Understanding Autonomic Control via Human Deep Brain Stimulation

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A thesis submitted in partial fulfilment of the requirements of the University of Westminster for the degree of Doctor of Philosophy

December 2021

Abstract (300 words)

The Central Autonomic Network (CAN) consists of higher cortical areas, basal ganglia, and brainstem areas that are important in the control of the autonomic nervous system (ANS). This thesis concentrates on the control of the respiratory and cardiovascular systems both alone and in combination in the context of exercise. Deep Brain Stimulation (DBS) is a type of therapy in patients in which electrodes are inserted into the brain to treat neurological disorders such as Parkinson's disease. The presence of electrodes allows the study of the effects of stimulation of components of the CAN, as well as measurement of electrical activity (local field potentials (LFPs)) to assess whether a nucleus is integral to a specific change in autonomic output. The sum of my work outlined in this thesis demonstrates that common DBS targets such as subthalamic nucleus (STN) and pedunculopontine nucleus (PPN) alter both cardiovascular and respiratory control. Furthermore, these changes have clinical implications not previously highlighted. This includes the relief of breathlessness for some nuclei (such as the motor thalamus) and induction of breathlessness for others (such as STN). In addition to clinical implications, insights are provided into the 'central command' system of autonomic control in the brain, such as the role of the anterior cingulate cortex (ACC) in the cardiovascular response to intermittent exercise. Besides advancing understanding of the regulation of these autonomic processes, this work has also directly resulted in first in-human clinical trials of DBS for the treatment of autonomic symptoms of multiple systems atrophy.

Acknowledgements

I would like to thank my supervisors, Dr Bradley Elliott, and Dr David Gaze. Their guidance and support have been paramount in my personal development during this work and in forming the thesis. Dr Elliott in particular has been helpful, highly responsive, and encouraging at all times.

I would also like to thank the University of Westminster for allowing me to take on this PhD by publication and providing a reduced fee in the first year related to the Covid pandemic.

I would like to thank all of my co-authors, particularly students but also colleagues at the University of Oxford who have provided advice and support and of course helped perform the studies that are integral to the work.

I would like to thank Professor Tipu Aziz from the University of Oxford (and one of my colleagues) who encouraged me to apply for a PhD by publication in the first place. He has been my mentor for most of my academic career and indeed supervised my MD degree in 2005-2007.

Finally, I would like to thank my wife, Caroline, and sons (Isaac, Benedict and Dominic) for supporting me with the evenings spent writing the thesis.

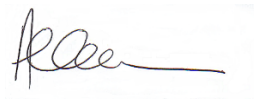
Author's declaration

I declare that the present work was carried out in accordance with the Guidelines and Regulations of the University of Westminster. The work is original except where indicated by special reference in the text.

The submission as a whole or part is not substantially the same as any that I previously or am currently making, whether in published or unpublished form, for a degree, diploma or similar qualification at any university or similar institution.

Until the outcome of the current application to the University of Westminster is known, the work will not be submitted for any such qualification at another university or similar institution.

Any views expressed in this work are those of the author and in no way represent those of the University of Westminster.

Signed:  **Date:** 22nd July 2021

Contents

List of published papers related to this thesis.

1. Hyam JA, Brittain JS, Paterson DJ, Davies RJ, Aziz TZ, **Green AL**. Controlling the Lungs via the Brain: a Novel Neurosurgical Method to Improve Lung Function in Humans. *Neurosurgery* 2012 70(2): 469-78, doi: 10.1227/NEU.0b013e318231d789
2. **Green AL**, Debrah E, Roy HA, Rebelo P, Moosavi SH. Letter to the editor: Thalamic deep brain stimulation may relieve breathlessness in COPD. *Brain Stimul*. 2019 12(3):827-828. doi: 10.1016/j.brs.2019.02.019.
3. Chalif JI, Sitsapesan HA, Pattinson KT, Herigstad M, Aziz TZ, **Green AL**. Dyspnea as a side effect of subthalamic nucleus deep brain stimulation for Parkinson's disease. *Respir Physiol Neurobiol* 2014; 192: 128-133, doi: 10.1016/j.resp.2013.12.014
4. Hyam JA, Wang S, Roy H, Moosavi SH, Martin SC, Brittain J-S, Coyne T, Silburn P, Aziz TZ, **Green AL**. The pedunculopontine region and breathing in Parkinson's disease. *Ann Clin Transl Neurol* 2019 6(5):837-847. doi: 10.1002/acn3.752
5. Sverrisdóttir YB, **Green AL**, Aziz TZ, Bahuri NF, Hyam J, Basnayake SD, Paterson DJ. Differentiated Baroreflex Modulation of Sympathetic Nerve Activity During Deep Brain Stimulation in Humans. *Hypertension*. 2014 63(5):1000-10, doi: 10.1161/HYPERTENSIONAHA.113.02970. Epub 2014 Feb 10
6. Pereira EA, Lu G, Wang S, Schweder PM, Hyam JA, Stein JF, Paterson DJ, Aziz TZ, **Green AL.** Ventral periaqueductal grey stimulation alters heart rate variability in humans with chronic pain. *Exp Neurol*. 2010; 223(2):574-81, doi: 10.1016/j.expneurol.2010.02.004
7. Gillies MJ, Huang Y, Hyam JA, Aziz TZ, **Green AL** Direct neurophysiological evidence for a role of the human anterior cingulate cortex in central command. Auton Neurosci. 2019 216:51-58, doi: 10.1016/j.autneu.2018.09.004.

List of Abbreviations

(d)ACC	(dorsal) Anterior Cingulate Cortex
AIMS	Abnormal Involuntary Movement Scale
ANS	Autonomic Nervous System
AVPNs	Airway-related Vagal Preganglionic Neurones
BA	Burst Amplitude (MSNA)
BF	Burst Frequency (MSNA)
BI	Burst Incidence (MSNA)
BOLD	Blood Oxygen Level Dependent (MRI signal)
BP	Blood Pressure
BRS	Baroreceptor Sensitivity
CAN	Central Autonomic Network
CNS	Central Nervous System
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CV(S)	Cardiovascular (system)
D12	'Dyspnoea-12' Score
DBS	Deep Brain Stimulation
DTI	Diffusion Tensor Imaging
ECG	Electrocardiogram
FEF_{50}	Forced Expiratory Flow at 50% vital capacity
FEV1	Forced Expiratory Volume in 1st Second
GPi	Globus Pallidus Interna
HF	High Frequency
HR(V)	Heart Rate (Variability)
KFN	Kolliker-Fuse Nucleus
LF	Low Frequency
LFP	Local Field Potentials
MAP	Mean Arterial Pressure
MIC	Medullary Inspiratory Centres
MLR	Midbrain/ Mesencephalic Locomotor Region
MRC	Medical Research Council
(f)MRI	(functional) Magnetic Resonance Image
MSNA	Muscle Sympathetic Nerve Activity
NA	Nucleus Ambiguus
NRA	Nucleus retroambiguus
NTS	Nucleus of the Tractus Solitarius
PAG	Periaqueductal Grey Area
PBN	Parabrachial Nucleus
PD	Parkinson's Disease
PSD	Power spectral density
vmPFC	(ventromedial) Prefrontal Cortex
PVG	Periventricular Grey Area
PEFR	Peak Expiratory Flow Rate
PPN	Pedunculopontine Nucleus
PNS	Parasympathetic Nervous System
PRG	Pontine Respiratory Group
QOL	Quality of Life
RR	Respiratory Rate
RVLM	Rostroventrolateral Medulla
SGRQ	St George's Hospital Respiratory Questionnaire

SNS	Sympathetic Nervous System
ST	Sensory Thalamus
STN	Subthalamic Nucleus
UAO	Upper Airway Obstruction
VIM	ventral intermediate nucleus (of the thalamus)
VPL	Ventroposterolateral Nucleus
VPM	Ventroposteromedial Nucleus

List of Tables & Figures

1: INTRODUCTION

1.1 The Autonomic Nervous System

The Autonomic Nervous System (ANS) is traditionally considered to be part of the peripheral nervous system and is concerned primarily with the control of internal organs and, in general, acts unconsciously(LeBouef T, 2021). There are three main divisions: sympathetic, parasympathetic, and enteric. This thesis is concerned with the former two.

The distinction between 'peripheral' and 'central' is, however, rather arbitrary. Whilst the 'effector' parts of the system are peripheral, the ANS can be influenced by higher structures such as the brain,

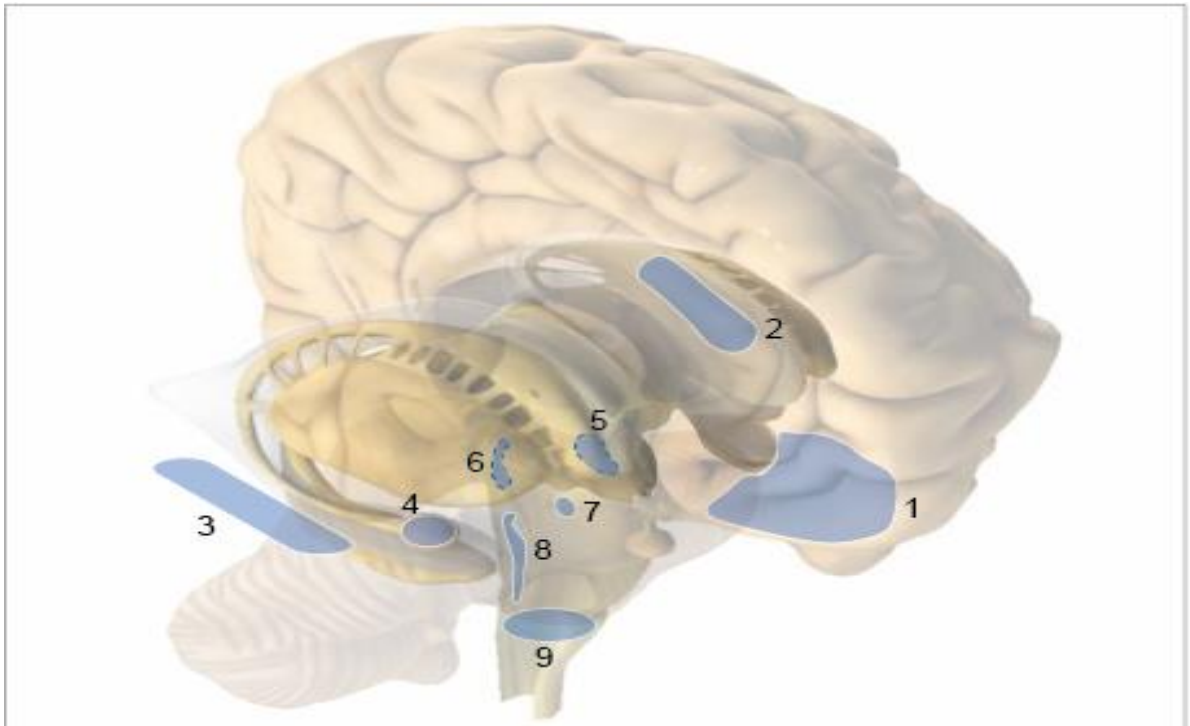


Figure 1: Areas in the brain involved in the Central Autonomic Network (CAN). Taken from Green and Paterson 2020(Green, 2020) with permission

and conversely, higher functions such as emotions and cognition can be influenced by afferent inputs – a concept termed 'interoception'.

The Central Autonomic Network (CAN) describes sites in the central nervous system (CNS) that control the ANS (figure 1). In addition to receiving autonomic afferents from multiple organs and coordinating an autonomic response, they are responsible for integration of these responses with other brain functions(Green, 2020). This is possible because of connections to other systems such as cognitive, motor, nociceptive, and the reticular and forebrain monoamine and cholinergic systems involved in motivation, attention, emotion and circadian rhythms(Benarroch, 1998). This thesis will concentrate on brain areas that are used as targets for *Deep Brain Stimulation* (DBS) (figure 2). DBS provides novel insights into the function of brain areas as it allows us to electrically stimulate the brain in humans who are being chronically stimulated for therapeutic benefit. By combining stimulation with autonomic studies, we can explore the CAN and the role of individual nuclei in efferent autonomic control. In addition, by recording *local field potentials* (electrical activity from the DBS macroelectrode), we can infer the role of the nucleus under study during tasks that manipulate autonomic function. It is also important to recognise the limitations of using DBS as a tool; we are not able to 'choose' the nucleus under question and therefore some nuclei will go uninvestigated and not all nuclei that we stimulate are of autonomic interest; we are also limited to patients with disease such as Parkinson's disease (PD), rather than a 'normal' brain. The results therefore have to be interpreted in the context of potential autonomic abnormalities such as autonomic failure.

1.2 Stereotaxy and Deep Brain Stimulation

'Stereotaxy' (moving to a position in 3D space) has been used to explore the brain in animals for over 150 years. The first use was in the investigation of the vasomotor centre in the medulla oblongata reported by Dittmar in 1873(Blomstedt et al., 2007, C, 1873). Dittmar, along with Owsjannikow, working in Carl Ludwig's laboratory in Leipzig, designed a stereotactic frame that could be attached to an animal's head and brain targets could be inferred using coordinates based on known landmarks. 'True' stereotaxy using Cartesian coordinates was made possible via a collaboration between the British physiologist Robert Henry Clarke and a pioneering British Neurosurgeon, Victor Horsley(Blomstedt et al., 2007) and it was the 'Horsley-Clarke' frame that was adapted by two Americans – Spiegel and Wycis – for human use in 1947(Spiegel et al., 1947). The first human stereotactic procedures utilised *lesioning* techniques to destroy (lesion) nuclei in the brain that were thought to be overactive in disease states. Spiegel and Wycis started out performing precise psychosurgery such as lesioning the dorsomedial thalamus (part of the limbic pathway) to replace the popularized prefrontal leucotomy(Spiegel et al., 1947). These techniques were soon applied to movement disorders, such as in 'pallidotomy' in which absolute alcohol was stereotactically applied to the medial *globus pallidus interna* (GPi) by Cooper to treat the rigidity in PD. In the West, the introduction of electrodes into the human brain is largely attributed to Heath, a

psychiatrist in New Orleans, who ran a large (and somewhat controversial) research programme on institutionalized psychiatric patients(O'Neal et al., 2017). The application of DBS for chronic pain

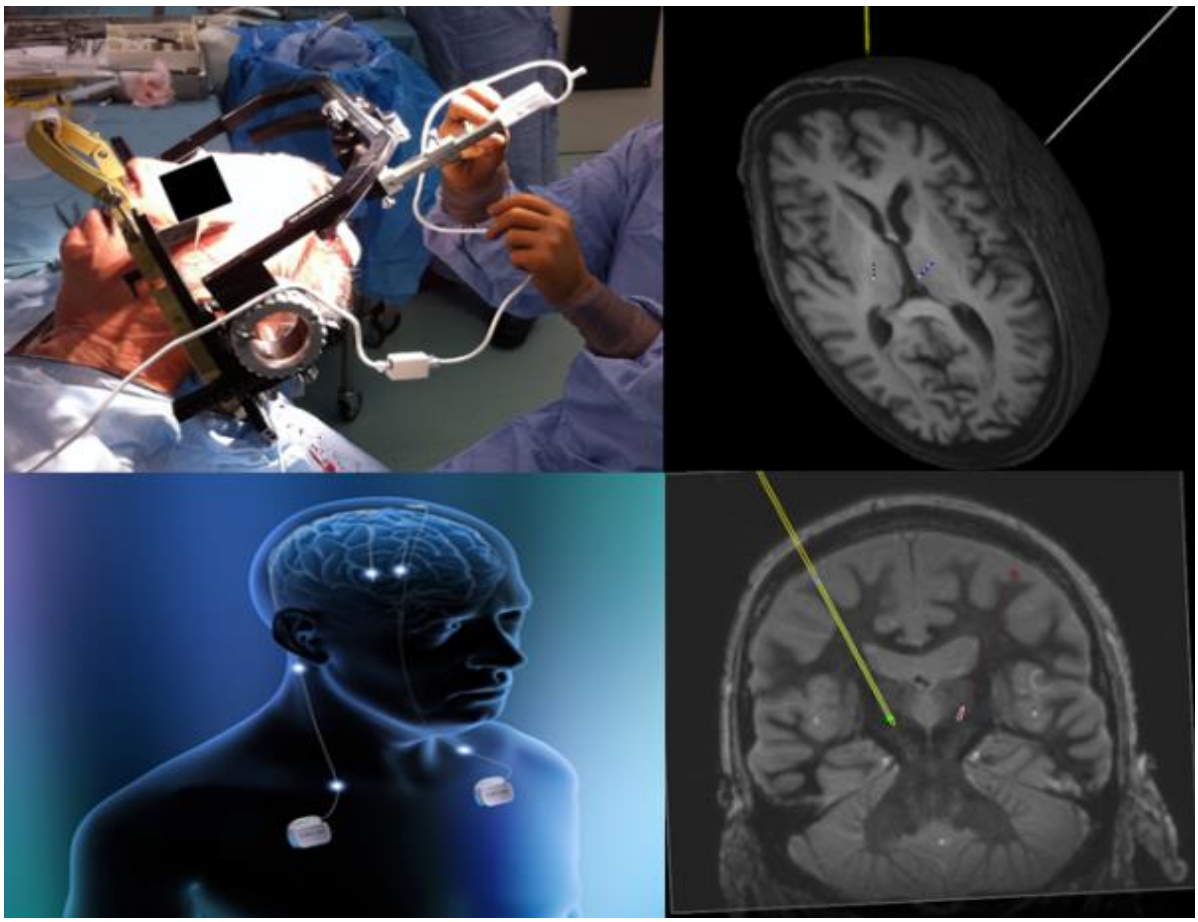


Figure 2. Deep Brain Stimulation involves stereotactic placement of brain electrodes using MRI to target. The electrodes are attached to subcutaneous pulse generators. Taken from (Green AL, 2020) with permission

predominated in the 1970-1980s(Hosobuchi, 1986) whereas lesioning for PD subsided due to the introduction of levodopa in 1960(Degkwitz et al., 1960). However, from the late 1970s onwards, as patients with PD (a degenerative condition) required ever increasing doses of levodopa and suffered intolerable side-effects, investigators started looking at DBS for movement disorders again(Brice and McLellan, 1980, Benabid et al., 1987). To date, DBS has been performed in over 160,000 patients(Lozano et al., 2019) and continues to increase. Recent advances in technology allow better symptom control (such as 'directional' electrodes that steer the electric current to the optimal position and thus avoid side-effects), better compatibility with other healthcare modalities (such as Magnetic Resonance Imaging (MRI)), and rechargeable batteries to avoid the need for replacement (that requires an operation). Experimental systems employ the ability to record from electrodes or to pair to a wearable device – so called 'closed-loop' systems. In addition to the advances in technology, an ever-increasing number of brain targets and indications are being researched, such as psychiatric disorders (Tourette's syndrome(Baldermann et al., 2016), Anorexia Nervosa(Villalba Martínez G, 2020), Obsessive Compulsive Disorder(Martinho et al., 2020), Depression(van der Wal et

al., 2020), Addiction(Luigjes et al., 2019), Schizophrenia(Corripio et al., 2020)), Dementia(Maltête D, 2020), Epilepsy(Fisher and Velasco, 2014), Pain(Boccard et al., 2013), Tinnitus(Cheung SW, 2019), and even Autonomic Disorders(Green AL, 2020).

This thesis will concentrate on the Autonomic effects of DBS, with reference to a number of the author's studies that focus on this area – namely control of respiration and the cardiovascular system. Whilst many of these systems do not act in isolation (take for example the role of both the cardiovascular and respiratory systems in exercise), DBS allows us to break them down into components by studying the effects of stimulation and recording of LFPs whilst studying individual aspects.

2: SUMMARY OF PUBLISHED WORK

DBS and Respiration

2.1. Study 1: Controlling the Lungs via the Brain (Hyam et al.)

Thirty-seven patients with implanted DBS electrodes of various targets (movement disorders or pain syndromes) performed Spirometry whilst the stimulation was randomised and double-blinded to Off or On. Ten PAG and Ten STN patients were recruited. Control groups were patients with similar conditions (movement disorders or pain) with electrodes in non-CAN nuclei i.e., GPi or sensory thalamus respectively.

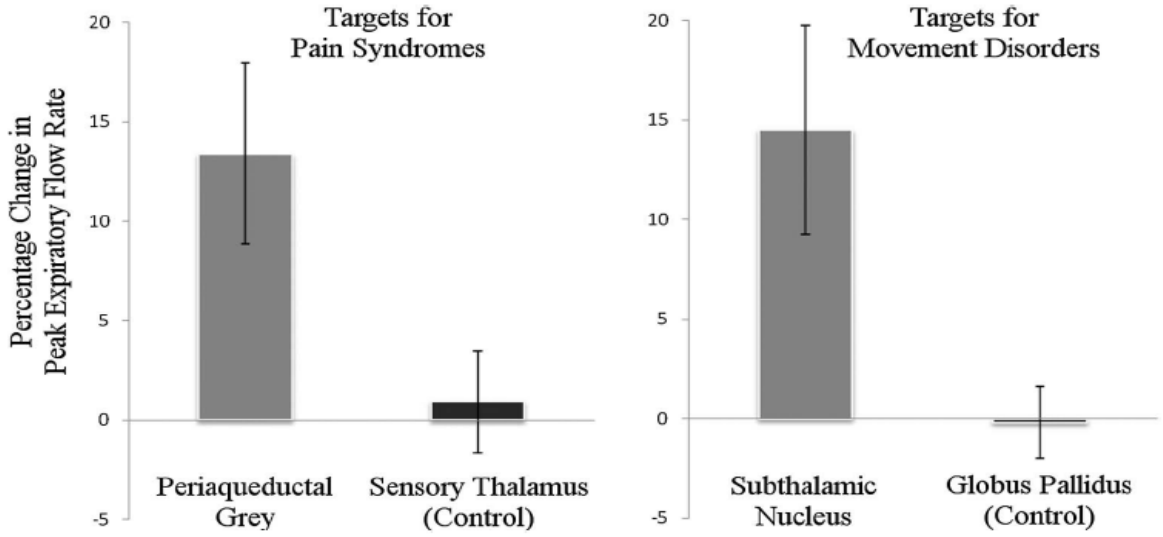


Figure 3. Changes in PEFR (%) with DBS stimulation of various targets

Peak expiratory flow rate (PEFR) increased by 14% in both PAG and STN groups, whilst control groups did not change (figure 3). Airway calibre alteration is mediated by changes in smooth muscle tone, and is an autonomic function accompanied by changes in vascular permeability of airway capillaries, and glandular secretion(Barnes, 1990). Airway relaxation (increasing diameter and therefore PEFR) is mediated by circulating catecholamines and is part of the Sympathetic Nervous System (SNS)(Barnes, 1995). Airway constriction, on the other hand, is mediated by the Peripheral Nervous System (PNS) directly via airway-related vagal preganglionic neurons (AVPNs) that synapse with vagal postganglionic neurons within the lungs that innervate smooth muscle directly(Hadziefendic and Haxhiu, 1999). Animal studies using retrograde labelling techniques (such as pseudorabies virus) show that multiple brain areas connect to the AVPNs such as amygdala, Periaqueductal grey area (PAG), dorsal pons, and medulla(Hadziefendic and Haxhiu, 1999, Haxhiu et al., 1993). It has been hypothesized that these higher centres exert a tonic inhibitory control over the AVPNs(Haxhiu et al., 1993, Hadziefendic and

Haxhiu, 1999). These sites also connect to areas important for extra bronchial respiratory musculature. For example, within the medulla, the retrofacial nucleus, Nucleus of the Tractus Solitarius (NTS), and the nucleus retroambiguus (NRA) receive projections from the PAG(Duffin and Lipski, 1987, Holstege and Kuypers, 1982, Sakamoto, 1996) and contain inspiratory neurons that drive phrenic and external intercostal motor neurons(Holstege, 1991, Lipski et al., 1983, Shah et al., 1990). The PAG also projects to the Parabrachial Nucleus (PBN), stimulation of which alters the Hering-Breuer reflex(Motekaitis et al., 1994, Motekaitis et al., 1996) and reduces lung resistance in animals(Bandler and Tork, 1987, Holstege, 1989).

An interesting paradox in our study is that whilst PEFR changed significantly, *forced expiratory volume in 1 second* (FEV1) did not. PEFR predominantly represents large airway calibre(Hyatt and Black, 1973). This is because the turbulence in the larger upper airways limits the largest flows that occur in the first 15ms (PEFR) more than the lower airways that contribute to a greater proportion over the remainder of the first second. This may be evidence that PAG and Subthalamic Nucleus (STN) stimulation predominantly alter upper airway function. Another explanation is that the periods of stimulation testing were too short (10-minute wash-out/ wash-in periods) and that lower airways may be more sensitive to slower changes secondary to stimulation.

2.2 Study 2: Case Report: Thalamic DBS Improves Dyspnoea in COPD (Green AL, 2019)

We routinely treat two disabling effects of cerebral stroke; tremor and chronic pain(Boccard et al., 2013, Hyam et al., 2015). Standard targets for tremor include the ventral intermediate (VIM) nucleus of the thalamus, and, if there is a dystonic element, the GPi(Tsuboi T, 2020). For pain, 'routine' targets are PAG and ventroposterolateral (VPL) or ventroposteromedial (VPM) nucleus of the thalamus (VPL for limb and VPM for face pain). We treated a patient with both post-stroke pain and tremor and implanted all four nuclei (VPL rather than VPM) in order to treat both aspects(Green AL, 2019). The patient coincidently suffered from Chronic Obstructive Pulmonary Disease (COPD) and a had a FEV1 of 0.08 L (41% predicted for his demographics). DBS was successful in that his tremor score (using the Abnormal Involuntary Movement Scale – AIMS) was improved by 53% with stimulation and his pain was improved also. However, more striking was that comparison of pre-operative and post-operative videos (performed for assessing the effects of DBS on the movement disorder) revealed that his pursed lips breathing had disappeared whilst the thalamic DBS was On and returned when it was switched off (see video: Letter to the editor: Thalamic deep brain stimulation may relieve breathlessness in COPD - ScienceDirect). Pursed lips breathing is a common finding in COPD and is a natural mechanism to increase positive pressure on exhalation thereby keeping the airways open and

aiding the excretion of CO_2(Nguyen J, 2020). The lack of it following DBS implies that the patient was not feeling breathless with stimulation.

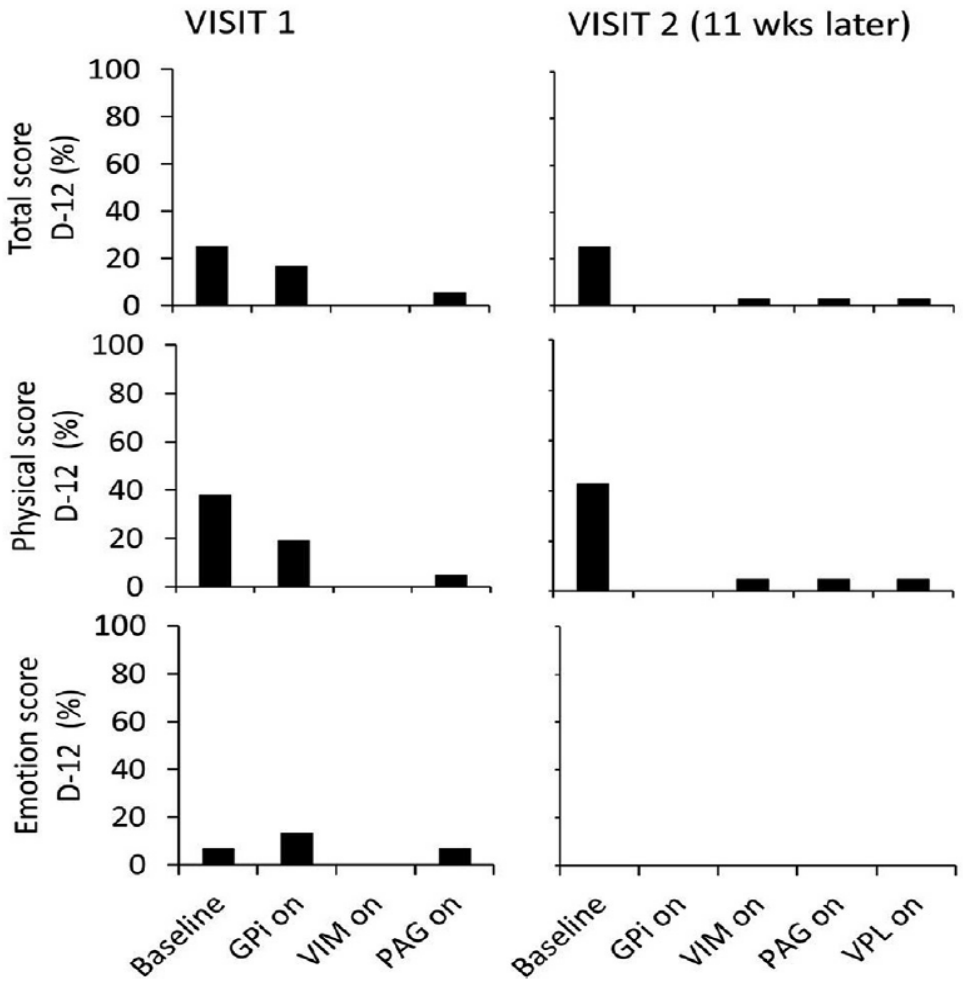


Figure 4. D-12 scores at 3 days and 11 weeks. Taken from (Green AL, 2019) with permission

Dyspnoea is a subjective sensation and whilst it may relate to respiratory distress, it is not well correlated with physiological markers. It is therefore best measured using a questionnaire such as the Dyspnoea-12(Yorke et al., 2010), a validated, multidimensional instrument that looks at both physical and emotional components. 3 days after implantation, we applied stimulation to the various electrodes in a random order and found that VIM stimulation relieved both the physical and emotional components of dyspnoea (figure 4). GPi stimulation reduced the physical (intensity) score but increased the emotional score. PAG stimulation reduced the physical score, but the emotional score remained unchanged. At 3 months, baseline scores remained unchanged, but all targets reduced the physical score. The baseline emotion score at 3 months had disappeared.

2.3 Study 3: Breathlessness in PD (Chalif et al., 2014)

Parkinson's disease (PD) is the most common condition treated with DBS and over 150,000 cases have been performed worldwide. Descriptions of respiratory dysfunction in PD are relatively recent(Baille et al., 2019) and are not well characterized, although aspiration pneumonia is the principle cause of death (Ebihara et al., 2003, Fontana et al., 1998). It is likely that respiratory function is compromised both from physical 'ventilatory' dysfunction as well as the sensation of dyspnoea itself which is multifactorial and includes dyspnoea resulting from ventilatory dysfunction.

13 STN patients were prospectively compared to 7 PD patients undergoing VIM DBS (predominantly tremor). Outcomes were questionnaire-related and included the St George's Hospital Respiratory Questionnaire (SGRQ) - a 50-question self-report quality of life (QOL) measure of respiratory health.(Jones et al., 1992) Overall results showed that whilst pre-operative SGRQ scores were similar in both groups, post-operative symptom subscale and impact subscale scores were significantly higher in STN patients but not VIM patients (figure 5). However, activity and total scores were no different nor were any of the other scores measured (MRC dyspnoea scale, D-12, Neuropsychology scale). Sub analysis showed that the five STN patients who scored highest on the D-12 had scores comparable with a cohort of patients with COPD and on the SGRQ fell above the 90th percentile. Thus, the dyspnoea in these patients was significant. As a result of our findings, we reviewed the fMRI data from a previous study(Pattinson et al., 2009a) and found that the STN had increased BOLD activity in response to respiratory stimulation with CO_2 and breath-holding. Review of a PET study from 2001 also shows increased metabolism in the STN region although it was not specifically mentioned in the report(Liotti et al., 2001).

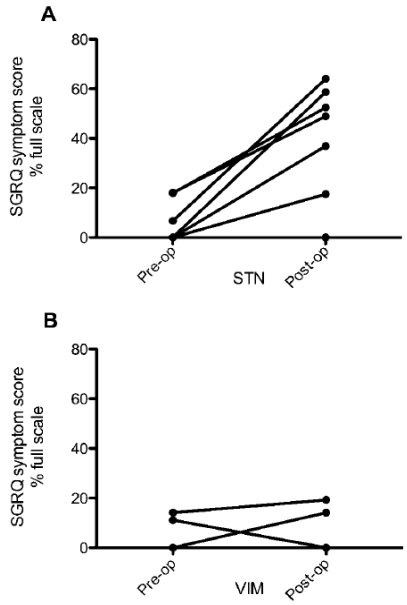


Figure 5. Pre- and post-operative SGRQ scores for A) STN vs B) VIM patients (note 3 patients in the VIM group had pre- and post- scores of 0 and are not visible on the graph

2.4 Study 4: The Pedunculopontine Nucleus (PPN) and Respiratory Control (Hyam et al., 2019)

The pedunculopontine nucleus (PPN) straddles the midbrain and pons and is located just lateral to the decussating fibres of the superior cerebellar peduncle(Jenkinson et al., 2009). It is used as a target in PD to alleviate gait abnormalities and postural instability(Jenkinson et al., 2004, Nandi et al., 2008). The mesencephalic locomotor region (MLR) includes the rostral PPN (relevant to the area of stimulation in humans(Inglis and Winn, 1995, Skinner et al., 1990a, Skinner et al., 1990b)) and modulates autonomic variables in decerebrate or anaesthetised animals(Bedford et al., 1992, Chong and Bedford, 1997). Glutamatergic neurones from the MLR project directly to the medullary respiratory generator and are thought to influence changes in respiration linked to locomotion(Gariépy JF, 2012). We hypothesised that a) PPN stimulation would improve upper airway obstruction (UAO) in PD and b) changes in local patterns of oscillatory activity in the alpha band (7-11 Hz) (measured using LFP analysis) would correlate with voluntary respiration. This second hypothesis is based on previous studies demonstrating that 7-11Hz synchrony correlates with gait performance in the PPN of PD patients(Thevathasan et al., 2012).

Nine PD patients were compared to were compared to seven 'control' patients undergoing GPi stimulation for dystonia. Tests were performed 'ON' dopamine medication with stimulation ON and OFF. Where possible, PPN LFPs were simultaneously recorded (n=6). We found that PEFR increased significantly with rostral PPN stimulation but not GPi stimulation (figure 6A). In the PPN group, maximal flow at 50% forced vital capacity (FEF_{50}) was 90% predicted OFF stimulation and normalised (100%) with stimulation (although significance was not reached, plausibly because the study was

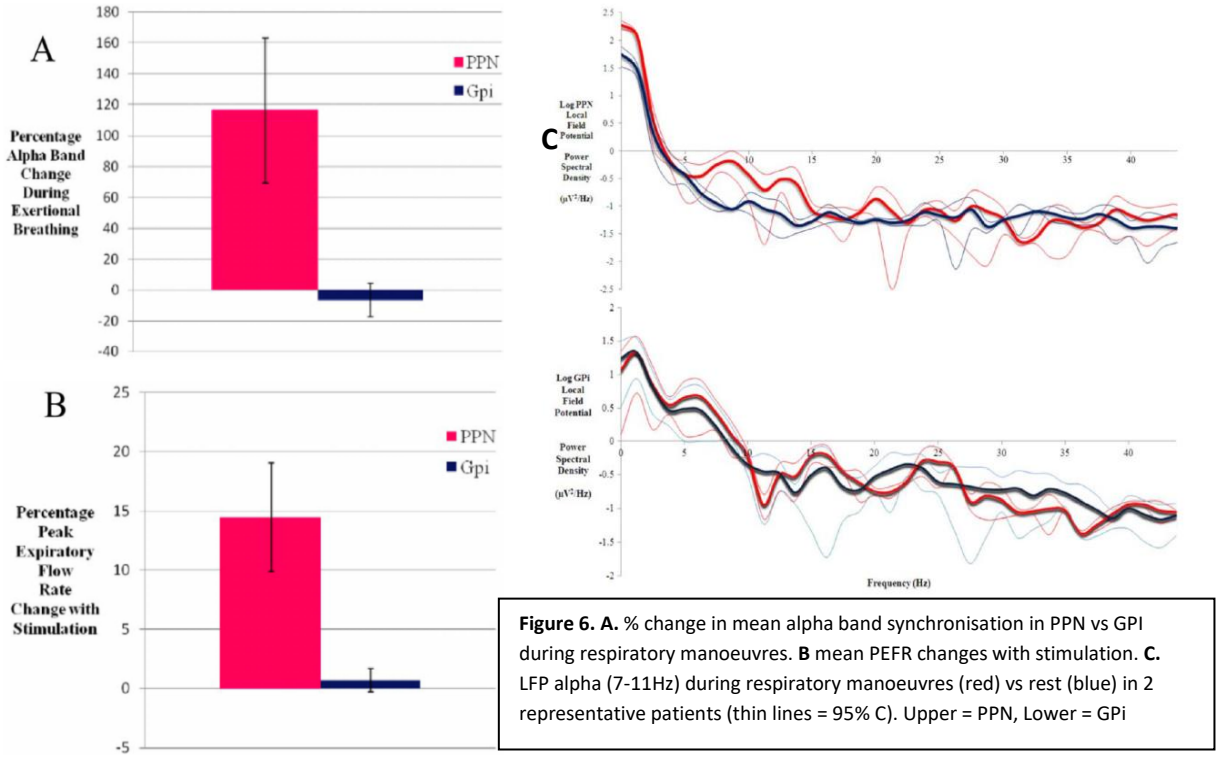


Figure 6. A. % change in mean alpha band synchronisation in PPN vs GPI during respiratory manoeuvres. **B** mean PEFR changes with stimulation. **C.** LFP alpha (7-11Hz) during respiratory manoeuvres (red) vs rest (blue) in 2 representative patients (thin lines = 95% C). Upper = PPN, Lower = GPi

under powered). There was a marginal but insignificant increase in FEV1 with stimulation. One criterion for UAO is a FEV1/PEFR ratio greater than 8.5 ml/L per min(Vincken et al., 1989). This ratio improved in all PPN patients and in one patient who satisfied the criteria for UAO (ratio 8.83ml /L per min), mean FEV1/PEFR reduced to 8.19 with stimulation meaning that he no longer had clinical UAO. This individual had almost 30% improvement in PEFR. The fact that the FEV1 change in all patients was marginal suggests that the change is being driven by changes in PEFR and is secondary to changes in upper airway function rather than lower airway function.

In the PPN, mean LFP power in the alpha band was significantly higher during forced respiratory manoeuvres (figure 6B. The alpha band power increased during maximal inspiration and peaked during forced expiration). No LFP changes in the alpha band were detected in the GPi. The importance of this study is that upper airway obstruction is a major cause of morbidity in PD and can lead to death. UAO manifests as a reduced PEFR and FEF_{50}, and an increased FEV1/PEFR ratio(Vincken et al., 1984, Hovestadt et al., 1989, Empey, 1972). All three indices improved with stimulation (two significantly). PEFR represents the first 15ms of forced expiration which is predominantly contributed to by the large proximal airways and is limited by turbulence of flow in these airways(Vincken et al., 1984). In contrast, FEV1 occupies a longer time window and likely represents lower airway performance as well and this did not change significantly. This fits with the LFP changes that were predominantly at the peak of forced expiration.

DBS and the Cardiovascular System

2.5 Study 5: Differentiated Baroreflex Modulation of Sympathetic Nerve Activity During Deep Brain Stimulation in Humans (Sverrisdottir et al 2014)

The arterial baroreflex is a short-term feedback loop that regulates arterial blood pressure on a beat-to-beat basis(Kirchheim, 1976). There is evidence that baroreflex modulation of sympathetic outflow is differentiated and occurs at two CNS locations; one that determines whether a burst will occur and the other that determines the strength of the burst(Malpas and Ninomiya, 1992, Kienbaum et al., 2001). Although the exact locations within the CNS have not been formally identified(Kienbaum et al., 2001), the brainstem has been implicated. In order to test the hypothesis that different CNS locations would have different effects on the baroreflex, we directly measured efferent post-ganglionic muscle sympathetic nerve activity (MSNA) and cardiovascular parameters (Electrocardiogram (ECG) and Mean Arterial Pressure (MAP) in a cohort of patients undergoing DBS in the ON and OFF phases(Sverrisdottir et al., 2014). The patient cohort (17 patients) was divided into those undergoing DBS for PD (STN (6), GPi (2), VIM (1) or PPN (1)), and those with neuropathic pain (PAG dorsolateral (1), PAG ventrolateral (1), sensory thalamus (2), anterior cingulate cortex (ACC) (3)).

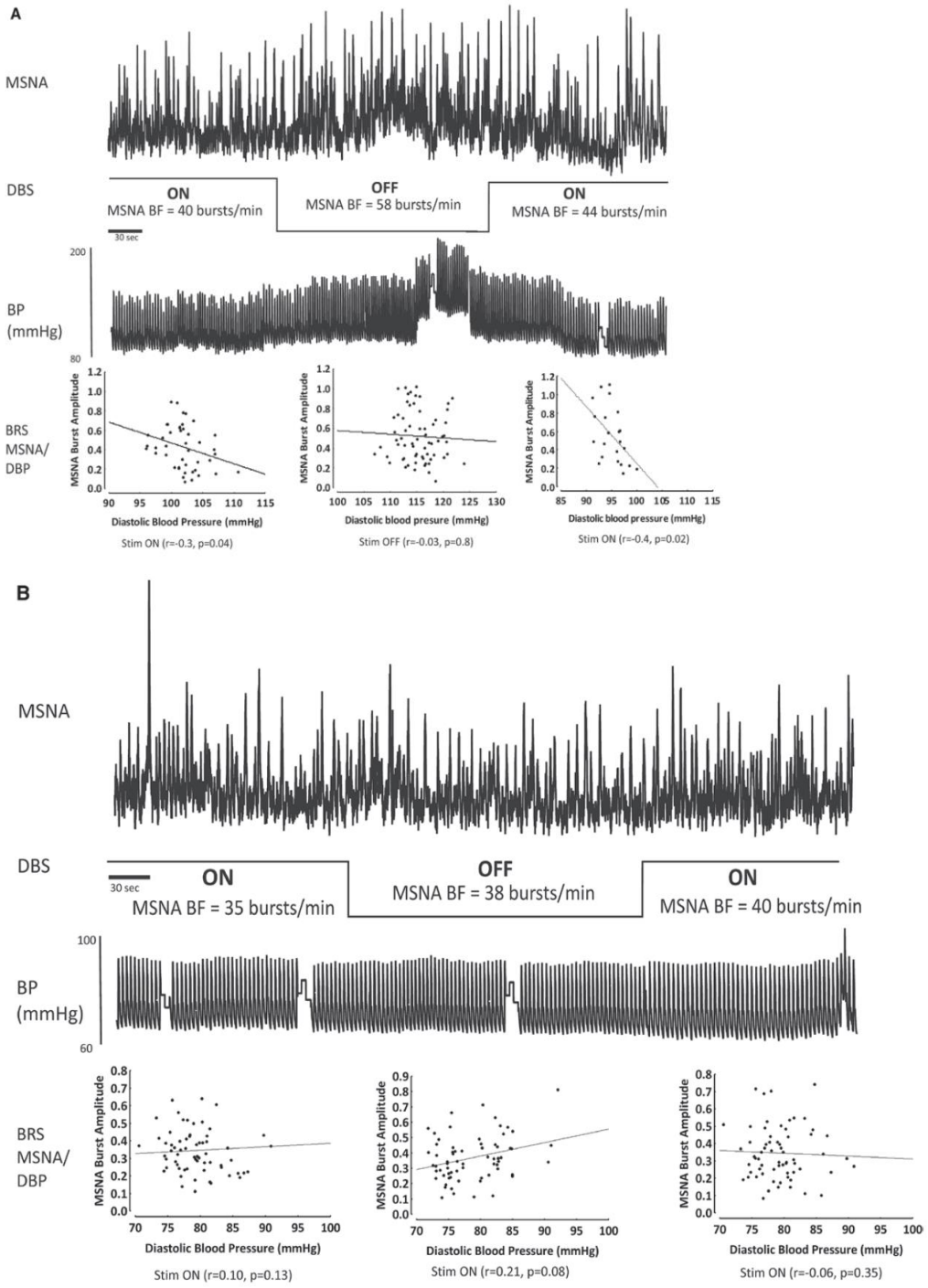


Figure 7. Mean voltage neurogram of MSNA, BP and BRS diagrams for DBP during DBS ON and OFF with bilateral dorsal STN stimulation. **B.** Same as A but for ventral part of dorsal STN

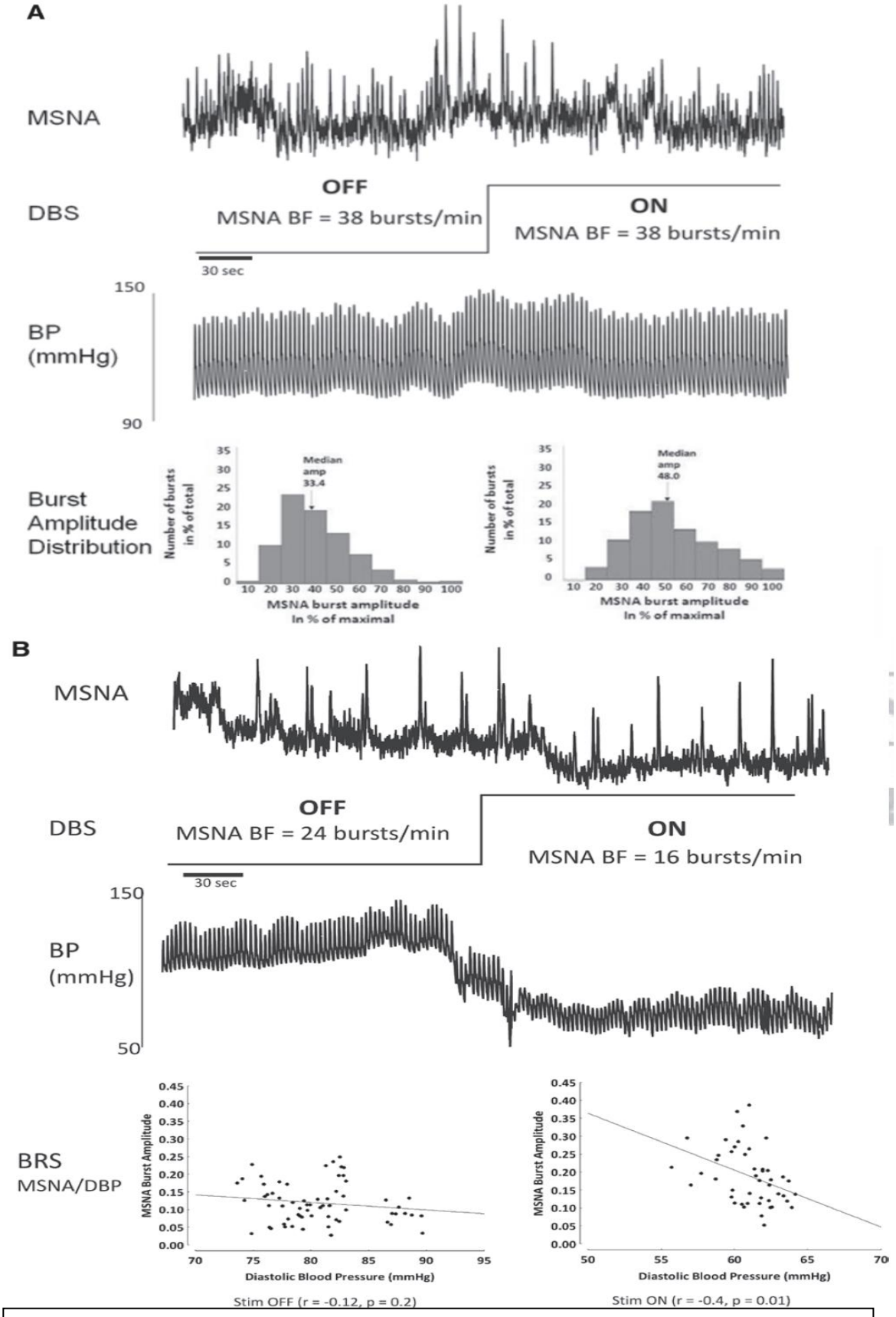


Figure 8. A. MSNA Neurogram, BP and median relative burst amplitude with dorsal PAG stimulation ON vs OFF. **B.** MSNA, BP and BRS diagrams for ventral PAG stimulation

In the PD group, stimulation of GPi, MT or PPN did not lead to any changes in either haemodynamic parameters or MSNA. However, STN stimulation depended on the part of the STN stimulated. Dorsal STN stimulation resulted in an increased Baroreceptor sensitivity (BRS) to the vasculature and a significant reduction in MSNA Burst Frequency (BF) and Burst Incidence (BI) (figure 7A) which was paralleled by reduction in MAP and Heart Rate (HR). The fall in BP after tilt was also reduced in this group. MSNA burst amplitude remained unchanged. These effects were not seen with stimulation of the less dorsal targets (figure 7B). In the pain group, the ACC and sensory thalamus results were similar to the non-STN movement disorder results in that there was no significant change in any of the parameters. Dorsal PAG stimulation resulted in a shift of the MSNA burst amplitude (BA) to a mesokurtic form – towards a greater number of medium-high amplitude bursts compared to low amplitude bursts (overall increased burst amplitude – see figure 8A) This was accompanied by a reduction in BP variability. Unlike the STN subjects, stimulation did not alter BRS or MSNA BI. Ventral PAG stimulation, on the other hand, had a very different effect, causing an increase in vascular BRS and a decrease in MSNA BF and BI, similar to stimulation of the dorsal STN (figure 8B). These changes were paralleled by reductions in ABP and HR. MSNA burst amplitude shifted to a leptokurtic form demonstrating a greater number of low amplitude bursts. Cardiac BRS remained nonsignificant during all DBS ON and OFF phases in all subjects.

2.6 Study 6: Ventral PAG Stimulation Alters Heart Rate Variability (HRV) in chronic pain (Pereira et al., 2010)

Whilst microneurography is the 'gold standard' way to measure changes in sympathetic activity, a simple and effective way to measure autonomic 'tone' is to calculate *heart rate variability* (HRV)(Malik M, 1996). HRV is calculated by measuring continuous heart rate such as using ECG or even a one-lead wearable device. In this study, we analysed HRV using a spectral analysis method. Previous research has identified that high frequency (0.15-0.4Hz) HRV power is a marker of vagal parasympathetic control(Malik M, 1996). Low frequency power (0.04-0.15Hz) may be predominantly affected by sympathetic cardiovascular activity but is also affected by both vagal and sympathetic tone(Pagani et al., 1997, Pumprla et al., 2002, Malik M, 1996). Changes in the LF/HF ratio are useful in indicating the balance between the two systems on the heart. For example, changes in LF/HF ratio are present in a number of diseases such as cardiac failure, diabetes mellitus and after myocardial infarction(Kuch et al., 2004, Mestivier et al., 1997, Saul et al., 1988).

In this study, we measured HRV in 16 patients undergoing DBS of the PAG for chronic neuropathic

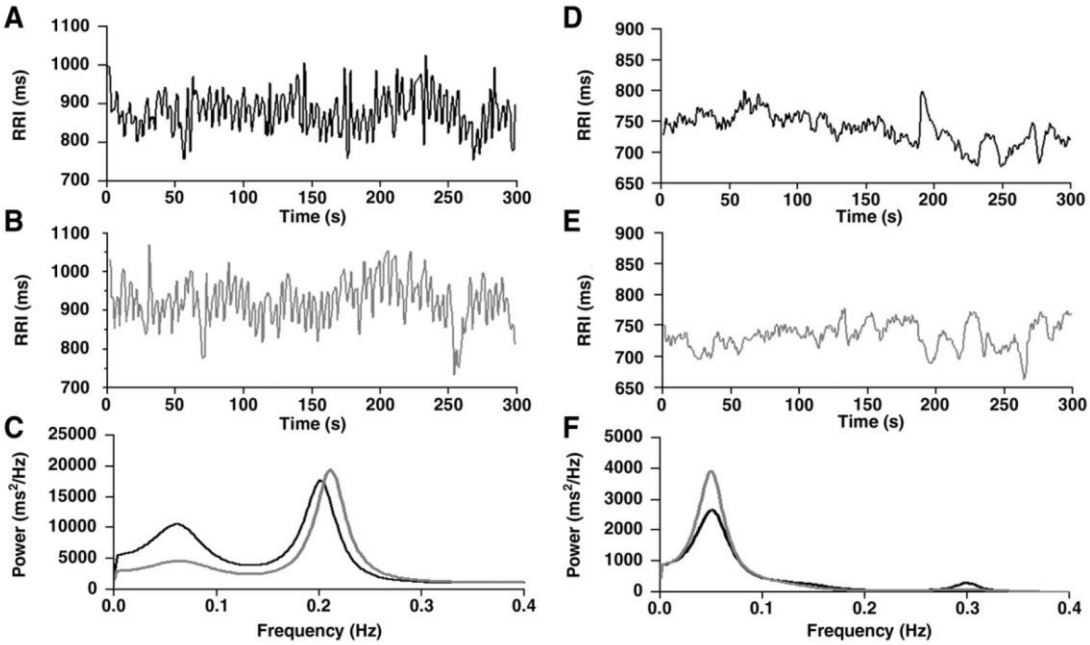


Figure 9. RR interval time series (A, B, D, E) and their power spectra (C, F) in two patients. Left: ventral PAG; right: dorsal PAG. Black line: OFF DBS, Grey line: ON DBS

pain. The case mix was heterogenous with half of the patients having had pain following a stroke and the remaining eight pains of other aetiologies. Patients were divided into two groups – those with more ventral electrodes and those with more dorsal. We performed a randomised, blinded trial in each patient between DBS ON or OFF whilst they rated their pain. Figure 9 shows representative results of one ventral and one dorsal PAG patient, whilst figure 10 shows the group results comparing ventral to dorsal stimulation. In the group as a whole there were no significant changes in HR. However, ventral PAG DBS significantly reduced the LF/HF ratio whereas dorsal DBS did not. This change was largely driven by increased HF power in the ventral group. In contrast, LF power did not vary significantly between the groups. A correlation analysis between changes in HRV power and analgesia induced by stimulation found that both HF and LF/HF power changes correlated well with pain reduction ($p = 0.04$ and $p = 0.01$ respectively).

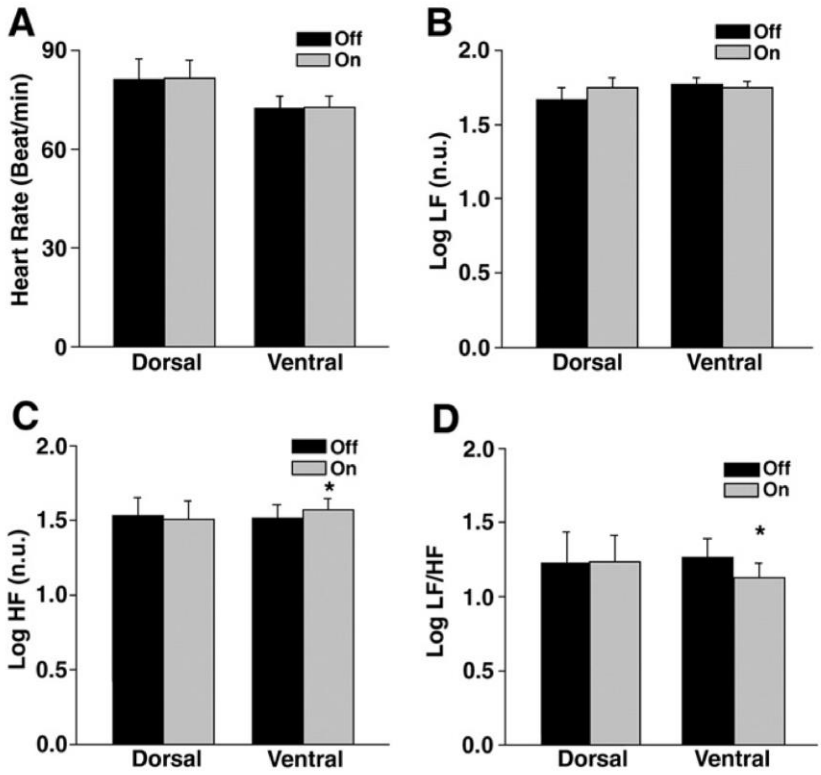


Figure 10. Dorsal and Ventral group HR and HRV with stimulation. A) Mean HR (+/- se). B) HRV LF (0.04-0.15Hz), C) HRV HF (0.15-0.4Hz). D) LF/HF ratio.

2.7 Study 7: Central Command and the Anterior Cingulate Cortex (Gillies et al., 2019)

So far in this thesis, cardiovascular and respiratory regulation have been considered separately. However, in reality the two aspects (and others) of autonomic function and control are integrated into physiological responses necessary for normal survival and behaviour. An example is the multitude of interacting physiological responses to exercise stimuli. In this study, we explored the role of the anterior cingulate cortex (ACC) in the 'central command' of intermittent isometric exercise in four patients undergoing DBS for chronic neuropathic pain (two with bilateral electrodes and two with unilateral). We simultaneously recorded LFPs and cardiovascular parameters. Patients were given a ten-second countdown before beginning right upper limb biceps flexes against a 2kg weight attached to the wrist at a rate of 30-60 per minute for two minutes. This was followed by three minutes rest and a repeat of the protocol. The whole protocol was repeated six times per subject. LFPs were compared between the last ten seconds of rest and the first ten seconds of exercise in each trial. Fundamental spectral frequencies were compared between 10 second epochs of rest, anticipation of exercise and exercise. As shown in previous studies, CV parameters increased significantly during anticipation of exercise and further during actual exercise(Green AL, 2007) concordant with the concept that the CVS is being controlled in a top-down manner before the start of exercise. LFP analysis revealed significant changes in power spectral density (PSD) during anticipation of exercise ($p = 0.004$), particularly in the 25-60Hz frequency band (figure 11). During exercise there was a decrease

in the 8-12Hz band (alpha power) compared to rest and a further increase in the 25-60Hz band. Compared to anticipation, there was a decrease in the 4-8Hz (theta) band during exercise. Pearson's correlation analysis showed a positive correlation ($r = 0.417$, $p = 0.016$) between the power change in the 25-60Hz band and the change in HR during anticipation relative to rest. Taken together, these results provide evidence for a role of the ACC in central command related to exercise.

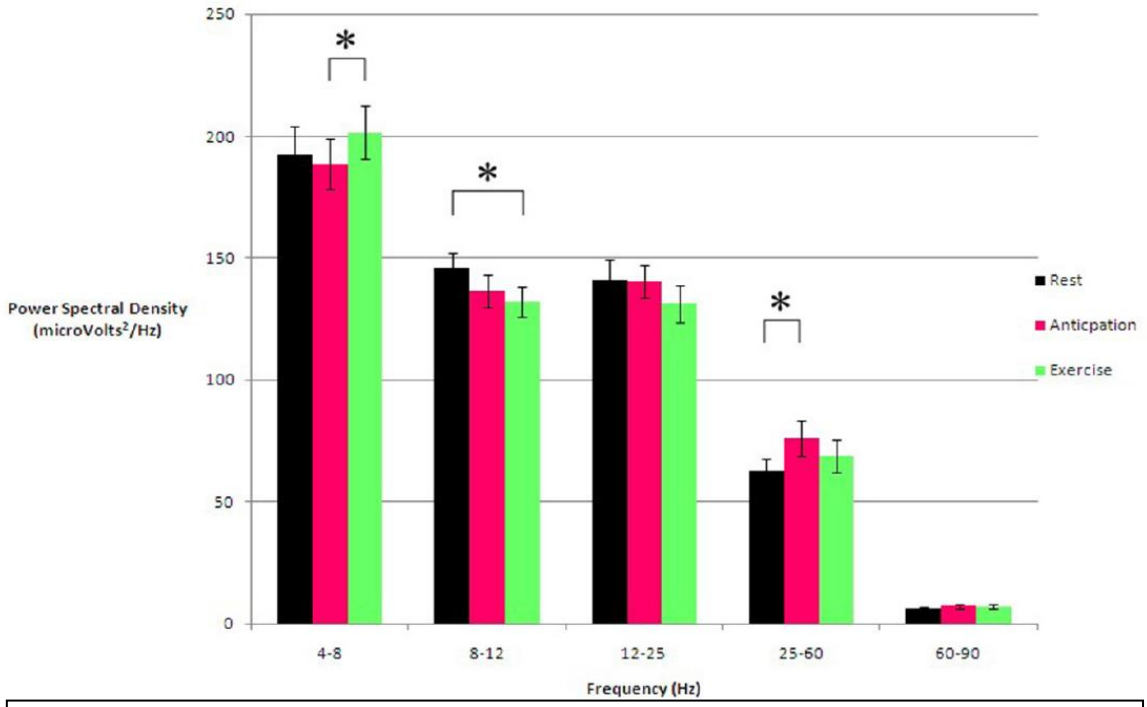


Figure 11. LFP power spectral density changes between Rest, Anticipation and Exercise divided into frequency band (*p< 0.01)

3: Discussion

Respiratory Control (Studies 1-4)

Respiratory control in the brain is complex and involves factors such as rhythm generation (such as the pre-Botzinger complex and ventral medulla), chemoreceptors that detect CO_2 mechanoreceptors to detect chest wall movement, and higher areas to integrate such signals with 'higher' functions such as emotion, arousal, and vocalization. Such integration is then used to control coordination of diaphragm, larynx, and airway. Periods of isocapnic hyperpnoea (increased breathing rate with normalised CO_2) demonstrate a bilateral network that includes sensory and primary motor cortices, thalamus, limbic system, cerebellum and brainstem(Colebatch et al., 1991, Evans et al., 1999, McKay et al., 2008, McKay et al., 2003, Ramsay et al., 1993). Hypercapnia leads to increased metabolic activity in the limbic system as seen using Positron Emission Tomography (PET)(Corfield et al., 1995) bilateral activations in basal ganglia, thalamus, red nucleus, cerebellum, parietal cortex, cingulate and rostral pons(McKay et al., 2010) as seen using fMRI. In subcortical areas and brainstem, similar experiments show increased BOLD signal in thalamic nuclei (left ventroposterolateral (VPL), left ventrolateral (VL), bilateral AV), GP, putamen, pons and medulla(Pattinson et al., 2009b). These sites correspond to areas of the CAN and brainstem areas correspond to Kolliker-Fuse and parabrachial nuclei (PBN) which receive vagal afferents from pulmonary stretch receptors and glossopharyngeal chemosensory afferents via the NTS. An important confounding factor of fMRI studies is that altering CO_2 leads to cerebral vasodilatation and can affect low frequency BOLD signal variations(Wise et al., 2004). Thus, there are advantages of directly measuring and stimulating human brain areas (albeit with the disadvantage that the whole brain cannot be imaged).

Prior to my studies on the respiratory effects of DBS, a small number of studies had identified respiratory rate (RR) changes as a result of electrical stimulation. For example, (Lipp et al., 2005) describe a case in which an electrode in close proximity to the posterior hypothalamus induced an increase in BP and RR. DBS of the anterior limb of the internal capsule has also been shown to increase RR in the context of emotions such as panic and fear and effects are voltage-dependent(Okun et al., 2007, Shapira et al., 2006).

My studies on respiration (studies 1-4) demonstrate that DBS can be used as a tool for both understanding the neural circuitry underlying respiratory control, as well as probing potential clinical applications. I have demonstrated that manipulation of deep brain nuclei alters normal respiratory physiology i.e., in subjects without respiratory disease. Study 2(Green et al., 2019) shows that the effect can be profoundly beneficial in the context of respiratory disease, albeit in a single patient.

Study 3 demonstrates that therapeutic DBS for movement disorders can have either adverse or beneficial effects on breathing. Prior to these studies, there had been no systematic study of the effects of DBS on breathing in humans and this work helps to lay a groundwork for further studies by assessing candidate nuclei. In addition, it is the first body of work to propose that DBS may have respiratory side-effects and to demonstrate it in a patient cohort. This will help the field in designing DBS systems to take into account these effects and to give a better patient experience. Respiratory disease is a cause of major morbidity and death(Societies, 2017). There are two forms of obstructive airways disease: reversible and obstructive. Regarding reversible airways disease, there is a considerable body of evidence that supports a role of the CNS in its pathophysiology(Barnes, 1995). For example, in asthma there exists a parasympathetic hyper-responsiveness(Shah et al., 1990) demonstrated by a reduced low frequency component of HRV(Garrard et al., 1992). Studying the CNS component of reversible airways diseases may aid our understanding of the pathophysiology or help to design new treatments aimed at altering the CNS component. Whilst my early results are encouraging, further investigation needs to establish a) whether DBS can cause sufficient bronchodilatation to reverse asthma and b) whether the response in the neural circuitry in an asthmatic will be the same, given the degree of dysautonomia that pre-exists. There are also unanswered questions on mechanisms such as whether PAG stimulation exerts via the inhibitory effects of medullary nuclei on the AVPNs, direct reduction of sympathetic activity that we have shown (Sverrisdottir et al., 2014), or a combination. Regarding STN, the possible mechanisms are less clear. Because of its role in inhibiting initiated responses in go/ no go tasks(Antoniades et al., 2014, Brittain et al., 2012), it has been implicated in breath holding, although there is no evidence for this in imaging studies(McKay et al., 2008). There have been a number of studies looking at the effects of STN stimulation on speech with particular respect to laryngeal muscle function. For example, (Gentil et al., 2003) saw improvement in voice with STN stimulation (increased lip and tongue force, more stable and sustained vowel production and reduced pauses during phrase repetitions). However, other studies have shown worsening dysarthria with STN stimulation(Tripoliti et al., 2011). Another putative mechanism, similar to the mechanism of PAG stimulation, is that STN stimulation alters sympathetic output. I observed altered sympathetic output with STN stimulation although the order of magnitude of such changes is small(Sverrisdottir et al., 2014).

I have shown that DBS can increase or decrease dyspnoea (breathlessness) depending on the target and/or disease state (studies 2-3). Dyspnoea is not well understood, especially the cerebral mechanisms. Cortical areas identified using fMRI that are specific to dyspnoea include limbic, paralimbic and cerebellar activation(Evans et al., 2002). Evidence for a role of the thalamus come from studies that show that thalamic activation is related to the level of respiratory drive(Chen et al.,

1992). In fact, the areas involved in dyspnoea are similar to those involved in networks of chronic pain(Apkarian et al., 2005) which may be explained by the fact that the sensation of breathlessness has many similarities to the sensation of chronic pain, both physiologically and emotionally.

Regarding the PPN, the rostral part (where our electrodes predominantly are) is equivalent to the MLR in animals. Chong and Bedford showed, in rats, that MLR stimulation increases arterial blood pressure (ABP) and heart rate (HR) as well as locomotion(Chong and Bedford, 1997). A subset of MLR neurons have been identified that increase ventilation with locomotion(Gariepy et al., 2012). The PPN consists of a large population of cholinergic neurons that normally have an inhibitory effect on muscle tone(Takakusaki et al., 2011). It may be that DBS modulates these neurons in a situation in which tone is increased (rigidity) and therefore improves their function, and this may include the respiratory muscles in addition to the axial somatic musculature. An alternative hypothesis is that PPN stimulation increases arousal/ attention. The PPN forms part of the ascending arousal system and alpha activity has been postulated to be an index of active suppression to block distractors to enable focussing on a desired subject(Ward, 2003). Another aspect that should be borne in mind is that the brainstem regions being stimulated are in very close proximity to other nuclei that may influence respiratory control. For example, the KFN and PBN (see figure 1) are situated below and adjacent to the PPN respectively. Specific parts of this complex have been shown to modulate respiration when stimulated such as causing hyperpnoea, inspiratory responses, and apnoea(Chamberlin and Saper, 1994), and can also cause locomotor-respiratory entrainment(Giraudin et al., 2012).

Cardiovascular Control (Studies 5-7)

An important component in beat-to-beat cardiovascular control is the arterial baroreflex. Arterial baroreceptors are located in the carotid sinus and aortic arch and distension of the arterial walls stimulates these stretch receptors to fire. Afferent information is projected to the NTS via the glossopharyngeal and vagus nerves(Wieling W, 2001). Within the baroreceptor reflex circuit, the NTS projects to the RVLM indirectly via the CVLM. In response to baroreceptor stimulation, the NTS stimulates the CVLM to inhibit the RVLM's tonic sympathetic outflow. At the same time the NTS excites the NA and DMNX thus producing an increase in parasympathetic tone via vagal outflow with a simultaneous reduction in sympathetic tone. Therefore, increases in blood pressure are counteracted by a shift in the autonomic balance towards parasympathetic activity resulting in a reduction of heart rate via the sinoatrial node and negative inotropic and vasodilatory effects. Low arterial pressure leads to the opposite effects. There are two main findings from my study probing the baroreflex; firstly, that dorsal STN stimulation in PD improves BRS to the vasculature in those with

concomitant autonomic dysfunction, and secondly, that dorsal or ventral PAG stimulation in chronic neuropathic pain results in a differentiated sympathetic discharge pattern and haemodynamic response, similar to the differentiated response of PAG in pain processing and cardiovascular control(Lovick, 1993). There is good evidence that the frequency and intensity (amplitude) of central sympathetic nerve traffic are controlled independently by the arterial baroreflex(Malpas and Ninomiya, 1992, McAllen and Malpas, 1997, Sverrisdottir et al., 2000). The origin of this differentiated control is unknown, but a previous study has suggested that the baroreflex modulation of sympathetic outflow occurs at two separate CNS locations; one that determines whether or not a burst will occur and the other that determines the strength of the discharge(Kienbaum et al., 2001). Our findings lend weight to this hypothesis, especially the difference between dorsal and ventral PAG that could be two separate efferent pathways within this mechanism. In fact, stimulation of no single area resulted in changes in both BI and amplitude.

My results on HRV (study 6) have helped to shed further light on the differential effects between ventral and dorsal PAG stimulation. I found that ventral PAG DBS reduces sympathetic activity, but it is likely that the effects are a combination of sympathetic/ parasympathetic changes. Whilst these results are consistent with animal studies showing changes in CVS parameters between ventral and dorsal PAG stimulation, it is difficult to interpret the influence of changes in pain relief between the ON and OFF conditions. Pain reduced in both groups but the changes in HRV were only observed in the ventral group. The relationship between the ANS and pain is complex and there is much evidence that the ANS is altered in chronic pain(Birklein et al., 1998). However, it is likely that the analgesic mechanisms of ventral and dorsal PAG DBS are different. Whilst ventral DBS may act via a vagal mechanism, dorsal DBS may act via a 'fight or flight' effect associated with sympathomimetic effects(Green et al., 2006a, Green et al., 2006b). There is good evidence that dorsal PAG DBS works via an intrinsic endogenous opioid mechanism based in the caudal dorsal PAG(Sims-Williams et al., 2017) whereas this does not appear to be the case for ventral. DTI analysis in our study, show different connections between CAN targets and ventral PAG (predominantly amygdala, nucleus accumbens, ACC, ventromedial prefrontal cortex) compared to dorsal PAG (ventral posterior thalamus and primary somatosensory cortex).

Central Command

For over 100 years, evidence has emerged that 'higher' centres(Krogh A, 1913) and information from working muscle(Zuntz N, 1886, Johansson, 1893) regulate the cardiorespiratory responses to exercise. The concept of 'cortical irradiation' first proposed by Krogh & Lindhard(Krogh A, 1913) suggested that

higher centres were involved in the anticipatory response to exercise. The aim of my ACC central command study (study 7) was to re-visit Krogh and Lindhard's classic paper on 'cortical irradiation' driving the anticipatory cardiorespiratory response to exercise, in addition to tying together our work on the effects of DBS on respiratory and cardiovascular control. The experimental design does not permit the unambiguous conclusion that the dorsal ACC *drives* heart rate changes during anticipation of exercise. I have demonstrated a correlation but to show a direct relationship would require experimental designs utilising neural stimulation. This unique data providing awake dACC recordings during a task that dissociates central from peripheral influences on HR does however provide evidence that the dACC is active selectively during periods associated with central command. These results are consistent with a number of studies that demonstrate that the ACC is part of central network that drives sympathetic autonomic processing(Gentil et al., 2009, Gianaros et al., 2012), often in the context of either anticipation (such as cognitive tasks) and the experience of pain(Seifert et al., 2013). Whilst ACC responses involved in anticipation are not exclusively associated with autonomic output(Frith and Allen, 1983), Critchley et al have also shown the converse; that the ACC can generate cardiovascular arousal independent of cognitive and motor activity(Critchley HD, 2003).

4: Future Work

Much of the work in this thesis is aimed at understanding the neurocircuitry underlying cardiorespiratory control using the opportunity of studying human patients implanted with DBS electrodes. However, there will always be limitations with respect to investigating the central nervous system in this way, as compared to animal studies because of the following reasons; a) the need to use electrodes that are being implanted for existing conditions in specific nuclei i.e. we have a limited range of brain areas to choose from; b) the fact that we are implanting electrodes into patients with underlying neuropathology (albeit the disease may or may not be relevant to autonomic function); c) we are not able to use histology to confirm electrode placement except once a patient has died and undergone post-mortem studies, which is uncommon. However, in terms of understanding physiology, the work is useful because it a) confirms the findings from animal studies and ensures that they are relevant to humans, and b) allows the integration of physiology

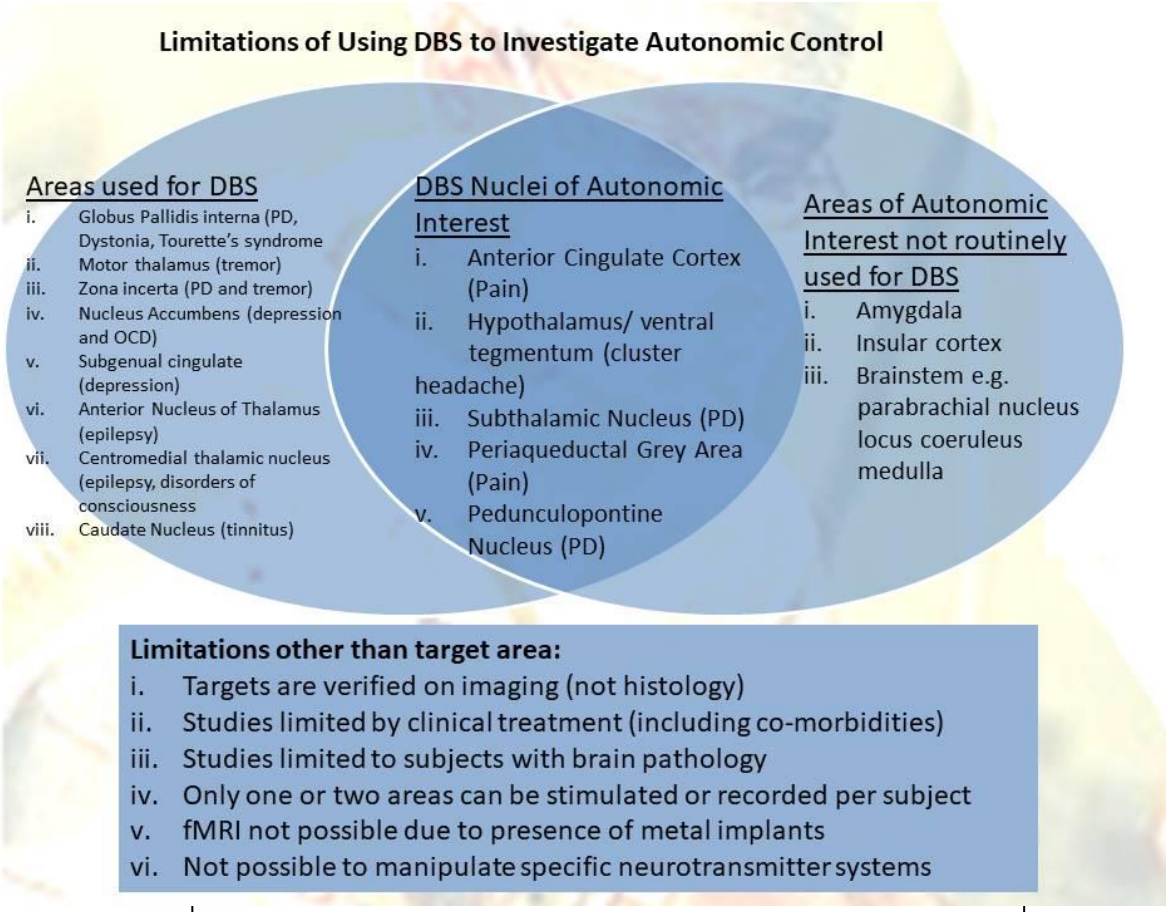


Figure 12. Summary of Brain Areas used and not used for DBS

with higher human functions that are not possible in animals (such as cognition or self-reported outcomes). Figure 12 summarises the limitations of using DBS to investigate autonomic control.

Besides unique insights into autonomic mechanisms in human models, perhaps the most useful aspect of this work is that it highlights and provides some groundwork for translation of the autonomic findings into therapies for patients(Hyam et al.). This takes the form of modifying existing DBS treatments in order to optimise autonomic outcomes and producing new therapies specifically for autonomic control. The combination of my findings of PPN DBS effects on BP and the predominance of orthostatic hypotension in a subtype of patients with MSA has led to our ongoing first-in-man study of PPN DBS in MSA (Deep Brain Stimulation for Autonomic and Gait Symptoms in Multiple System Atrophy - Full Text View - ClinicalTrials.gov) – the STAG-MSA trial.

In 2005, Gotoh designed an elegant system that could control beat-to-beat BP in the rat using PAG stimulation, with feedback from peripheral arterial pressure monitoring, and an intervening microprocessor(Gotoh et al., 2005). In this thesis, I have demonstrated that the neural substrate in the human, at least in principle, should respond in the same way. Similarly, with respiratory control it is likely to be possible to produce a closed-loop electrical system that responds to breathlessness and either supresses it (if it is abnormally increased) or increases breathing, depending on what is physiologically appropriate. There are two main factors that would be needed in order to design DBS to control either the cardiovascular or respiratory system. First, closed-loop technology has to be developed so that stimulation can respond to abnormal cardiorespiratory physiology. My findings show that brain recordings (LFPs) can be measured via DBS electrodes and that these signals are altered in specific cardiovascular states (such as during central command). More work is needed to identify neural signatures that signify specific outputs such as BP or heart rate (if these exist). Another alternative is to feedback from peripheral sensors such as implantable or wearable devices. This is indeed happening in the field of DBS for Essential Tremor(Herron et al., 2017). In the follow up to our STAG-MSA trial, we will develop a device capable of closed-loop orthostatic BP control and have preliminary data on the benchtop to show that BP data can be used to alter stimulation (unpublished results).

The second factor that may have to be improved to unlock potential cardiorespiratory applications of DBS is safety. DBS carries a 1:2-300 risk of stroke and whilst it is feasible to use it in a debilitating neurodegenerative procedure, this is more difficult to justify in a condition such as refractory hypertension which may be asymptomatic. Technology to reduce risk includes planning software that better enables the surgeon to visualise blood vessels. However, given that there is always a risk with inserting an electrode into the brain, perhaps the answer may come from external stimulation such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). At present, these technologies can only stimulate diffusely on the cortical surface but it is possible that there will be future techniques to ‘focus’ stimulation in a deep brain area, such as a recent technique

called ‘temporal interference’ (Xin et al., 2021). Another possible technique may be insertion of endovascular electrodes such as using nanowires(Watanabe et al., 2009).

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APPENDIX (following pages) : Published papers related to this thesis

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