart whether it is the insular cortex damage that is the key to the observed blunted perception of breathlessness. However, what these studies do highlight is that the lesion deficit approach can provide insight into the role of specific structures that might not be learnt through imaging alone, and perhaps more importantly for a clinical perspective, can provide insight into what happens if that area is damaged.

What follows is a case report of a patient with low grade glioma located in the insular cortex. Low grade glioma is a type of non-cancerous brain tumour that develops and progresses very slowly but can still be very disruptive. As such, if feasible, it is usually recommended that the patient have the growth removed.

The aim of this study was to investigate whether low grade glioma effects breathlessness perception.

6.2.1 Methods

Clinical details of the patient

This study was approved by the Oxford Regional Ethics Committee (Study number 14/SC/0231 study title" Dyspnoea perception in stroke and glioma patients).

The patient was a 43-year-old right-handed male (height 198cm; weight 120kg) with recently diagnosed glioma affecting the insular cortex of the right

hemisphere. He reported smoking 10 cigarettes a day on average, but there was no medical history of heart or lung disease. There was a familial history of heart failure. He takes 125mg of Lamotrigine and 2mg of Diazepam twice a day and had taken his normal dose on the morning of the day of testing.

The participant provided written informed consent with the knowledge that they were participating in a study investigating breathlessness. They attended the laboratory at the John Radcliffe hospital for 2 hours. It was confirmed by the participant's clinical team that he possessed the cognitive and verbal abilities to understand the nature of the test. A physician was present for the duration of testing and no adverse events occurred.

6.2.2 Protocol

Respiratory function testing

Various respiratory function tests were initially performed to ensure that lung function and respiratory control mechanisms were unaffected in this patient. This included simple spirometry from which forced expiratory volume in 1 sec and the forced vital capacity were determined.

A breath holding test was conducted which measured how long they could hold their breath at functional residual capacity, and what level their end-tidal CO_2 reached upon exhalation (i.e. breakpoint PCO_2). The participant also completed a hypercapnic ventilatory response test. This involved increasing the inspired CO_2 to the same level as that in the incremental air hunger test (see below) but allowing unrestricted ventilation.

Incremental air hunger test

An incremental air hunger test lasting 10 minutes was conducted. Inspired CO_2 was increased every minute by an amount that raised end tidal PCO_2 by 1.3mmHg per minute. ventilation was restricted to the participants resting level.

Throughout the trial the participant used a visual analogue scale (VAS) to rate their air hunger. Breathlessness was assessed using the Dyspnoea-12 questionnaire which is a validated multidimensional dyspnoea instrument. This questionnaire was administered at the end of each trial. Items on the questionnaire were randomised for each trial. See chapter 2 for a discussion as to the items included in the D12 and the validity of this questionnaire.

The participant also completed an in-house debrief questionnaire which invited volunteered comments followed by a forced choice of respiratory descriptors from a pre-set list. The list of respiratory descriptors included those commonly used to describe air hunger and others to describe sense of breathing work and effort. The patient selected the items that they felt fit the overall sensation they had experienced. This is in line with the debriefing method described by Lansing et al., (2009 review).

6.2.3 Data processing and analysis

Incremental air hunger test: Continuous recordings of PCO_2 recorded at the mouth throughout the incremental test were graphically presented alongside the 15 s ratings of air hunger on the VAS. The breath by breath tidal volume and airway pressure tracings were also included in this graphical presentation to demonstrate that ventilation was constrained at the baseline level and to see if

any changes in air hunger ratings are reflected in how much the patient sucked against the ventilatory constraint.

D12 questionnaire: The total, physical, and emotional scores for the D12 were expressed as a % of the maximum scale. Because this is a case report involving a single patient, no statistical analysis was conducted. Instead, the results will be outlined in a descriptive form.

6.2.4 Results

The participant had a Forced Expiratory volume in 1s (FEV1) of 4.53 (95% predicted). The participant held their breath for 24 seconds during the breath holding task with an end-tidal CO_2 of 37mmHg at the beginning of the task and an end-tidal PCO_2 of 47mHg at break point.

Incremental air hunger test

For the incremental air hunger test the PCO_2 was raised from 41mmHg to 52mmHg over a 9-minute period. The participant consistently rated less than 3mm over the course of the ramp test (mean rating± 0.7±1). Ventilation was fixed at 1.01L for the duration of the trial. (Figure 6-3)

Hypercapnic ventilatory response test

During the hypercapnic ventilatory response test the participant's tidal volume increased from 1.01L when CO_2 was not elevated to 1.78L with an elevated end tidal PCO_2 of 47mmHg. The VAS did not increase by more than 1.3mmVAS above 'none'. Airway pressure increased throughout the test but did not rise above -6cmH_2O (Figure 6-4).

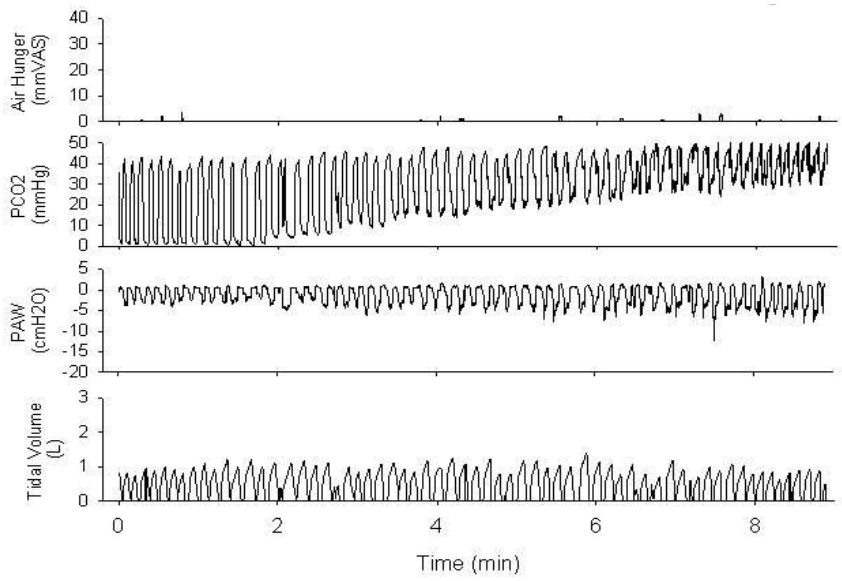


Figure 6-3 Incremental air hunger test

Continuous recordings of PCO_2 (second panel), airway pressure (PAW; third panel) and tidal volume (bottom panel) throughout the 9-minute period of hypercapnia with constrained breathing. Note ratings of air hunger did not rise above 1.3 mm of the VAS (Top panel)

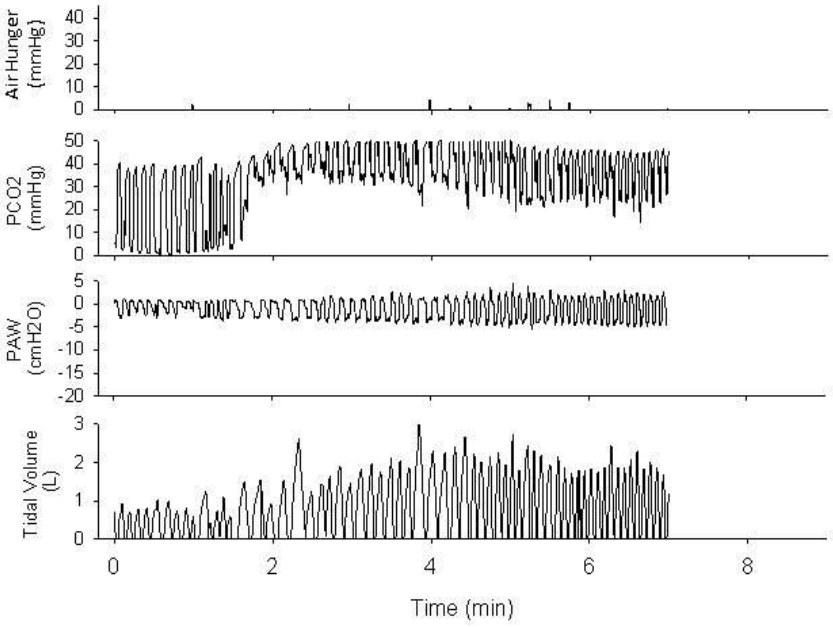


Figure 6-4 Hypercapnic ventilatory response

Continuous recordings of PCO_2 (second panel), airway pressure (PAW; third panel) and tidal volume (bottom panel) throughout the 9-minute period of hypercapnia with constrained breathing. Note ratings of air hunger did not rise above 1.3 mm of the VAS (Top panel)

D12

For both breathing trials the participant scored 2.78% of the total score on the D12. The only item being ticked for all trials was 'my breathing requires more work'. This item is related to the physical component of breathlessness often referred to as 'work and effort' as oppose to air hunger. The participant commented that he ticked this box because of him not being used to breathing through a mouthpiece and so he was having to focus a lot more on his breathing than he normally would.

6.2.5 Discussion

6.2.6 Key findings

The participant studied did not appear to feel air hunger in response to increased CO_2 in either the incremental air hunger test or the steady state air hunger test. This conclusion is based on the very low VAS ratings given throughout both the breathing trials. In general, an increase in end tidal PCO_2 of less than10mmHg is sufficient to make a person feel extreme breathlessness (Banzett et al., 1996). However, in this instance an increase of 11mmHg end tidal PCO_2 only elicited a very mild response. This conclusion is further supported by the minimal negative airway pressure that the participant created. Unpublished data from within this lab has shown that producing high amounts of negative airway pressure is a consequence of experiencing air hunger (see methods chapter). This negative pressure is generated by actions such as sucking hard on the mouthpiece when the bag is empty in an attempt to draw more air into the lungs.

During the hypercapnic ventilatory response test the participant did increase their tidal volume by 0.77L suggesting that they had an intact reflex ventilatory drive from the brainstem in response to chemoreceptor stimulation. However, there did not appear to be any urge to breathe when the ventilatory response to hypercapnia was constrained implying that a deficit in air hunger perception is located at the cerebral level –most likely the insula cortex which is impacted by the presence of the glioma. Interestingly, the participant volunteered the comment that he was aware that something felt different about his breathing, but it was not bothering him. This suggests that it is the affective domain of breathlessness that is predominantly diminished again implicating the insular cortex which is a part of the limbic system known for its functional link to affective valence.

The breath-holding data however is potentially contradictory to the main finding. This is because the patient appears to have an appropriate breath-hold response both in terms of breath hold time and in terms of the breakpoint level of PCO_2. It is presumed that the urge to breathe plays a role in triggering the breakpoint of the breath-hold and since the patient appears to have diminished perception of air hunger one reasonably expects a raised breath hold time and breakpoint CO_2 reflecting increased tolerance to the combine hypercapnia and hypoxaemia. It is interesting to speculate that a factor other than the urge to breathe is triggering the breath-hold breakpoint in this patient. This is consistent with the fact that the participant volunteered that he was not used to breathing through a mouthpiece and was having to focus a lot more on his breathing than he normally would. Reading into this comment, it could suggest

that other cues such as the sense of breathing work or effort may be compensating for the lack of an urge to breathe in determining the breakpoint of the breath-hold.

This case report has demonstrated that unilateral lesion damage is sufficient to diminish the affective component of dyspnoea. It is interesting that it does not appear that other pathways have been reorganised so as to compensate and maintain accurate air hunger perception. It would be of benefit to follow this patient over time to identify whether the air hunger perception is permanently altered by the tissue damage.

This finding also highlights the role that imaging work can play in experiments involving clinical models (Price and Friston, 2002). In this instance, future work could include the comparison of structural brain imaging pre and post-surgery to identify whether those suffering from blunted dyspnoea response have a damaged area in common which is still healthy in those with a normal perception. Furthermore, tractography imaging, which shows white matter pathways in the brain, could be taken on multiple occasions over a set period alongside air hunger testing. Therefore, if a person's perception altered over time, it would be possible to link these changes in perception to the reorganization of white matter tracts captured using tractography.

The findings of this case report support functional brain imaging studies which have found the insula to be active when inducing breathlessness in healthy volunteers (Banzett et al., 2000, Evans et al., 2002). It has been reported previously that insula damage in stroke patients contributes to the loss of the affective component of perception in unpleasant sensations such pain in stroke

victims (Ploner et al., 1999). Therefore, the results published here add further weight to the argument that a functional insular cortex is vital to accurate detection and perception of unpleasant stimuli.

6.2.7 Wider impact

As well as providing new insights into the cerebral mechanisms of breathlessness, this case report has clinical relevance for patients who are diagnosed with low grade glioma of the insular cortex. The effect of neurological trauma on unpleasant sensation perception is a neglected area currently, but it is necessary to better improve our understanding for the sake of patient quality of life. The risk of having a reduced breathlessness perception is that the patient will not notice a decline in respiratory help and is therefore, less likely to seek medical advice at an early stage. This secondary condition could place strain on an already vulnerable person. An increase in sudden death has been noted in patients with insular-glioma (Sanai et al., 2010) and it could be speculated that this could be due to a blunted perception to unpleasant sensation such as pain or dyspnoea, or other abnormalities, as a result of the impact of the tumour.

This finding emphasises the need for neuro-oncology surgeons to be made aware of the possible adverse effects of insular-glioma on dyspnoea perception and to incorporate risk management of blunted dyspnoea perception into their practice. During surgery to remove low grade glioma the patient remains awake and assessment of autonomic before, during and after surgery is routine practice. Therefore, checking for blunted dyspnoea perception would be a test that could be included into the battery in order to make clinicians aware of any

patient who may be at a higher risk of developing secondary health complications due to loss of perception.

6.2.8 Critiques and future directions

The main limitation of this case report is that it only assesses the individual's dyspnoea response before their glioma removal surgery. Therefore, a part of the story is missing. The results described here indicate that the participant does have a blunted dyspnoea perception, and with complimentary lung function testing, the assumption could be made that this abnormal result is due to the tumour. However, what happens to breathlessness sensitivity post-surgery remains unknown. If post-operatively, dyspnoea perception remains blunted, a possible interpretation could be that the blunted perception is not due to the tumour pushing on a region involved in dyspnoea. An alternative explanation is that the surgery has not been able to remove enough of the tumour projections in the insular cortex. Conversely, if breathlessness perception returns to a level similar to that seen in healthy volunteers (Banzett et al., 1996) in experimentally induced air hunger experiments, the conclusion could be drawn that the tumour was impacting breathlessness perception, but once that pressure was removed, the surrounding tissue could return to its normal function. It was the original aim of this case report to repeat the protocol after surgery. However, due to clinical complications the participant had his surgery delayed by several months. With future participants the protocol would include pre and post-operative testing.

This case report is by definition, of only one participant and therefore, only tentative conclusions can be drawn. In order for a definitive study to be

conducted, 16 pre-operative insular-glioma patients would need to be recruited with an equal number of healthy controls. If the aim was to study insular-glioma patients pre and post operatively, with them serving as their own controls, 16 would also need to be recruited. Throughout recruitment, 3 individuals who initially expressed an interest in the study later declined to participate citing stress about their diagnosis or about their upcoming operation as the reason. This suggests therefore, that studies of this nature which rely on patients participating before receiving treatment, will suffer from a high attrition rate. In cases such as these, sensitivity needs to be had with regards to recruitment and approaching prospective participants. An example of this would be for the clinical team to be selective about who they introduce the study too, making sure to not overwhelm those who appear more vulnerable.

6.2.9 Conclusions

The findings presented in this case report suggest that unilateral low-grade glioma affecting the insular cortex may cause a blunting of dyspnoea perception. The consistently very low VAS and D12 rating despite an increase of end tidal PCO_2 of over 10mmHg is suggestive of the patient suffering a reduced perception to the unpleasant sensation of air hunger. However, because of a lack of information about the participant's post-operative air hunger response, conclusions about the effect of the tumour cannot be drawn. An alternative explanation for example, may be that the participant's dyspnoea perception may have pre-existed before the development of the tumour and went unnoticed by the patient. Future studies should aim to recruit more participants

with the same condition and to repeat the same battery of tests before and after surgery. There is the possibility that a tumour affecting the insular cortex may cause the development of respiratory issues to go unnoticed by the individual until they reach an advanced stage that requires medical intervention. This needs further investigation.

7 Discussion

Within the field of dyspnoea research, a large effort has been made to try to develop therapeutic options for intractable breathlessness when the underlying pathology cannot be cured. It has been difficult however, to find an appropriate therapy for a sensation that is so broad in terms of the symptoms and intensity that can be experienced. Some options have been criticised for having varying levels of effectiveness across patients, for example inhaled furosemide (Grogono et al., 2019), and others such as opioids for safety concerns (Grogono et al., 2019).

Ultimately, a more comprehensive understanding of the cerebral mechanisms behind dyspnoea is needed for us to be able to develop targeted therapeutics that work effectively, safely, and consistently. This thesis contains novel methodology for studying dyspnoea in neurological patient populations and presents data which contributes to our understanding of the neural mechanisms involved in breathlessness. Furthermore, this approaches feeds on the recent emphasis on multi-morbidity and indeed a specific chapter on dyspnoea in neurological patients with co-respiratory conditions is included. The discussion to follow appraises the main findings of this thesis, and how the findings from multiple studies fit and complement each other. How these novel findings fit within the established field of dyspnoea will also be discussed, as well as suggestions for future research into breathlessness perception.

7.1 Overview of major findings

7.1.1 The effect of deep brain stimulation on breathlessness perception

The development of deep brain stimulation (DBS) had an important impact on the clinical management of multiple neurological disorders including Parkinson's disease, chronic pain, multiple sclerosis (MS) and epilepsy. In addition to this, it also presented a unique opportunity for researchers to expand beyond the question of whether whole brain structures are implicated in breathlessness work; instead, focusing on whether specific nuclei are involved in dyspnoea. This thesis presents definitive evidence for the first time that suggests that DBS of the motor thalamic region is associated with a significant relief of experimentally induced air hunger in patients with bilateral electrodes implanted in the motor thalamus. The extent of the relief on average, exceeded the accepted minimally clinically important difference (MCID) of 9.7% on the Visual analogue scale (Johnson et al., 2013). This has both a research and clinical implication. Firstly, this study has demonstrated that specific nuclei within the diencephalon are involved in the modulation of breathlessness perception. This finding is complimentary to the existing neuroimaging data but is able to take us further in our efforts to pinpoint the precise neural mechanism associated with intractable dyspnoea. Secondly, from a clinical point of view, the data indicates that a patient with intractable breathlessness would detect noticeable relief from their symptoms. This means that DBS of the motor thalamus could potentially offer therapeutic relief from intractable dyspnoea common in patients with COPD, late stage cancers, and heart disease. This

suggestion is further supported by the observations of chapter 5 that patients with COPD and DBS electrodes for disordered movement noticed a reduction in breathlessness overall, with electrodes turned ON in comparison to their electrodes being turned OFF, thereby offering additional benefits to this specific cohort of multi-morbidity patients. Several patients within the COPD cohort mentioned that they viewed this as a positive side effect of their treatment.

However, there is a secondary clinical implication of this discovery to be considered. It could be of concern that neurological patients without respiratory disease who receive DBS within the VIM are vulnerable to suffering a reduced perception of breathlessness. This blunted perception could contribute to the patient having respiratory issues which go unnoticed and are therefore, not treated during the early stages of the condition. This could lead to patients presenting at an advanced stage, which could have an impact on their clinical outcomes. As such, it is important to consider informing patients who have DBS to monitor their respiratory health more stringently, and to ask for help from medical professionals quickly if any issues develop. Counter-intuitively, it is the patients who appear to be doing well that are potentially at greatest risk.

The precise mechanism behind why DBS of the motor thalamus can relieve experimentally induced air hunger remains unclear. However, a possible explanation is that DBS of the thalamus may block the ascending signals that report the need to breathe. This is supported by clear evidence in one patient showing that there is a shift in threshold for experimentally induced air hunger

to the right, with no change in slope. This could not be confirmed among the whole group because of the limited number with reliable slope measurements.

A mismatch between the signals reporting the need to breathe and the signals reporting the current ventilation level is considered to be the mechanism behind air hunger (Chen et al., 1992). Further support for this comes from chapter 5 which focused on DBS of the motor thalamus in patients with chronic obstructive pulmonary disease (COPD). Individuals with COPD report air hunger as the most prevalent symptom they experience. Therefore, the fact that they felt relief when stimulation was turned ON suggests that it is the motor thalamus having a 'phantom lesion' which is blocking the signals.

In addition to using DBS to create phantom lesions, this thesis also included a case report (section 6.1) which outlines the possibility of using the DBS circuitry to record neural signature of air hunger originating from the VIM. The first demonstration of such a signal is provided in the case report in section 6.1. This signal (an overall reduction in power content of the frequency spectrum of the local field potential) was specifically related to air hunger and was not present during other control breathing conditions that do not cause air hunger. This further corroborates the findings in chapters 3 and 5 that the thalamus is involved in the perception of air hunger. If there is a way of recording this signature non-invasively from surface recordings, this could elicit a new wave of experimental opportunities to unravel the cerebral mechanisms of dyspnoea without relying on patients undergoing surgical interventions.

In sharp contrast to the findings in chapter 3 and 5, chapter 4.1 presented data that showed stimulation of the STN caused an increase in the overall

breathlessness experienced by the participant. The STN that resides relatively close to the motor thalamus and is a region that has been shown to have strong connections with the limbic system including the anterior cingulate cortex. It is intriguing to speculate that the motor thalamus preferentially connects to regions involved in relief of air hunger whereas the STN connects to regions involved in generating air hunger. It could be proposed therefore, that these key areas are disrupted by DBS, thus leading to an increase in dyspnoea. This finding has its own clinical implication. It could be suggested that a potential contraindication for DBS of STN for Parkinson's disease has been found. This is especially important when placed into the context of increasing evidence that respiratory dysfunction is present in some individuals with Parkinson's disease.

7.1.2 The effect of neurological damage on breathlessness

Breathlessness has been an under investigated non-motor symptom of Parkinson's disease. Recently, evidence has been produced that supports the statement that a proportion of individuals with Parkinson's disease suffer breathlessness (Baille et al., 2019). Within chapter 4 of this thesis, a postal survey was conducted to try to quantify the level of breathlessness that individuals with Parkinson's disease have in their daily life. The results of this study complement the current literature (Baille et al., 2019, Witjas et al., 2002) which showed that Parkinson's patients do report breathlessness when asked by a clinician in a hospital setting. In the study within this thesis, 21 out 33 participants (63%) recorded experiencing breathlessness at rest during the 3-day trial. The questionnaire data collected for this thesis is unique in that it uses a validated questionnaire (D12 questionnaire) that focuses on sensations of

breathlessness as opposed to asking the closed question had patients experienced breathlessness in the past month. Secondly, unlike previous studies in this area, it asked participants to complete it in their own home over multiple days, as opposed to in a clinical setting. These additional components mean that the data collected is more likely to be an accurate snapshot of what the participants experience in their daily life. The implication of this result is that neurologists should consider the effect of neurological disease on other domains such as bodily perception, including the perception of dyspnoea. By making a concerted effort to ask patients with Parkinson's disease whether they are experiencing dyspnoea, it gives clinicians the best chance of understanding how prevalent this non-motor symptom is, and possibly how to manage this symptom to improve the quality of life of their patients. It also gives researchers the opportunity to learn more about the perception of dyspnoea and the effect of abnormal neural pathology on it.

Also presented in this thesis was a case report focused on low grade glioma affecting the insular cortex (chapter 6.2). Data from this study suggests that unilateral tissue damage to the insular cortex is sufficient to blunt the perception of experimentally induced air hunger. Since this patient had the glioma on the right insular, this is consistent with the functional brain imaging studies that suggest the right insular cortex is the seat of air hunger perception (Banzett et al., 2000, Evans et al., 2003). In healthy volunteers, an increase of inspired CO_2 of more than 10mmHg is sufficient to get them to rate the maximum level of breathlessness on a visual analogue scale (VAS) for the majority of individuals (Banzett 1996). However, in this case report, it can be

seen even with an increase in inspired CO_2 of over 10mmHg, the patient rated on average 1.3mm on the VAS. This data is just a case report but is highly suggestive that the right insular cortex plays a key role in accurate breathlessness perception, and tissue damage to this region significantly impacts this ability. It is also poignant that the patient specifically volunteered the information that he was aware of breathlessness but it was not bothering him, suggesting that it is the affective dimension that is specifically affected.

7.2 Critiques and limitations of the work within this thesis

7.2.1 Limited sample size

Studies involving neurological populations can potentially struggle with recruitment. This is due to multiple factors. Firstly, the population that fit the criteria for the study may not be very large. An example within this thesis is the work conducted in chapter 5 involving patients with DBS electrodes in the VIM and with a comorbidity of COPD. This narrow inclusion criteria dictated the number of participants that were able to be recruited. A second reason why studies using neurological populations can struggle is that some of these individuals will be vulnerable and hesitate to commit to research for fear of it affecting their condition. They are undergoing major surgical procedures which are profoundly life changing. This was something that was relevant to the case report focused on the glioma patient in chapter 6.2. Because of these concerns, many may decline to participate and others may initially agree only to withdraw their consent during the protocol. It is important that the patient's autonomy is respected at all times. With this in mind it is necessary for

researchers to have realistic expectations about what can be achieved when using vulnerable populations.

7.2.2 Variability across the population

When working with a patient population, a potential difficulty is the variability in medication between patients in the cohort. This was a challenge that the work within this study faced. It is ethically ambiguous to ask patients to withhold their medication due to the intense side effects that neurological patients can face if they miss a dose of medication. The consequence of this however, is that medication becomes a potential cofounding factor. An alternative approach to this limitation would be to include medication requirements in the inclusion criteria. This however, presents its own challenges. With regards to the studies involving patients with Parkinson's disease especially, (chapter 4) it would be difficult to specify medication and still recruit sufficient numbers of participants. This is because the pharmacological management of Parkinson's disease is variable, with individuals sometimes taking years to find a tailored drug regime that suits them. Only two participants out of 33 who responded to the postal survey in chapter 4.2, reported the same medication regime.

An additional source of variability comes from electrode placement. All participants with electrodes had them located in either the motor thalamus, or the STN. However, due to small anatomical differences between individuals, the exact location of the electrodes in space may vary. These slight variations in stimulation may contribute to individual differences in the air hunger response. On the other hand, however, it would be challenging to form a cohort whose

electrode placement were all in the same anatomical location. One possible resolution would be to compile scans of each participants brain so as to verify electrode location. This would make it possible to better quantify the deviation between participants. Unpublished preliminary data from the clinical neuroscience research group at John Radcliffe Hospital suggests that there was no difference in electrode placement for the one individual who showed an increase in air hunger with VIM DBS in chapter 3.

7.2.3 Practice sessions

One final caveat of this study is the limited practice each participant had before completing the experiments that involved a breathing apparatus (chapters 3, 5, 6). The protocol can be challenging for the participant to follow, especially if the sensation of air hunger is novel to the participant. The complexity of the protocol has the potential to leave participants feeling overwhelmed or misunderstanding instructions. This in turn can cause the data acquired to be unreliable. The best way to manage this would be to allow the participant to have multiple practice sessions. This would allow them to master the protocol before data collection began. Unfortunately, due to the short time the patients are available for testing, this was not possible. In an attempt to account for the limited practice time, participants were encouraged to ask questions and were prompted during the breathing test itself if they were not completing the test correctly. Furthermore, as each participant is their own control in all of the studies presented, any differences between ON and OFF state are unlikely to be accounted for by lack of practice.

7.3 Future directions

7.3.1 Further work with lesion deficit models

Lesion deficit models have been vital to the understanding of which brain regions are involved in dyspnoea. This thesis has included a case report (chapter 6) which showed that the unilateral presence of a low-grade glioma was seemingly sufficient to alter the perception of experimentally induced air hunger. This finding fits with neuroimaging data presented by (Banzett et al., 2000) that showed the right insular cortex to be active in humans during breathlessness. Future work would benefit from conducting a large cohort study to investigate whether this finding is (i) replicable in a larger population of individuals with glioma of the insular cortex and (ii) to investigate whether this altered perception remains after surgery. The additional use of diffuse tensor imaging techniques (DTI) coupled with the knowledge of the regions of interest identified by the functional brain imaging studies, would also make it possible to investigate the white matter cortical tracts that are implicated in breathlessness generation and relief. If after surgery the blunted air hunger perception is maintained, the focus would be on which white matter fibres have been destroyed by the lesion and possibly by the tissue resection that has led to the blunted perception. Alternatively, if the perception of air hunger returned after surgery to remove the glioma, it would be possible to use DTI to look at whether neuroplasticity has occurred to the extent that the brain has managed to recover the cognitive deficits that the damage caused. Currently, there is no study that has included breathlessness perception in their patients' outcomes pre and post-surgery. Patients with low grade glioma are good candidates for

this type of work, because it is a condition that tends to present in younger patients who are less likely to have comorbidities that could be cofounding factors.

An additional lesion deficit model that could be utilised to understand dyspnoea is using patients with stroke affecting the insular cortex. Patients with ischemic stroke of the insular cortex would be good candidates to understand whether tissue damage in this brain region causes blunted dyspnoea perception. This study would require the use of age and sex matched healthy controls. An additional follow up to this project could be to follow the patients and healthy controls over a long period of time and record the frequency of respiratory related health problems that both the cohorts suffer. It could be hypothesized that with a blunted perception of breathlessness, individuals who have had an ischemic stroke would suffer a higher frequency of respiratory events because they are less likely to notice respiratory symptoms until they are quite advanced. It is important however, to acknowledge the limitations of this model. Most notably, that the location and volume of the lesion caused by the stroke can vary greatly between patients. Therefore, it would be sensible to combine this lesion deficit model with structural neuroimaging techniques. This would make it possible to assess whether the patients who had had a stroke of the insular cortex and suffered from blunted perception of experimentally induced air hunger had a common region of tissue damage.

A follow on from these two suggested lesion deficit models is using these same neurological populations to assess whether it is only the perception of experimentally induced air hunger that is altered, or whether work and effort is

also affected. Adding in a work and effort test to the protocol for the case study on the patient with glioma was initially considered. However, it was concluded that due to limited time constraints, this would add a layer of complexity to the study that was not feasible at that time. Future studies that focus on this area should be aware that these patients can be vulnerable and may be unlikely to tolerate a very lengthy protocol. It may be advisable therefore, to separate the protocols into different testing sessions on different days.

7.3.2 The use of transcranial magnetic stimulation (TMS)

Future studies may be able to use TMS as a viable non-invasive alternative to stimulating the motor thalamus with implanted electrodes. This would have the distinct advantage of being able to use healthy volunteers which means it would be more feasible to recruit large cohorts of people. Currently however, this line of research is limited by TMS being unable to target some structures in the brain with sufficient specificity and power. This is increasingly problematic when trying to reach sub-cortical areas which are deeper in the brain such as the thalamus which resides in the limbic system. In the future, it may be possible to manipulate several induced magnetic fields so that they interact in a way which will produce targeted focal and reversible lesions in the motor thalamus. This would be fortuitous for future research focused on the cerebral mechanisms of dyspnoea.

7.4 Concluding remarks

The key messages from this unique investigation of neurological patients to better understand cerebral mechanisms of breathlessness are as follows:

- Motor thalamic nucleus has a role in the modulation of air hunger. It may be a conduit for the ascending dyspnoea signal that can be reversibly blocked by DBS.
- The STN on the other hand appears to have a role in generating breathlessness possibly via its extensive connections to the limbic system identified as the seat of breathlessness perception in functional brain imaging studies.
- Together the above findings will help to start the process for unravelling the neural network for breathlessness perception as has been done for cerebral mechanisms of pain. How this might tie in with recent ideas about the Bayesian brain (in terms of discord between patient expectations of ascending sensory signals and the actual signals) is yet to be seen.
- New data is provided on the prevalence of dyspnoea as a non-motor symptom in Parkinson's disease which confirms the importance of monitoring this symptom in these patients. The data presented as a whole in this thesis supports the need to monitor breathlessness more generally for neurological populations.
- A case report has provided evidence for complete elimination of the affective domain of breathlessness by glioma of the right insular cortex further enhancing the importance of the limbic system in perception of dyspnoea.

- A second case report has suggested that it is possible to find a neural signature specific to dyspnoea that can be used in future investigation of the cerebral mechanisms of dyspnoea.

The novel approach adopted in this thesis to investigate cerebral mechanisms of breathlessness has corroborated existing evidence presented by function brain imaging studies and provided new data to (i) begin to unravel the neural network for breathlessness perception in the brain and (ii) identify new specific nuclei to target for dyspnoea relief which is the ultimate goal.

Overall, the field of dyspnoea is undergoing an exciting period of discovery which is underscored by the findings reported in this thesis.

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