THE UNIVERSITY OF MELBOURNE, AUSTRALIA

Duloxetine for Pain in Parkinsons Disease

Shahrul Azmin Md Rani

MBChB, MMed

ORCID ID:0000-0003-4102-7915

Submitted in total fulfilment of the requirements of the degree of

DOCTOR OF PHILOSOPHY

August 2020

Department of Neurology

Royal Melbourne Hospital

Department of Medicine, Royal Melbourne Hospital

The University of Melbourne

Preface

The content of this thesis comprises my original work and does not contain any material previously published by someone else except where indicated in the text. The work has been conducted since the commencement of my higher degree candidature at the University of Melbourne and has not been submitted for conferment for other qualifications.

Abstract

Pain in Parkinsons disease is common and poorly managed. The body of literature showing that pain adversely impacts on the quality of life of Parkinsons disease patients is overwhelming. Different strategies have been adopted to address pain in Parkinsons disease but results have been mixed.

The pathophysiology of pain in Parkinsons disease is thought to involve dopaminergic and extra-dopaminergic factors. Duloxetine, a serotonin and noradrenaline reuptake inhibitor has been used for pain in multiple sclerosis and painful diabetic peripheral neuropathy.

We embarked on a project to explore the role of duloxetine in Parkinsons disease patients with pain in a randomized double blind placebo controlled trial using validated pain questionnaires, pain sensitivity measurements and functional imaging techniques.

We showed a statistically significant improvement in the pain scores of the affective component of the Short-Form McGill Questionnaire and a trend towards improvement in pain tolerance following evoked pressure stimulus in the duloxetine group as compared to the placebo group. Additionally, the changes were not associated with changes in the affective states of the participants, as measured by the Geriatric Depression Scale and Positive Affect and Negative Affect Schedule. We did not find any statistically significant difference in the task-based fMRI and the resting state fMRI between the groups.

In conclusion, our study showed that duloxetine may be most effective in addressing symptoms arising from the affective dimension of pain in Parkinsons disease patients.

Author Declaration

This is to certify that:

1. This thesis comprises my original work except where indicated otherwise
2. Due acknowledgments have been made in the text to all other materials used
3. This thesis is less than 100,000 words in length exclusive of table, figures, bibliography and appendices

Signed

Shahrul Azmin Md Rani

Acknowledgements

I owe a massive debt of gratitude to my two supervisors and teachers, Dr Andrew Evans and Assoc. Prof. Dr Michael Farrell.

Dr Evans helped me find my feet when I first arrived in Australia, held my hand when I needed support and provided inspiration through his breadth of knowledge, clinical acumen and humility.

Prof. Farrell has been my mentor and my guide in the foreign world of functional neuroimaging, dispensing advice with patience and wisdom.

In addition of my teachers mentioned above, this PhD would have suffered a premature death if not for the assistance provided by the souls mentioned below.

Dr Simon Sung, who helped set me up in the early days.

Drs Tamara Canento, Belinda Cruse and Christine Wools, who helped tie up the various loose ends at the tail end of my study.

Mr Michael Kean and his team of MRI technologists at the Murdoch's Children Research Institute, for assisting me in putting the participants through the scanner for some 'magnet time'.

Finally, my thanks and appreciation to my family, Suehazlyn and Hamka for agreeing to join me on this journey and for enduring the pain of my occasional disagreeable temperament (evoked by stress) throughout the journey.

TABLE OF CONTENTS

List of Abbreviations

ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
BOLD	Blood oxygen-level dependent
COMT	Cathecol-O-methyltransferase
DBS	Deep brain stimulation
DNIC	Diffuse noxious inhibitory controls
fMRI	Functional magnetic resonance imaging
JNP	Just noticeable pain
LEDD	Levodopa equivalent daily dose
MEG	Magnetoencephalography
MP	Moderate pain
NAcc	Nucleus accumbens
NSAID	Non-steroidal anti-inflammatory drug
NMDA	N-methyl-D-aspartate
PAG	Periaqueductal grey
PCC	Posterior cingulate cortex
PD	Parkinsons disease
PDQ-39	Parkinsons disease questionnaire-39
PET	Positron emission tomography
QST	Quantitative sensory testing
RVM	Rostroventral medulla
SEP	Somatosensory evoked potential
SNP	Single nucleotide polymorphism
SNRI	Serotonin noradrenaline re-uptake i
SPECT	Single-photon emission computed tomography
UPDRS	Unified Parkinsons disease rating scale

List of Tables

List of Figures

Thesis Overview

Parkinsons disease is the second commonest neurodegenerative syndrome after Alzheimers disease.(Nussbaum & Ellis, 2003) Although it is difficult to determine the prevalence rate due to differences in epidemiological methods, it is generally accepted that in unselected populations in Europe, Parkinsons disease affects 1 to 2 per 1000.(von Campenhausen et al., 2005) The prevalence rate increases to 1% in those above the age of 60 years old.(de Lau & Breteler, 2006)

The toll that Parkinsons disease inflicts on the economy is crippling. In Singapore, the estimated annual healthcare cost is USD 10,129 per patient(Zhao et al., 2011). The health care costs exceed USD 13,000 annually in the United States of America.(Huse et al., 2005; O'Brien, Ward, Michels, Tzivelekis, & Brandt, 2009) In Australia, the total financial cost of Parkinsons disease amounts to AUD 15,400 per annum per patient in 2014, signifying an increase of 61% since 2005. (Deloitte, 2015)

The economic pressures will continue unabated. It is estimated that the medical bill for Parkinsons disease will at least double by the year 2040.(Kowal, Dall, Chakrabarti, Storm, & Jain, 2013) This is due to the projected doubling of the number of people with Parkinsons disease by the year 2040 to at least 12 million patients worldwide, driven principally by an aging world population, coupled with additional factors such as declining smoking rates and increasing industrialization.(Dorsey, Sherer, Okun, & Bloem, 2018)

Classically, Parkinsons disease has been associated with motoric symptoms such as resting tremor, bradykinesia and rigidity. Over the recent decades, non-motor symptoms such as pain and depression have been increasingly recognized as equally important aspects of Parkinsons disease.

This has major economic implications. Research has shown that non-motor symptoms are more prevalent than previously thought.(Barone et al., 2009) It

has also been shown that non-motor symptoms can exert a greater adverse impact than motor symptoms on the quality of life of Parkinsons disease patients.(Schrag, Jahanshahi, & Quinn, 2000) Finally, non-motor symptoms often go unreported and undetected; its presence frequently missed during clinic consultations.(O'sullivan et al., 2008) This may mean that the actual burden of disease due to Parkinsons disease is under reported and the economic impact may arguably be grossly under-estimated.

Although aggressive efforts are underway in the pursuit of a cure, the management of Parkinsons disease presently is essentially symptomatic. The cornerstone of Parkinsons disease management is dopamine replacement therapy. To some extent, this approach has been successful in providing relief from motor symptoms but is less effective in addressing non-motor symptoms such as pain and depression.

The management of pain in Parkinsons disease is especially challenging. Studies exploring the use of analgesic therapies such as paracetamol, NSAIDs and opioids in other chronic condition such as back pain and fibromyalgia show poor results.(Chou et al., 2015) The same limitations also occur in Parkinsons disease patients with pain and there is a distinct lack of evidence-based guidelines for its treatment. A study showed that in Parkinsons disease patients that were prescribed analgesia, primarily in the form of paracetamol and NSAIDs, only a third reported relief from pain symptoms.(Skogar et al., 2012) A randomized double-blind placebo-controlled trial using an opioid based analgesia for Parkinsons disease patients experiencing chronic pain failed to show improvements in average 24-hour pain scores at 16 weeks, despite experiencing significant nausea and constipation.(Trenkwalder et al., 2015)

Another impetus for better management of pain is the opioid crisis. The U.S Drug Enforcement Administration published a report in 2015, stating that “overdose deaths from prescription drugs and heroin have reached epidemic levels”, prompting President Donald J. Trump to declare the opioid crisis as a national emergency on the 10th of August 2017.(Gostin, Hodge, & Noe, 2017) Ninety

Americans die from opioid overdose daily.(Rudd, Aleshire, Zibbell, & Gladden, 2016) Although currently thought to be a problem primarily impacting the United States of America, recent data has shown that the problem is spreading to other nations globally. The opioid crisis is thought to be a consequence of an overly liberal policy of opioid prescribing in the 1990's. This policy, to some extent, is a reflection of the limitation of drugs available to treat chronic pain.

With this in mind, there is a strong argument on the need to investigate other pharmaceutical agents, beyond the traditional 'pain-killers', to manage pain in Parkinsons disease. In addition to confirming that certain pharmacological agents 'work', it is equally important to try to determine the mechanism of how the agents exert its effect.

Duloxetine is a serotonin and noradrenaline reuptake inhibitor with antidepressant and pain-relieving properties. It is licensed by the US Food and Drug Administration (FDA) for the treatment of depression and painful diabetic peripheral neuropathy. In comparison with other antidepressants, duloxetine has a relatively balanced high affinity to both noradrenaline and serotonin reuptake transporters. A study conducted in an open-labelled design framework showed that duloxetine may be of benefit in managing pain in Parkinsons disease.(Djaldetti, Yust-Katz, Kolianov, Melamed, & Dabby, 2007) Possible explanations of the mechanism of action for pain relief include recruitment of intrinsic analgesic pathways that involve both dopaminergic and extra-dopaminergic systems.(Bellingham & Peng, 2010)

The overarching aim of this research is to provide a better framework for managing pain in Parkinsons disease. We hope that our findings will advance the research on pain in Parkinsons disease and add to the body of knowledge relating to pain conditions in the elderly population in general.

Chapter 1: An Introduction to Pain

1.1 The History of Pain

The theory of pain has evolved over the ages. During the period of the ancient civilizations, the theory of pain was imbued with a lot of mysticism and divine intervention.(Meldrum, 2003) With the age of enlightenment, the theory of pain evolved with underpinnings based on scientific experiments and empirical findings.

In ancient Chinese civilization, pain was attributed to the imbalance of *yin* and *yang*, as described in the ancient traditional Chinese medicine text *Huang Di Nei Jing* (translated The Medical Classic of the Yellow Emperor).(Chen, 2011) The philosophy in traditional Chinese medicine with regards to pain is the restoration of the *yin* and *yang* imbalance.

In ancient Western civilization, Homer in the 8th century BC wrote regarding "*Telemachus, who soothed his pain and worries with opium*" in his opus *the Odysse*y.(Rey, Wallace, Cadden, Cadden, & Brieger, 1995) The Father of Medicine, Hippocrates (460-370BC) believed that pain stems from an imbalance of fluids in the body (humor), and the heart was the central organ for pain.(Linton, 2005) Aristotle, the Greek philosopher (384-322BC) argued that pain is an emotion, considering how it impacts on one's disposition.

Ibnu Sina (Avicenna 980-1037), a Persian polymath and physician put forth the concept of pain to be an independent sensation, distinct from touch or temperature recognition. This became the precursor to what later became to be the *specificity theory of pain*.

During the renaissance period, the French philosopher Rene Descartes (1596-1650) transformed the concept of pain from the spiritual to the mechanical. In *L'Homme*, Descartes introduced the concept of pain as a nerve impulse, travelling from the periphery to the brain. With this, the central organ for pain was

transferred from the heart to the brain and this new ideology regarding pain had a profound influence on pain research for the next three centuries (Figure 1.1).(Hadjistavropoulos & Craig, 2004)

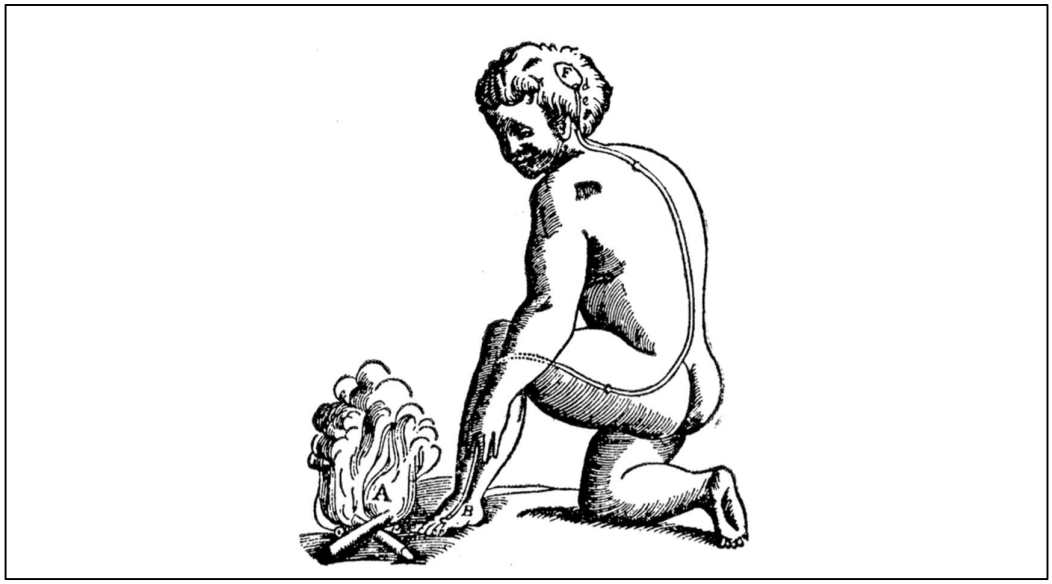


Figure 1.1 Transmission of nociceptive stimulus.

Stimuli from the periphery (thermal heat) is converted to nerve signals and travels to the brain. Descartes R, et al. L'homme et un Traitté de la ormation du Foetus du Mesme Autheur. Paris: Charles Angot, 1664

1.2 Modern Theories of Pain

1.2.1 Specificity theory of pain

Major inroads towards understanding pain were made in the 20th century and 2 competing school of thoughts emerged with regards to the theory of pain. The specificity theory postulates that pain is subserved by dedicated nerve pathways. This theory builds on the work by Avicenna and was first proposed by the Scottish anatomist Charles Bell (1774-1842), who commented that ventral and dorsal roots of the spinal cord differed in their role; the ventral roots more focused with motoric tasks.(Perl, 2007) Charles-Edouard Brown–Sequard (1817-1894) further developed this theory by documenting loss of pain sensation contralateral and distal to a transverse hemisection of the spinal cord.(Chen, 2011) Lending credence to this was the discovery by Emil duBois-Reymond (1818-1896) that different stimuli triggered a nerve impulse that has the same electrochemical characteristics, irrespective of the stimuli, be it heat or touch or vibration.(Perl, 2007) It was therefore surmised that if the nature of the nerve impulse is the same, the nerve ending and pathways must provide the differential to enable the higher centres of the brain to isolate the different sensations from the periphery.

1.2.2 Intensity theory of pain

A competing school of thought was the intensity theory as espoused by Wilhelm Erb (1840-1921).(Chen, 2011) The intensity theory postulates that pain is an amalgamation of cumulative nervous stimuli that compounds into the sensation of pain, once a certain threshold is breached.

1.2.3 Gate control theory of pain

In 1965, Drs. Ronald Melzack and Patrick Wall introduced a concept that triggered a paradigm shift in the concept of pain.(Melzack & Wall, 1965) The accepted wisdom prior to that point in time was that the sensory impulse

originating from the periphery travelled along the neuraxis in a passive and unadulterated manner with no modulation in the intensity of the impulse.

Using the building blocks of the pattern theory of pain, they proposed another concept called the gate control theory of pain. In this theory, a neural gate located at the dorsal horn of the spinal cord controls the ascending transmission of neural signals along the spinal cord. The neural gate is influenced by emotional and attentional states and modulated by higher centres of the brain.

1.3 What is Pain?

The International Association for the Study of Pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".(Raja et al., 2020) Pain can be evoked by tissue injury, disease and noxious environmental stimuli.

Pain may be acute or chronic. The experience of acute pain results from the activation of nociceptors following tissue damage. Acute pain is a defence mechanism, an adaptive process that strives to prevent further tissue damage and thus important for survival and the preservation of life. Adaptive effects of pain include the avoidance of noxious stimuli, vigilance of injured tissue to encourage healing and the amelioration of the disease that is evoking pain.

Chronic pain occurs when pain persists for more than 3 months, or when the pain persists despite the completion of the healing process. Chronic pain is a maladaptive process and is coloured by psychological, social and physical factors, and may adversely impacts on the quality of life of sufferers.

Chronic pain can be classified into 3 further categories. Firstly, nociceptive pain which refers to pain relating to tissue disease or damage i.e. osteoarthritis. Secondly, pain relating to disease or damage to the somatosensory system which is termed neuropathic pain. Finally, chronic pain can also be due to a combination of neuropathic and nociceptive pain.

Pain is a multidimensional sensory experience. It can be divided into several dimensions, namely;

a) Sensory-discriminative; refers to the qualitative aspects of pain i.e. intensity and localisation of the pain. The lateral pain pathway subserves the sensory-discriminative dimension of pain.

b) Affective-motivational; refers to how the pain affects emotionally (i.e. fearful, tearful) and the motivational drive to seek relief from the pain (i.e. analgesia, suicide).

c) Cognitive-evaluative; refers to the sufferers' belief and attitudes towards pain. The cognitive-evaluative and affective-motivational dimensions of pain are both subserved by the medial pain pathway.

1.4 Pain and nociception

Nociception occurs when specialized receptors in the periphery become activated by noxious stimuli and alerts the organism that the state of health of the organism is in jeopardy. In contrast, pain can be considered an 'opinion of the brain' about the state of health of the organism, and relies on the aforementioned nociceptive input and also influenced by other factors such as the attentional and psychological state of the organism.

The relationship between nociception and pain is non-linear. Under certain condition, the response to noxious stimuli and the resultant pain experience can be exaggerated. This is usually due to dysfunctional processing of incoming sensory information in the central nervous system. In neuropathic pain, this can manifest as hyperalgesia and allodynia.

In hyperalgesia, there is a leftward shift in the response stimulus function relating to the pain magnitude towards the intensity of the stimulus. The resultant clinical effect is increased intensity of pain perception. In contrast,

allodynia refers to an experience of pain following an otherwise non-noxious stimulus.

This phenomenon can occur in an adaptive or a maladaptive setting. In the adaptive setting, hyperalgesia can encourage adoption of behaviour that would enhance the recovery following damage and injury i.e. extra vigilance of a limb following a fracture. A maladaptive response usually occurs in the setting of chronic pain.

Importantly, hyperalgesia and allodynia are clinical terms and does not imply the underlying mechanism. Indeed, one pathological condition e.g. diabetic peripheral neuropathy can result in different symptoms of neuropathic pain e.g. hyperalgesia or allodynia in different individuals. Furthermore, the symptom of neuropathic pain can be the result of completely different conditions e.g. multiple sclerosis, post-stroke pain.

Hyperalgesia and allodynia can be categorised according to the modality used to evoke pain, namely mechanical (dynamic, static and punctate) and thermal (hot and cold) stimuli. Dynamic mechanical allodynia is thought to be mediated by low threshold Aβ fibres,(Koltzenburg, Torebjörk, & Wahren, 1994; Landerholml & Hansson, 2011) whereas punctate allodynia and hyperalgesia is thought to be driven by activity of Aδ fibres with minor input from C fibers.(Ziegler, Magerl, Meyer, & Treede, 1999) It is thought the static allodynia is due to sensitized peripheral nociceptors.(Koltzenburg, Lundberg, & Torebjörk, 1992)

The molecular mechanism underlying allodynia and hyperalgesia are many. This includes the up-regulation of specific potassium and sodium channels triggered by the release of algogenic substances such as substance P, cytokines and nerve growth factors following injury.(Basbaum, Bautista, Scherrer, & Julius, 2009) A phenotypic switch, which describes the phenomenon of expression of neuropeptides important in sensitization of nociceptive stimulus i.e. substance P, calcitonin-gene-related peptide (CGRP) and BDNF, by peripheral afferent fibers not normally involved in the transduction of nociceptive stimulus, such as the Aβ

afferent fibers, is another mechanism that is thought to instigate hyperalgesia and allodynia.(Nitzan-Luques, Minert, Devor, & Tal, 2013)

Proper recognition of the symptoms of hyperalgesia and allodynia is important, especially in the clinical trial setting investigating new compounds for analgesia. Indicators such as pain intensity and degrees of pain relief may be insufficient as an outcome measures to determine treatment response. In a meta-analysis looking at pharmacological treatment for neuropathic pain, no superiority of test compound over placebo was observed in many of the study trials.(Finnerup, Sindrup, & Jensen, 2010) It is argued that one of the explanation is that many of the trials failed to identify responders due to the selection of outcome measures that failed to discern groups with different underlying pathophysiological mechanism.(Attall et al., 2011) Arguably, incorporating outcome measures that represents hyperalgesia and allodynia that denotes purported underlying mechanisms would enable improved delineation of treatment response.

1.5 The Pain System

The pain system can be generally divided in 3 major components;

- Peripheral afferent nerve fibers that transduce noxious stimuli into nociceptive neural signal via specialized receptors located at sensory nerve endings.
- Central neural pathways consisting of interneurons and projection neurons transmitting to brain areas involved in integration of nociceptive stimuli and processing of pain.
- Disparate brain areas involved in converting noxious stimuli into pain experience. These areas have inputs that integrate attentional and emotional factors in the resultant pain experience.

At each component of the pain system, mechanisms exist that serves to either inhibit or enhance the noxious neural signal depending on certain situational factors.

1.5.1 Peripheral afferent nerve fibers

Noxious stimuli are detected by peripheral afferent nerve fibers possessing specialized receptors (nociceptors) located at their sensory nerve endings. Nociceptive neural signals are generated following activation of these nociceptors by their corresponding noxious stimuli e.g. thermal stimuli activating thermal nociceptors. Noxious stimuli are not detected due to an over stimulation of other kind of receptors, such as receptors for light touch.(Willis & Westlund, 1997)

The peripheral afferent nerve fibers can be grouped according to their diameter width and myelin properties. Relevant to the process of nociception are the Aδ and C peripheral afferent fibers.

The C peripheral afferent nerve fibers are the smallest diameter fiber (0.4-1.2 μm) involved in sensation. The fibers belonging to this group are unmyelinated and thus transmit nerve impulses at a comparatively slower conduction velocity of less than 2.5m/sec.

In comparison, the Aδ peripheral afferent fibers have a bigger width diameter (2-6μm) and possessing myelin, allows a higher conduction velocity of 4 to 30m/sec. Generally speaking, C peripheral afferent nerve fibers outnumber Aδ fibers by a ratio of 2 to 1. (Hulsebosch & Coggeshall, 1981; Langford & Schmidt, 1983)

There are other peripheral afferent fibers that are involved in relaying sensory information (Aα, Aβ, Aγ and B peripheral afferent fibers) but are not typically involved in nociception (Figure 1.2).

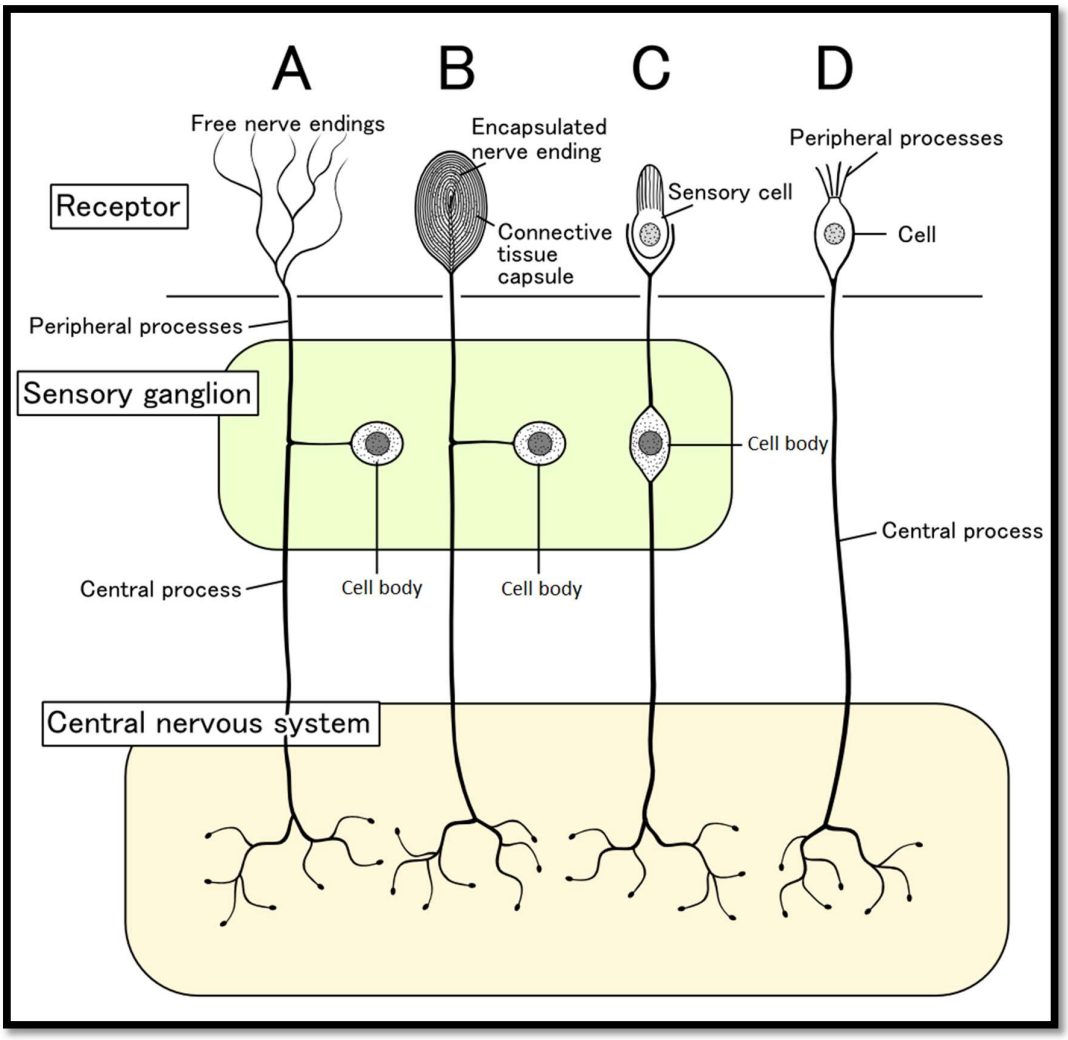


Figure 1.2. Types of peripheral afferent nerve fibers

A, A peripheral afferent fibers; B, B peripheral afferent fibers; C, C peripheral afferent fibers; D, D peripheral afferent fibers.

(The image is licensed under Creative Commons Attribution CC-BY-SA 3.0 by Shigeru23; https://commons.wikimedia.org/wiki/File:Structure_of_sensory_system_(4_models)_E.PNG)

1.5.2 Central neural pathways

The peripheral afferent nerve fibers relaying nociceptive information terminate in the substantia gelatinosa region (Rexed's laminae I-III) in the dorsal horn of the spinal cord. In the substantia gelatinosa, synaptic connections are made with second order neurons, which are either projection neurons or second-order interneurons (Figure 1.3).

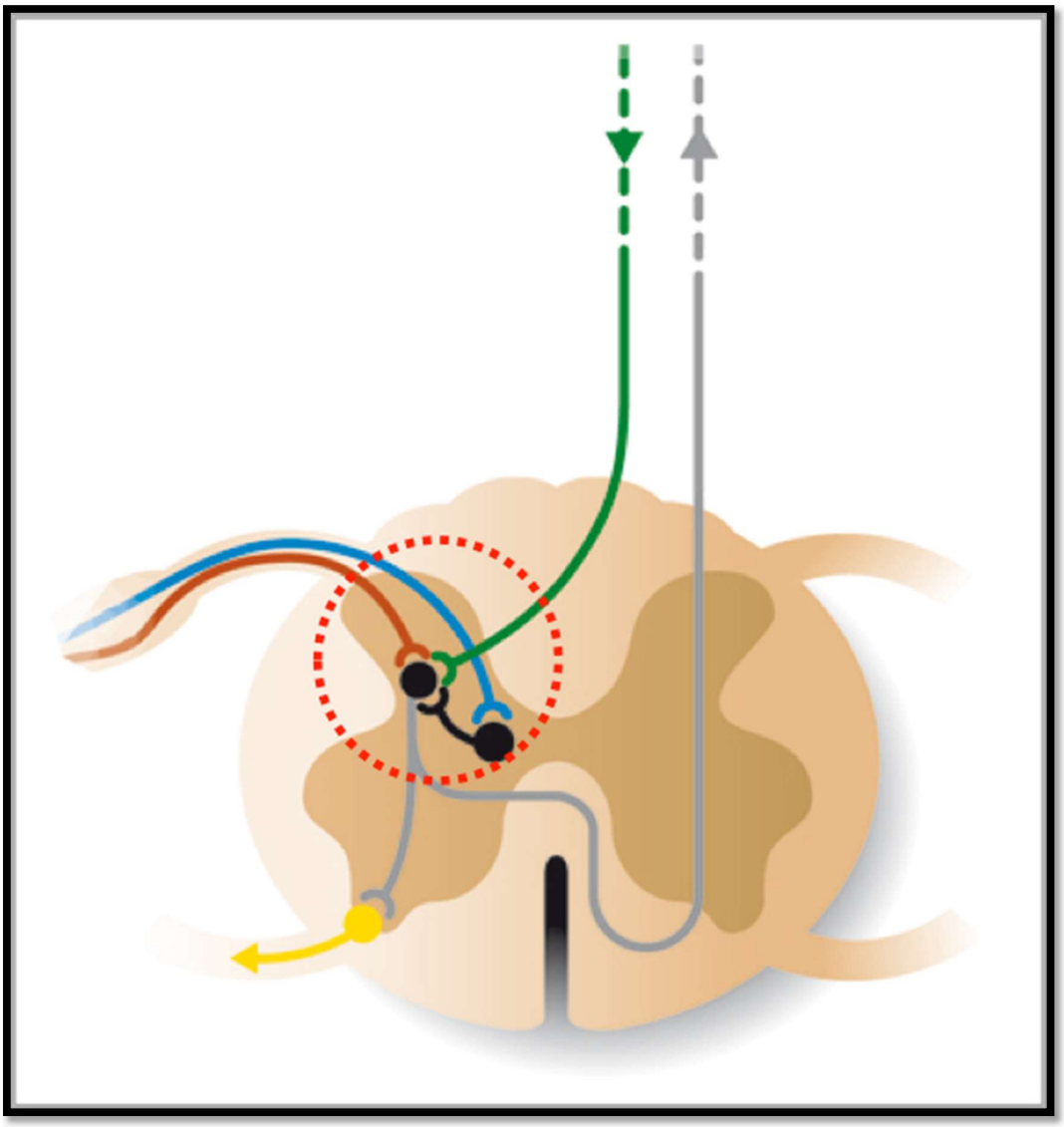


Figure 1.3 Dorsal horn of the spinal cord.
Representation of the peripheral afferent nerve fibers (brown and blue), interneurons (black), projection neuron (grey) and descending neurons (green) in the spinal cord.

The second order projection neurons transmit nociceptive information in ascending fashion up the spinal cord to the higher centres of the brain. This includes the thalamus, the midbrain periaqueductal grey matter, parabrachial areas of the pons and various components of the medullary reticular formation.(Craig, 1995)

The second order interneurons and its projections generally remain in the spinal cord. The interneurons can be categorised into either excitatory or inhibitory interneurons and modulate the incoming sensory information from the primary afferent neurons, depending on a variety of factors and conditions. Glycine or GABA mediates the inhibitory interneurons whereas the excitatory interneurons are mediated by glutamate.

Finally, there is another family of neurons that populate the dorsal horn of the spinal cord. These are the descending axons of neurons originating from the pons and brainstem region, forming synaptic connections with projection neurons in the dorsal horn. These descending neurons are monoaminergic (serotonergic/noradrenergic) and impose either a facilitatory or inhibitory influence to the sensory information carried by the projection neurons (refer section **1.6 Modulation of pain**).

1.5.3 Higher order brain regions involved in nociception and pain.

Nociceptive signals in the dorsal horn primarily ascend to the brain stem via 2 pathways, namely a) spinothalamic tract via termination in the thalamus, or b) spinomedullary and spinobulbar projections with terminations in the medulla and the brainstem (Figure 1.4).

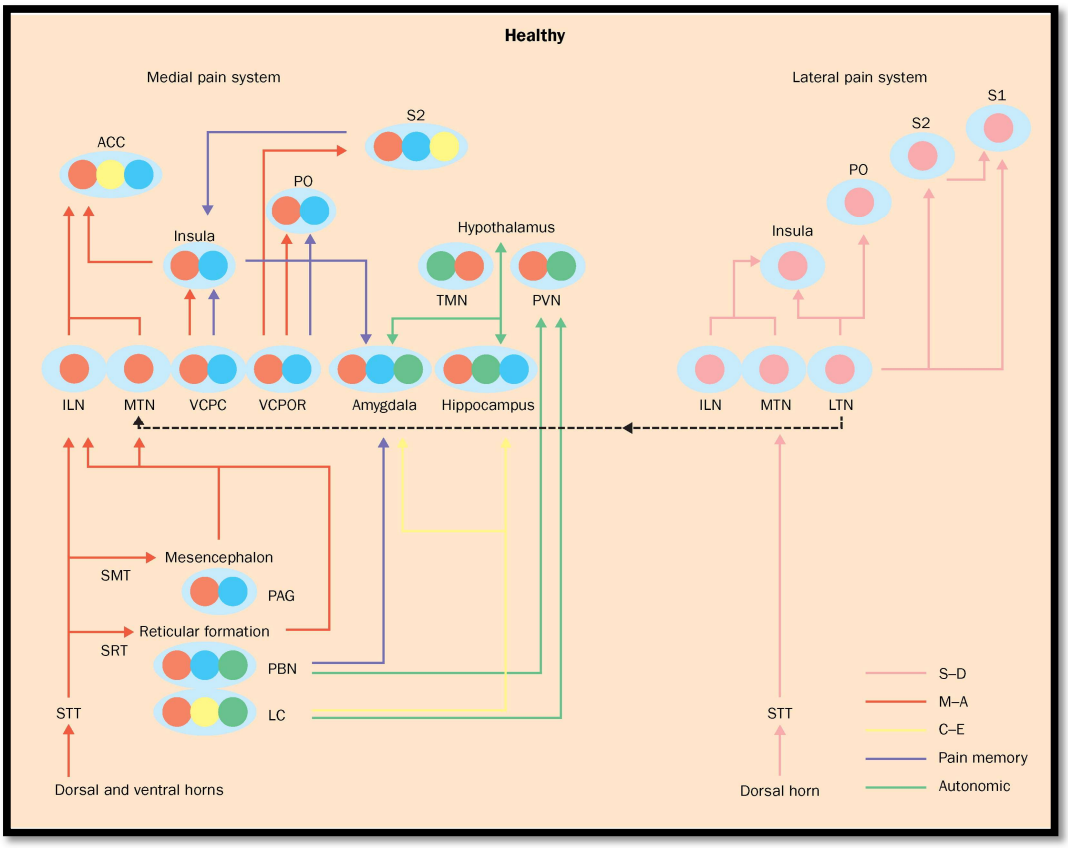


Figure 1.4 Medial and lateral pain systems

ACC, anterior cingulate cortex; C-E, cognitive-evaluative systems; ILN, intralaminar thalamic nuclei; LC, locus coeruleus; LTN, lateral thalamic nuclei; M-A, motivational-affective; MTN, medial thalamic nuclei; PBN, parabrachial nucleus; PAG, periaqueductal grey; PO, parietal operculum; PVN, paraventricular nucleus; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; S-D, sensory-discriminative; SMT, spinomesencephalic tract; SRT, spinoreticular tract; STT, spinothalamic tract; TMN, tuberomamillary nucleus; VCPC, ventral caudal parvocellular nucleus; VCPOR, ventral caudal portae nucleus.

(from Scherder J, Sergeant J, Swaab, D. Pain processing in dementia and its relation to neuropathology. Lancet Neurol 2003; 2: 677-86)

1.5.3.1 Lateral pain system

The spinothalamic tract, with terminations in the lateral thalamus, is considered to be the main the ascending pathway for the transmission nociceptive stimuli to the pain processing regions of the brain. From the thalamus, further projections are made to the insula, parietal operculum, primary and secondary somatosensory cortex. The nociceptive signal transmitted through this system

conveys somatopic information and mediates the sensory-discriminative dimension of pain.

1.5.3.2 Medial pain system

In addition to the lateral pain pathways described above, another parallel pain pathway that is phylogenetically older also transmits nociceptive information into the higher centres of the brain. This pathway follows a more circuitous route in the spinal cord, with multiple terminations within the brain stem, and includes the periaqueductal grey, parabrachial nucleus and the locus coeruleus via the spinoreticular and spinobulbar pathways. From the brainstem, further connections are made with multiple nuclei in the brain that regulates motivation, emotion, attention and memory. This includes the intralaminar thalamic nuclei, medial thalamic nuclei, insula, anterior cingulate cortex, parietal operculum, amygdala, and secondary somatosensory cortex. The medial pain system mediates the memory dimension of pain, cognitive-evaluative dimension of pain and the affective-motivational dimension of pain.

1.6 Modulation of pain

The relationship between the peripheral stimulus and the subsequent experience of pain is not linear. In other words, the pain experience can be modulated by various factors. This includes the presence of other competing somatic stimuli and psychological considerations such as expectation, attention and arousal.

The modulation of pain is an evolutionary adaptive response. The ability to either suppress or heighten the pain experience according to the present situational needs and requirements are an advantage that would enhance the survival and well-being of the organism.

For example, traumatic injuries sustained by soldiers during battle would be reported as painless, but would otherwise be extremely painful during other

situational circumstances. This facilitates the 'flight and fight' response to perform other important life-saving actions.(Beecher, 1946)

There are several important circuits in the central nervous system that performs this important function of pain modulation.

1.6.1 Periaquaductal grey matter (PAG)

The periaqueductal grey matter (PAG) is one of the first supra-spinal structures to be identified for its role in modulating pain. The PAG confers both an excitatory and inhibitory influence on nociceptive processing.

Animal studies have shown that PAG stimulation results in the elimination of the expected response to noxious stimuli such as orientation, vocalization and escape, whilst remaining active and alert.(Mayer & Price, 1976) Indeed, electrical stimulation of the PAG was once used for patients with intractable chronic pain but discontinued due to intolerable side effects of headache, anxiety and depression.(Baskin et al., 1986; Raskin, Hosobuchi, & Lamb, 1987)

1.6.2 Projections into the PAG

Studies have shown the presence of direct and indirect (via the hypothalamus) connections from the amygdala to the PAG.(Bandler & Keay, 1996) The amygdala regulates emotional response, anxiety and stress. Additionally, the limbic forebrain, which is involved in emotive and affective function also projects into the PAG.(Bingel & Tracey, 2008)

Taken together, the connectivity between the PAG with the amygdala and the limbic forebrain suggests that the modulation of pain is influenced and integrated by emotional and affective factors such as fear and anxiety.

Additionally, the PAG is also reciprocally connected with several nuclei in the brain stem, including the rostral ventromedial medulla, locus coeruleus and the pontomedullary reticular formation.(Herbert & Saper, 1992)

1.6.3 Projections from the PAG

The PAG projects to 2 main sites, namely the rostral ventromedial medulla and the locus coeruleus.

1.6.3.1 Rostral ventromedial medulla

The rostral ventromedial medulla (RVM) is a group of neurons located in the midline on the floor of the medulla oblongata. It includes the reticular formation ventral to the nucleus reticularis gigantocellularis and the nucleus raphe magnus. The RVM exerts either an excitatory or inhibitory influence on nociceptive processing in the spinal cord due to the presence of 2 types of neurons, namely the ON (excitatory) and OFF (inhibitory) cells.(Heinricher, Morgan, Tortorici, & Fields, 1994) The projections of the RVM to the spinal cord are primarily serotonergic.

1.6.3.2 Locus coeruleus

The PAG, and to a lesser extent the RVM, also projects into a constellation of nuclei in the dorsolateral pontine tegmentum. Nuclei located in the area include the A5 (locus coeruleus) and the A7 (Kol-liker-Fruse) nuclei.(Bajic & Proudfit, 1999) These nuclei are noradrenergic and are the major source of noradrenergic projection to the dorsal horn of the spinal cord, contributing significantly to pain modulation.(Proudfit, 1992) In contrast to the serotonergic RVM descending modulation pathway, the noradrenergic descending modulation pathway primarily exerts an inhibitory influence on the nociceptive processing in the dorsal horn of the spinal cord.

1.6.4 Diffuse Noxious Inhibitory Control

In addition to the pain modulation pathways described above, Le Bars et al proposed another pain modulation pathway, which consists of a spinal-supraspinal-spinal loop.(Le Bars, 2002) The whole premise of this pain modulation system can be summarized by the adage of "pain inhibits pain". It is based on several basic principles. Firstly, that nociceptive stimuli activate a surround inhibition that enhances contrast between the stimulus zone and the adjacent areas. Secondly, as a consequence there is an overall enhancing effect of the pain intensity in the stimulated area and an overall inhibiting effect in the areas adjacent to the stimulus zone.

The supraspinal area involved in this pathway is the subnucleus reticularis dorsalis. It is located in the caudal medulla and receives afferents from the dorsal horn of the spinal cord via the ascending ventrolateral funiculi and in turn sending descending projection back down to the dorsal horn via the descending dorsolateral funiculi.

Essentially, a noxious conditioning stimulus to a part of the body imposes an inhibitory influence to the ascending nociceptive information arising from other parts of the body. Importantly, this inhibitory effect persists following the removal of the conditioning noxious stimulus.

1.7 Neural Plasticity

The transmission of sensory information to the central nervous system is not fixed or hard-wired. The intensity of the information can be modified by different mechanism at different levels of the central nervous system, from the periphery, dorsal horn and the supraspinal areas, depending on different situational factors. These changes can be short term, long term with associated changes in the protein phosphorylation and gene expression, and permanent with associated with neuronal loss and generation of new synapses.

Plasticity plays an important part in determining the experience of pain by controlling the gain of the system. Plasticity can be an evolutionary response to allow healing and recuperation to occur by protecting injured parts from further injury. However, plasticity can also be a maladaptive phenomenon and contributes to the persistence of pain long after resolution of tissue damage.

An example of plasticity taking place in the periphery is peripheral sensitization. Tissue damage triggers a release of cytokines and inflammatory mediators from the damaged tissue itself (e.g. bradykinins, prostaglandin), immune cells (e.g. IL-1β, TNF-α) and nerve fibers (e.g. substance P, BDNF).(Costigan & Woolf, 2000) These mediators in turn activate nociceptors at the free nerve ending of the peripheral afferent fibers, resulting in a lowered activation threshold and an augmented response to stimulation. Thus, subthreshold stimuli that would normally not generate a nociceptive nerve impulse now generate a nociceptive impulse. This translates to the symptom of primary hyperalgesia.

Central sensitization is an example of plasticity occurring in the spinal cord. Under normal conditions, incoming nociceptive signal triggers the release of the excitatory neurotransmitter glutamate, activating AMPA receptors post-synaptically in the dorsal horn of the spinal cord and sets the baseline response of the second order neurons. However, under conditions where there is a constant and repetitive incoming nociceptive stimuli, the normally dormant NMDA receptor are additionally recruited post-synaptically, resulting in an increase in gain of the nociceptive signal being generated in the second-order neurons. (Ultenius, Linderoth, Meyerson, & Wallin, 2006) This enhanced synaptic efficiency translates into an exaggerated pain response such as tactile dynamic allodynia and secondary hyperalgesia.

1.8 Assessment of Pain

In pain research, 2 important ingredients are essential for the assessment of pain, namely;

- the external stimuli that is used to evoke pain, and
- the evaluation method to measure the resultant pain experience. This can either be in the form of verbal, behavioural and physiological measures

The decision regarding the selection of external stimuli and evaluation method relies heavily on the study objective and outcome of the intended experiment. Each method is associated with its own unique characteristics and it is important to align these properties with the research question at hand.

1.8.1 External stimuli to evoke pain

1.8.1.1 Heat

Heat stimulation is one of the most common method used to evoke pain and can be delivered either by contact or radiant sources. Contact heat is applied using heated water baths and contact thermode.(Chen, Niddam, & Arendt-Nielsen, 2001) Radiant heat method employ an infrared light source although modern derivatives use a laser stimulus source e.g. CO_2, argon and YAG.(Lefaucher, Debray, & Jarry, 2001; Säterö, Klingenstierna, Karlsson, & Olausson, 2000) The temporal and spatial properties of heat stimuli are easily varied and stimulation activates a known group of nociceptors.

1.8.1.2 Cold

Cold stimuli can be administered using the same techniques used to deliver heat stimuli. Delivery can be either in the form of discrete stimuli or continuous stimulation. The most common continuous cold stimulation is the cold pressor test involving immersing a part of the body in ice-cold water (0-4^{o}c), which

produces pain that increases quickly.(Mitchell, MacDonald, & Brodie, 2004) Cold stimuli can also be delivered in the form of contact spray.

1.8.1.3 Ischaemia

A tourniquet is used to impede blood flow and exercising the limb distal to the obstruction produces an evoked pain induced by the resultant ischemia.(Graven - Nielsen et al., 2003) The evoked pain characteristics are similar to what is produced by the cold pressor method.

1.8.1.4 Mechanical

Mechanical stimuli can be applied to evoke pain by using Von Frey hairs and filaments, application of gross pressure using a pressure algometer, high velocity impact using probes and projectiles, and by balloon or fluid distension of viscera. Mechanical methods provide a wide range of intensities and duration but are influenced by physical factors such as tissue elasticity and rate and degree of compression.(Kosek, Ekholm, & Hansson, 1999)

1.8.1.5 Electrical

Electrical stimuli can be applied to the skin, teeth, muscle and viscera. It can also be applied to directly stimulate peripheral and central neurons.(Weidner et al., 2002) Varying the waveform of the electrical stimuli can stimulate different nerve fiber types.

1.8.1.6 Chemical

Chemical stimulation can be applied to intact, punctured or blistered skin, viscera and can be injected intramuscularly.(Gracely, 1999) The degree of control of the stimulus is less but provides unique pain process activation not available by other methods.

1.8.2 Evaluation of pain

1.8.2.1 Visual Analogue Scale

One of the commonly used scale in pain research is the Visual Analogue Scale.(Huskisson, 1974; Scott & Huskisson, 1976) Participants are required to indicate the pain intensity experienced based on a subjective score of between 0 (no pain) to 10 (worst pain imaginable). The participants are then asked to place a mark on a 10cm straight line, anchored at both ends by the value of 0 and 10. The advantage of this scale is ease of use, allowing it to be used in pain studies involving minors. The drawback is that the scale only allows the measurement of one pain dimension at a time i.e. how intense is the pain, or how unpleasant is the pain. Thus, the scale does not reflect the multi-dimensionality of pain and can be considered inadequate in giving a true picture of the pain experience when used on its own.

1.8.2.2 Brief Pain Inventory

This questionnaire was originally developed to measure cancer pain but has gained widespread acceptance and use in chronic pain studies.(Cleeland & Ryan, 1994) The questionnaire measures both the intensity of pain and the magnitude in which the pain interferes with daily life. There are 2 versions, long form and short form; the latter consists of 4 items measuring intensity and 7 items measuring pain interference.

1.8.2.3 Neuropathic pain questionnaires

Neuropathic pain can often be described by unusual terms, such as crawling, burning and shooting pain. Specific questionnaires have been developed to ensure that the types of pain that fall into this category are appropriately captured and include The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropatique en 4 (DN4), and pain DETECT.(Bennett, 2001; Bouhassira et al., 2005; Freynhagen, Baron, Gockel, & Tölle, 2006)

1.8.2.4 Short-Form McGill Questionnaire and King's PD Pain Scale (please refer to **Section 3.3.1 Scales and questionnaires)**

1.8.2.5 Non-verbal evaluation of pain

Non-verbal measures are sometimes used to complement data gained by verbal evaluation methods of pain, especially when there is concern regarding the reliability and validity of verbal capabilities. Techniques that fall under this category are microneurography and electromyogram (EMG) derived spinal reflexes techniques (H reflex, RIII reflex).(Torebjörk, 1993; Vallbo & Hagbarth, 1968)

1.8.3 Neuroimaging in pain

Prior to the advent of brain neuroimaging, pain studies were limited to data obtained from autopsy studies, direct recording of brain activity, patient experience and animal models of pain. Neuroimaging allows researchers to bridge the gap between experiences of pain and brain activity. Some neuroimaging techniques allow real-time interrogation of brain activity in response to nociceptive stimuli. Under the umbrella of neuroimaging, several techniques are used in pain research.

1.8.3.1 Functional MRI

The development of fMRI began in the 1990's.(Ogawa et al., 1992) Since then, it has become one of the most popular imaging tools in neuroscience, as evidenced by the explosion in the quantity of research publications relating to this technique. Whereas MRI scans measure anatomical structures, fMRI measures metabolic function.

Factors contributing to its popularity in neuroscience relates to its qualities in providing an unprecedented ability to image brain activity safely with comparatively good spatial and temporal resolution. Before the advent of fMRI,

imaging studies relied primarily on ionizing radiation techniques, in the form of computed tomography (CT) and positron emission tomography (PET).

The foundation of fMRI technology is based on the fact that active neurons results in a haemodynamic response that begins with an increase in blood flow to the local area of the brain. Consequently, this increase in blood flow leads to an increase in local blood oxygen levels. The magnetic properties of blood are different depending on its oxygen content. Deoxygenated blood is relatively more paramagnetic (attracted by magnetic fields) than oxygenated blood. The MRI scanner detects the signal produced by the difference in the magnetic properties of blood, determined by the ratio between oxygenated and deoxygenated blood that is a reflection of the underlying neuronal activity. This signal is called the blood oxygen level dependant (BOLD).(Pauling & Coryell, 1936; Thulborn, Waterton, Matthews, & Radda, 1982)

The change in the BOLD signal however is very small. To overcome this limitation, multiple runs of the same scan under the same procedure is performed to improve the signal to noise ratio.

The haemodynamic response function describes the anticipated changes in BOLD signal that reflects the underlying behaviour of neuronal activity in response to experimental stimuli. Thus, the regions of the brain with BOLD changes closely corresponding to the haemodynamic response function theoretically represents the structure most relevant to the experimental stimuli.

The main limitation in the use of MRI relates to its magnetic properties and therefore patients or participants with ferromagnetic substances implanted on their person are unable to undergo an MRI scan.

1.8.3.1.1 Functional MRI in pain

Functional imaging has greatly aided our understanding of pain and provides an important objective measure of central activity in studies relating to pain sensitivity. In pain imaging studies, evoked noxious stimuli are delivered during scanning to replicate the actual pain experienced by humans. The evoked noxious stimuli can be presented in a tonic or phasic manner, resulting in changes in the haemodynamic response in the brain that would be detected by the scanner. We now know that the brain regions involved in pain processing is dependent on the type of pain experienced i.e. acute or chronic, and on the different types of clinical states.

Functional imaging is used to map out the brain region involved in nociception by recording brain activation during delivery of noxious stimuli. These studies are descriptive studies and were the predominant type of functional imaging performed during the early years of functional MRI. These types of functional imaging have shaped our current understanding on the pattern of brain regions involved in the nociceptive process.(Peyron & Fauchon, 2019)

It is generally accepted that there is no single centre in the brain for pain, in much the same way that memory is not anchored to a single region of the brain.(Melzack, 1990) Functional imaging has demonstrated that pain in the brain is represented by multiple and disparate nuclei that can be termed the pain neuromatrix that includes but not limited to the thalamus, hypothalamus, insula S1 and S2, primary motor cortex and anterior and posterior cingulate cortex.(Peyron, Laurent, & Garcia-Larrea, 2000; Talbot et al., 1991) Other regions of the brain are also recruited during the pain experience depending on the interplay between the context, environment and internal factors of the person experiencing pain, and include the basal ganglia, cerebellum, amygdala, hippocampus and areas of the temporal and parietal cortices.(Treede, Kenshalo, Gracely, & Jones, 1999) These regions are not specific for nociception and are involved in other function i.e. cognitive, emotion, motor, further emphasizing the multidimensionality of pain (Figure 1.5).

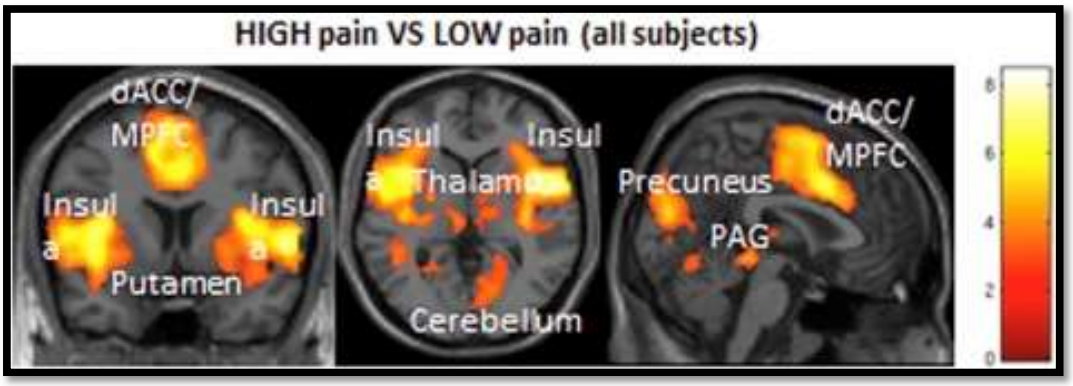


Figure 1.5 Evoked pain activation maps following noxious thermal stimuli
(from Gollub R, Kirsch I, Maleki N, et al. A functional neuroimaging study of expectancy effects on pain response in patients with knee osteoarthritis. The Journal of Pain 2018; 19(5):515-527)

Functional imaging can be used to study how different interventions can change brain activation and modulate pain. These interventions can include cognitive and therapeutic interventions (Figure 1.6). These types of functional imaging are more informative as it allows activations of brain regions to be linked in the context of the interventions and adds to the knowledge gained from descriptive studies described above. For example, hypnosis and distraction results in a change in the anterior cingulate cortex activity that was associated with reduced pain perception in healthy subjects. (Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Rainville et al., 1999; Valet et al., 2004) Negative emotions have been shown to enhance pain-evoked activity in the anterior cingulate cortex.(Apkarian, Baliki, & Geha, 2009) This has aided our understanding of the function of the cingulate cortex and we now know that the rostral anterior cingulate cortex is involved in affective reaction to pain and the mid-cingulate cortex relates to cognitive processes.(Vogt, Berger, & Derbyshire, 2003) Another important region that functional neuroimaging has enhanced our understanding relating to pain modulation and placebo analgesia is the prefrontal cortex (PFC).(Krummenacher, Candia, Folkers, Schedlowski, & Schönbächler, 2010) This region is an important area for short term memory maintenance, maintenance of performance control during interfering stimuli and continuous monitoring of the external world.(Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001) An fMRI study showed increased activation of the PFC just prior to the delivery of placebo analgesia (anticipation) and increased activation in the ACC,

IC and the thalamus during placebo analgesia.(Wager et al., 2004) Possible explanation of the action of the PFC is via a top-down mechanism that inhibits ascending nociceptive pathways such as the ACC, IC, thalamus and spinal cord. Interestingly, a study in healthy subjects using PET and fMRI imaging revealed that placebo analgesia was associated with increased endogenous opioid activity in the PFC, ACC and the IC.(Zubieta et al., 2005)

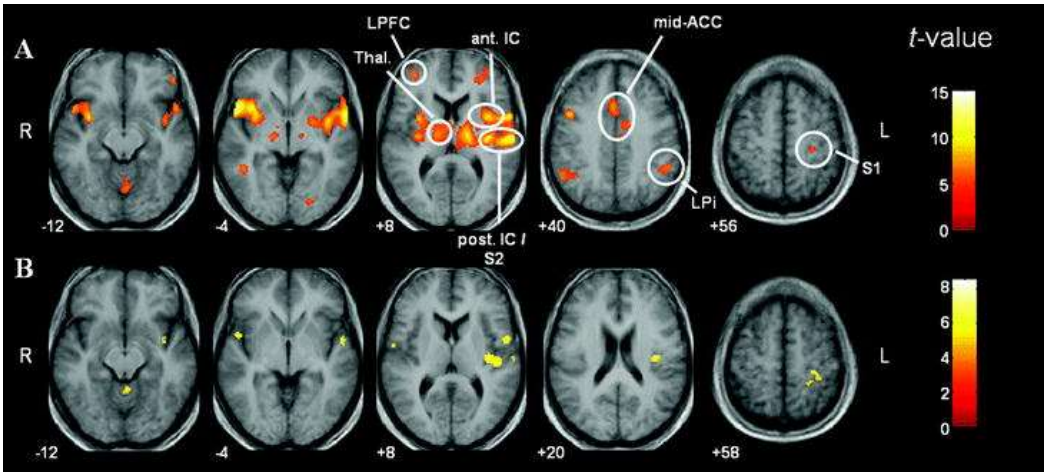


Figure 1.6 Effects of distraction on cerebral pain processing. A, Without distraction; B, With distraction. (Matre D., Tran T.D. (2009) Imaging Modalities for Pain. In: Biobehavioral Approaches to Pain. Springer, New York, NY)

Therapeutic intervention can provide further clarity regarding the neurotransmitter deficiency, especially in certain clinical states relating to pain. In fibromyalgia, increased pain perception was associated with reduced activation of the anterior cingulate cortex and reduced μ-opioid receptor binding potential.(Schrepf et al., 2016) A reduced μ-opioid receptor binding potential signifies dysfunctional opioidergic metabolism and thus implicates this neurotransmitter system as one of the contributory factors in fibromyalgia symptomatology. The locus coeruleus and the noradrenergic neurotransmitter system play an important role in pain modulation, especially relating to the descending pain inhibition pathway.(Llorca-Torralba, Borges, Neto, Mico, & Berrocoso, 2016) Human fMRI studies investigating the locus coeruleus and other brain stem structures involved in pain have been limited due to the difficulty in imaging this area due to its small structure, until recently. A

spinal/supraspinal fMRI study demonstrated significant correlation between pain scores in healthy subjects with activation of the locus coeruleus following noxious thermal stimuli.(Khan & Stroman, 2015) Several studies on healthy subjects have demonstrated a reduction in the activity of the ipsilateral dorsolateral pontine tegmentum (a region that includes the locus coeruleus) in the setting of secondary mechanical hyperalgesia, suggesting a dysfunction in the descending inhibition pathway.(Rempe et al., 2014, 2015) Further, in neuropathic patients, bilateral deactivation of the dorsolateral pontine tegmentum was demonstrated during mechanical hyperalgesia and allodynia.(Becerra et al., 2006)

1.8.3.1.2 Functional MRI in various clinical pain conditions

Functional imaging can also be used to study pain arising from different clinical states, such as multiple sclerosis, diabetes, fibromyalgia and Parkinson disease. However, drawing a generalized conclusion from these types of imaging studies is often problematic. It is sometimes difficult to interpret the different brain activations in different clinical states following a specific stimulus as our knowledge relating to that stimulus in healthy subjects and under physiological conditions is probably incomplete. These imaging studies are sometimes inadequately powered due to a limited sample size, presumably due to the difficulty in recruiting patients. Nevertheless, several lines of consistent results have been teased out from studies of various clinical states with pain. In patients with chronic low back pain, there is involvement of the dorsolateral pre-frontal cortex, although it is unclear whether the involvement of this area is directly due to its involvement in pain processing or indirectly activated due to attentional or cognitive bias. Specifically, using voxel-based morphometry, grey matter density in bilateral dorsolateral pre-frontal cortex were reduced in chronic back pain patients, as compared to healthy controls.(Apkarian et al., 2004) Using diffusion tensor imaging techniques, another study showed that increased white matter connectivity of the pre-frontal cortex was an independent risk factor for the development of chronic back pain.(Vachon-Presseau et al., 2016) In functional imaging, activation of brain regions may be related to the nociceptive

specifically, or to other associated processes; the more intense the pain, the more attention will be directed to it. In patients with neuropathic pain, innocuous stimuli resulting in allodynia activates the same brain pattern that one would find in healthy subjects presented with noxious stimuli.(Gustin et al., 2014; Gustin et al., 2011; Peyron et al., 2013) These studies provide evidence that in neuropathic patient suffering from allodynia, the "pain is real".

1.8.3.1.3 Functional MRI; resting state and other techniques

Functional imaging can also be used to measure brain activity at rest and uses the BOLD contrast to map temporally synchronous, spatially distributed, spontaneous signal fluctuations to generate measures of functional connectivity.(Fox & Raichle, 2007) This is called resting state fMRI and does not require presentation of stimuli during the period of scanning. This technique lends itself very well to the study of chronic pain. Chronic pain arising from various pathologies, including complex regional pain syndrome, fibromyalgia, diabetic neuropathy and chronic back pain has been shown to have changes in functional connectivity.(Kong et al., 2010) (for further detail, please refer to **Section 6.1 Introduction of aims and hypothesis**)

Other imaging method using functional MRI is the diffusion tensor imaging and structural fMRI. Diffusion tensor imaging uses diffusion of water in the brain to map the orientation of white matter tracts.(Conturo et al., 1999) Structural MRI provides information of grey and white matter of the central nervous system and voxel-based morphometry allows the tracking of changes in volumes of specific regions of the brain over time.(Smith et al., 2006)

1.8.3.2 Positron Emission Tomography (PET)

PET measures the metabolic process occurring in the brain using biologically active tracer molecules such as radionucleotide and relevant radiolabelled ligand.(Phelps, Hoffman, Mullani, & Ter-Pogossian, 1975) PET studies using radiolabeled ligand allow characterization of receptor occupancy and receptor

density in the brain. In contrast to MRI, the use of radioactive elements in the technique restricts repeat application.

1.8.3.3 EEG and MEG

One of the criticisms of both PET and fMRI is that it uses the haemodynamic response as a surrogate marker for neural activity. This is a relatively slow response when compared to the actual speed of neural events and therefore suffers from temporal resolution.

In contrast, electroencephalogram (EEG) methods measure actual electrical activity in the brain. The EEG measures voltage fluctuation in the brain via multiple electrodes placed on the scalp. (Kanda 2001) In pain research, noxious stimuli can be time locked to the resultant evoked potential, allowing for excellent temporal resolution.

MEG works using the same principle as EEG but measures magnetic field fluctuations during neuronal activation instead of voltage fluctuations.

Chapter 2: Pain in Parkinsons disease

Parkinsons disease is a progressive neurodegenerative disorder. The pathophysiological substrate is the deposition of Lewy bodies in a rostral caudal progression. The subsequent involvement of the substantia nigra pars compacta triggers motor symptom manifestations that includes cogwheel rigidity, bradykinesia, resting tremor and eventual postural instability. Additionally, non-motor symptoms also occur, occasionally manifesting before motor symptoms. Pain is an important non-motor symptom of the Parkinsons disease. In those reporting pain in Parkinsons disease, 62% report chronic pain.(Nègre‐Pagès, Regragui, Bouhassira, Grandjean, & Rascol, 2008)

Parkinsons disease patients can experience acute pain or chronic pain. Several different taxonomies exist (see **Section 2.3**) to capture the different characteristics of the pain experience, with the classification by Blair Ford being the most widely used.(Ford, 2010) The recently developed King's Parkinsons disease pain scale is the first disease specific pain scale for Parkinsons disease that allows longitudinal tracking of pain severity and is being increasingly used in prospective clinical trials.(Chaudhuri et al., 2015)

Musculoskeletal pain is one of the most commonly encountered manifestation of pain in Parkinsons disease in day to day clinical practice.(Lee, Walker, Hildreth, & Prentice, 2006) Patients can complain of back pain and joint pains. Interestingly shoulder pain is a common premotor symptom of Parkinsons disease, occurring on the side where the motor symptoms would eventually manifest.(Riley, Lang, Blair, Birnbaum, & Reid, 1989) The mechanism of action can be nociceptive due to localized damage to the joint architecture.(Ashour & Jankovic, 2006)

Musculoskeletal pain can also be due to prolonged increased muscle rigidity due to dopamine deficiency.(Ford, 2010) Patients with these symptoms often notice

deterioration in pain intensity during OFF periods and find that levodopa therapy alleviates the pain.

Radicular pain is described by Parkinsons disease patients as shooting pain that radiates along a peripheral nerve distribution.(Broetz, Eichner, Gasser, Weller, & Steinbach, 2007) Changes in posture occurring over time in patients with Parkinsons disease contribute to the development of this type of pain and may respond to physiotherapy to improve posture.

An enigmatic pain entity uniquely encountered in Parkinsons disease patients presents with bizarre characteristics such as burning mouth and perineal pain.(Ford, Louis, Greene, & Fahn, 1996) Various terms have been used to describe this type of pain including central pain. Due to its quality, the presence of this type of pain can be easily missed by the clinician during day to day consultation or even dismissed out of hand.(O'sullivan et al., 2008) The pathophysiological mechanism underlying this type of pain may involve dysfunction in pain processing areas of the central nervous system that relies on dopaminergic, noradrenergic and serotonergic mechanisms.(Wasner & Deuschl, 2012)

Parkinsons disease can afflict adults across the age spectrum but has a predilection for the elderly and the prevalence of pain also increases by age.(Loge & Kaasa, 1998) Therefore, some common threads and important differences can be gleaned by exploring the issues of persistent pain in the elderly.

First and foremost, it must be stated that persistent pain in the elderly cannot be equated to a chronologically older version of younger pain patients. Many factors i.e. biological, psychological and social come into play and these factors intersect and interact with each other. These factors have potential to amplify the experience of pain beyond the actual mechanistic underpinnings. Similarly, pain in Parkinsons disease can coexist with other painful co-morbidities afflicting the elderly population such as arthritis and musculoskeletal problems.

Ageing is associated with neuronal death and gliosis and can potentially disrupt important pain processing mechanisms. In the periphery, animal studies show an age-associated loss of noradrenergic and serotonergic neurons in the dorsal horn of the spinal cord involved in the descending projection neurons that are important in pain modulation.(Iwata et al., 2002). More centrally, there is a decline in receptor density and concentration of serotonergic and noradrenergic neurotransmitters, as well as deposition of neurofibrillary tangles and senile plaques in areas of the brain involved in nociception e.g. anterior cingulate cortex, prefrontal cortex.(Barili, De Carolis, Zaccheo, & Amenta, 1998; Sheline, Mintun, Moerlein, & Snyder, 2002) The impact of these pathologies could arguably be exaggerated in chronic dopaminergic deficiency considering the common biosynthesis pathway between dopamine and noradrenaline.

Pharmacokinetics and pharmacodynamics play a more central role in analgesia in the elderly and is liable to disrupt effective analgesia due to compromised drug delivery mechanisms e.g. altered bowel habits, thin skin.(Hämmerlein, Derendorf, & Lowenthal, 1998) In Parkinsons disease, constipation is a common problem and limits the use of certain pharmacological agents to manage pain.(Trenkwalder et al., 2015)

Unique disease characteristics of Parkinsons diseases can amplify the problems relating to pain in the elderly. Muscle rigidity in Parkinsons disease, usually seen during fluctuation and wearing off has been associated with increased frequency of pain and pain that interferes with work.(Allen, Wong, Canning, & Moloney, 2016) Presumably, rigidity results in pain due to altered body posture, resulting in stiffness, alteration in body mechanics and reduced flexibility.

Recent studies have indicated that systemic inflammation is involved in the neurodegenerative process. For example, increased concentration of TNF-α was associated with cognitive decline in patients with Alzheimers disease.(Holmes et al., 2009) A recent study showed increased IL1 concentration in Parkinsons disease patients with pain.(Li, Song, Huang, Huang, & Ye, 2018). Another study

showed that baseline CRP concentration were associated with the risk of death and predicted life prognosis of Parkinsons disease patients independent of age, cognitive function, nutritional conditions, disease duration and severity.(Sawada et al., 2015) Taken together, the association between persistent pain and increased inflammatory response may confer a poorer prognosis long term in Parkinsons disease patients.

2.1 Prevalence of pain in Parkinsons disease

Pain has been shown to be common in Parkinsons disease patients. The prevalence rate of pain in Parkinsons disease has been quoted to range between 30% and 85%, based on several studies.(Beiske, Loge, Rønningen, & Svensson, 2009; Del Sorbo & Albanese, 2012; B Ford, 1998; Nègre‐Pagès et al., 2008) The wide variation in the prevalence rate is thought to reflect varying clinical populations, differing methodologies used between studies e.g. different pain classifications and assessment tools.

2.2 Impact of pain in Parkinsons disease

While the behavioral responses to pain can have many adaptive effects, there are many chronic pain states in Parkinsons that can lead to distress, impaired quality of life and increase the burden of disease.

Politis et al surveyed 92 patients with early Parkinson disease and found that pain was reported to be the most troublesome non-motor symptom, suggesting that there is a pressing need for improved identification, assessment and treatment for pain in Parkinsons disease. (Marios Politis et al., 2010)

Additionally, several small studies have demonstrated the deleterious impact of pain on the quality of life of Parkinsons disease patients.(Martinez-Martin et al., 2017; Quittenbaum & Grahn, 2004; Schrag et al., 2000) Notably, a recent study of 1957 patients with early to moderate Parkinsons disease with pain used

multiple regression analysis to determine factors impacting quality of life and showed that the effect of pain on quality of life was higher than that of motor symptoms or motor fluctuations.(Silverdale et al., 2018) In advanced Parkinsons disease, patients with pain were more likely to be depressed as compared to patients without pain, further compounding the burden of disease considering that depression is also a major predictor of poor quality of life in Parkinson disease. (Valkovic et al., 2015)

Pain in Parkinsons disease can potentially impact beyond the individual. Two studies showed that pain and activities of daily living measures are independent predictors of poor quality of life in Parkinsons disease patients.(Choi et al., 2017; Ozturk, Gundogdu, Kocer, Comoglu, & Cakci, 2017) It can be argued that there is an interplay between pain and activities of daily living as pain limits movements thus impacting on the ability to perform activities of daily living. This is important as studies have shown that care-giver burden and care-giver stress was associated with poor performance in activities of daily living in patients with Parkinsons disease.(Santos‐García & de la Fuente‐Fernández, 2015)

2.3 Classification of pain in Parkinsons disease

Over the years, there have been several attempts at classifying the different types of pain experienced by Parkinsons disease patients.

The earliest attempts at classifying pain organized different subtypes of pain according to the dopaminergic state of the patient i.e. whether the pain occurs during the OFF or ON period (Quinn, Lang, Koller, & Marsden, 1986). This type of classification became unpopular when it became apparent that the temporal association of pain with motor fluctuation and dopaminergic medication were not always consistent.

Subsequent classifications emphasized the idiosyncratic relationship of pain to dopaminergic state. The investigators of the DOPAMIP study classified pain into

either, a) pain unrelated to Parkinsons disease, or b) pain related to Parkinsons disease.(Nègre‐Pagès et al., 2008) "Pain related to Parkinsons disease", was further subdivided into whether the pain was thought to be either directly related, or indirectly related to Parkinson's disease. Further refinements were made by subsequent researchers to include the type of pain thought to be attributable to abnormal pain processing in the pain neuro-matrix.(Chaudhuri & Schapira, 2009)

Warner and Deuschl developed an elaborate classification system comprising of a 4-tier taxonomy in an attempt to capture all the possible types of pain that can occur in Parkinsons disease.(Wasner & Deuschl, 2012)

Attempts at formulating a classification system that is comprehensive enough to encompass all the different types of pain experienced by Parkinsons disease patients run the risks of being too unwieldy to be used in any meaningful effective way in day-to-day clinical practice and research. This is due to the inherent complexity and variety of pain that can occur in Parkinsons disease.

An effective pain classification system should have qualities of ease-of-use for daily clinical practice, yet possess adequate sensitivity to detect the different qualities of pain experienced by Parkinsons disease patients. Essentially, the classification must possess categories of pain that describes;

1. neuropathic pain
2. nociceptive pain
3. pain related to the dopaminergic state
4. pain attributable to dysfunctional pain processing

Arguably, this may be the reason why the pain classification proposed by Blair Ford is presently the most widely used, dividing pain into 5 categories; 1) radicular pain, 2) dystonic pain, 3) musculoskeletal pain, 4) central pain, and 5) pain associated with akathisia.(Blair Ford, 2010) The difficulties in classifying

and defining pain remain one of the key reasons why pain in Parkinsons disease is under treated and under reported.

2.4 Risk factors for pain in Parkinsons disease

2.4.1 Gender

Pain in Parkinsons disease has generally been found to occur more frequently in female patients than male patients. (Beiske et al., 2009; Defazio et al., 2008; Marsala et al., 2011) However, not all studies have supported this observation with an earlier manuscript reviewing the relevant literature concluding that there were no significant difference between genders with regards to pain in Parkinsons disease.(Rana, Kabir, Jesudasan, Siddiqui, & Khondker, 2013) A more recent meta-analysis however, has linked persistent pain with the female gender in Parkinsons disease.(Sung, Vijiaratnam, Chan, Farrell, & Evans, 2018b)

2.4.2 Genetic factors

Presently, a large body of literature exists that provides evidence that genetic factors modulate pain in health and disease. Particularly relevant to pain in Parkinsons disease are genetic abnormalities that are involved in dopamine metabolism or interact with dopamine biochemical pathways.

There are 3 different gene mutations that are involved in dopamine biosynthesis and metabolism that may be implicated in the development of pain in Parkinsons disease.

Cathecol-O-methyltransferase (COMT) single nucleotide polymorphism (SNP) has been one of the most extensively studied genetic abnormality. COMT is an enzyme that is important for the metabolism of dopamine, adrenaline and noradrenaline. Entacapone, a COMT inhibitor has been used together with levodopa for the treatment of motor symptoms in Parkinsons disease for many years. In the general population, COMT SNP polymorphism has been associated

with either an increased or decreased pain sensitivity phenotype. Relevantly, in Parkinsons disease patients, a COMT SNP mutation in RS 6267 allele, which causes a loss of function, has been demonstrated at a higher frequency in patients with pain as compared to patients without pain. (Li, Chen, Yin, & Zhang, 2014) Two mechanisms have been proposed for this phenomenon. Increased dopamine levels lead to a decrease in enkephalin concentration, resulting in an upregulation of mu-opioid receptors, increasing glutamate and substance P release, and thus increasing the sensitivity to noxious stimulation. (Zubieta et al., 2003) Another proposed mechanism utilizes the adrenergic pathway, where the increased adrenaline stimulates β 2/3-adrenergic receptor. (Nackley et al., 2007) There have been multiple studies that have demonstrated that β adrenergic pathways are involved in nociception. For example, β-adrenergic agonist administration produces a painful arthritis like syndrome and the use of propranolol, a beta β-adrenergic antagonist has been shown to reduce the severity of arthritis pain. (Baerwald et al., 1997; Valdes et al., 2017; Vyden et al., 1971)

Another potential genetic risk factor for pain in Parkinsons disease involves the dopamine D3 receptor (DRD3) Ser9Gly polymorphism, that causes a serine-glycine substitution in the N-terminus of the receptor, resulting in Ser-Ser, Ser-Gly and Gly-Gly alleles. (Lannfelt et al., 1992) Dopamine D3 receptors are present throughout the neuroaxis but are especially abundant in the mesolimbic areas of the brain. Evidence of involvement of the dopamine pathway for pain in humans has been demonstrated in a study involving fibromyalgia patients, which showed that pramipexole, a dopamine agonist with affinity for D3 and D4 receptors improved pain scores as compared to placebo.(Holman & Myers, 2004) Furthermore, another study has shown that the Ser-Ser allele is associated with reduced thermal pain threshold in patient with fibromyalgia. (Potvin et al., 2009) Although there have been findings linking this genetic mutation to depression and impulse control disorders in Parkinsons disease patients, there is yet any study that has shown any evidence of involvement of this polymorphism with regards to development of pain and pain sensitivity. (Bhattacharjee, Talbot, & Vijayashankar, 2017; Zhi et al., 2019)

Monoamine oxidase-B (MAO-B) is an enzyme involved in the metabolism of dopamine, benzylamine and phenylethylamine. The A/G polymorphism of MAO-B has been shown previously to be associated with variation in MAO-B enzyme activity.(Garpenstrand, Ekblom, Forslund, Rylander, & Oreland, 2000) A study showed post-operative male patients with MAO-B "G"-allele had a significantly higher pain scores as compared to patients with MAO-B "A"-allele. (Serý et al., 2006) Altered levels of MAO-B have been associated with depression, schizophrenia and alcoholism. MAO-B polymorphism has been implicated in motor complication in Parkinsons disease but there are no studies to date that have elucidated the relationship between MAO-B polymorphism with pain in Parkinsons disease. (Löhle et al., 2018)

Consistent with the hypothesis that the symptomatology of Parkinsons disease may also involve extra-dopaminergic factors, there have been studies showing an association between Parkinsons disease with patients with pain with genetic mutations with no known purported involvement along the dopaminergic metabolic pathway.

In a study of 229 Jewish Parkinsons disease patients, variants within the SCN9A and FAAH genes were associated with an increased risk of pain.(Greenbaum et al., 2012) Post-hoc analysis revealed that the SNC9A was associated with central and musculoskeletal pain; the FAAH rs324419 mutation was significantly associated only with musculoskeletal pain. The FAAH gene (fatty acid amide hydrolase) metabolizes endogenous cannabinoids and has been shown to reduce nociceptive signalling upon binding to cannabinoid type 1 receptor in the central and peripheral nervous system.(Scotter, Abood, & Glass, 2010) SCN9A encode sodium channel NAv1.7, one of many channels important in the propagation of action potential to the CNS. The SCN9A mutation causes a gain in function resulting in acute paroxysmal pain and erythromelalgia. (Fertleman et al., 2006; Yang et al., 2004)

2.4.3 Co-existing medical conditions

Studies have also shown that concurrent medical illness such as rheumatoid arthritis, diabetes mellitus and osteoporosis is associated with pain in Parkinsons disease.(Giovanni Defazio, Gigante, Mancino, & Tinazzi, 2013) This however may just be a reflection of increased pain burden experienced by the patient and may not necessarily infer any causative link between concurrent illness and pain in Parkinsons disease.

Similarly, depression has been shown to be associated with pain in Parkinsons disease. A multivariate analysis showed that pain was significantly associated with depression scores, even after adjusting for clinical severity.(Ehrt, Larsen, & Aarsland, 2009) This connection between depression and pain is not surprising, considering that the areas in the brain involved in pain processing and emotion share the same pathways in the nervous system.

2.4.4 Clinical factors pertaining to Parkinson disease

Unlike the conflicting results with regards to the link between demographic factors i.e. age, gender with pain, data from several studies has been fairly consistent in showing an association pain with factors relating to Parkinsons disease progression.

Allen et al explored the contribution of motor impairments to pain in Parkinsons disease and found that increased rigidity was associated with higher pain frequency.(Allen, Wong, Canning, & Moloney, 2016) Tinazzi et al found that the severity of pain in Parkinsons disease was significantly correlated with the severity of motor complications.(Tinazzi et al., 2006) Similarly, in a large cross-sectional study incorporating 450 Parkinsons disease patients, pain was associated with the presence of motor complications such as dyskinesia and motor fluctuations and with a younger age at disease onset.(Nègre‐Pagès, Regragui, Bouhassira, Grandjean, & Rascol, 2008).

Other factors that was associated with pain were increased disease duration, increased disease severity and higher levodopa usage.(Nègre‐Pagès et al., 2008) Most conclusively, a recent meta-analysis concluded that Parkinsons disease patients with persistent pain was associated with a longer duration of disease, as compared to patients with no pain.(Sung et al., 2018b) Taken together, the above findings clearly demonstrates that the development of pain in Parkinsons disease is inextricably linked to disease burden.

2.4.5 Pain sensitivity in Parkinsons disease

Over the years, numerous studies have been published relating to changes in pain sensitivity in Parkinsons disease. The findings however have oftentimes been contradictory. For example, a large study comprising of 106 patients with Parkinsons disease found reduced pain sensitivity (hypoalgesia) following electrical pain evoked stimuli.(Marsala et al., 2011) In contrast, another study found that mechanical, cold and heat evoked pain stimuli was associated with increased pain sensitivity (hyperalgesia) in Parkinsons disease patients, when compared to healthy volunteers.(Nolano et al., 2008)

The different types of evoked pain stimuli used may potentially contribute to the conflicting findings, as illustrated in the 2 studies described above. Indeed, other elements including differences in methodology, outcome measures, site of stimulation of evoked pain stimuli and the state of medication during assessments (i.e. ON or OFF medication) have all been implicated as possible factors for the heterogeneity in the pain sensitivity findings in Parkinsons disease patients.(Conte, Khan, Defazio, Rothwell, & Berardelli, 2013)

The are several purported pathophysiological substrate for increased pain sensitivity in Parkinsons disease patients. In the periphery, an autopsy study on Parkinsons disease patients identified neurodegeneration due to Lewy body deposition in the lamina propria I of the dorsal horn.(Braak, Sastre, Bohl, de Vos, & Del Tredici, 2007) This region is densely populated by descending neurons

from the brainstem that are involved in pain modulation such as the periaqueductal grey, medullary raphe nuclei and the coeruleus-subcoeruleus complex.(Eippert, Finsterbusch, Bingel, & Büchel, 2009)

More centrally, an extensive body of literature has provided evidence that implicates basal ganglia dysfunction and dopamine deficiency in the pathophysiology of hyperalgesia and pain. Several studies have demonstrated normalisation of evoked pain threshold in Parkinsons disease patients following levodopa administration.(Brefel-Courbon et al., 2005; Gerdelat-Mas et al., 2007; Schestatsky et al., 2007) The microinjection of dopamine agonists in various areas of the brain such as the orbitofrontal cortex, striatum and the insula has been associated with a reduction in nociceptive behaviour in animal studies.(Coffeen et al., 2008; Dang et al., 2010; Magnusson & Fisher, 2000) Finally, imaging data have shown an association between chronic pain conditions such as burning mouth syndrome and fibromyalgia with decreased dopaminergic activity and reduced dopamine receptor availability.(Hagelberg et al., 2003; Jaaskelainen et al., 2001; Wood et al., 2007)

The response of pain thresholds to dopaminergic therapy has been inconsistent. There are some studies reporting unchanged pain threshold, whereas others documenting increases in pain threshold following levodopa therapy.(Brefel-Courbon et al., 2005; Djaldetti et al., 2004; Marsala et al., 2011) Dellapina et al observed no changes in pain threshold following apomorphine administration in Parkinsons disease patients.(Dellapina et al., 2011) Taken together, this suggests that extra dopaminergic mechanisms also contribute to the pain sensitivity changes in Parkinsons disease.

Noradrenergic, serotonergic, cholinergic and peptidergic neurons also undergo degeneration in Parkinson disease.(Jellinger, 1999) The noradrenergic locus coeruleus, an important nucleus for the descending modulation pathway undergo a greater degree of neurodegeneration as compared to the substantia nigra in some Parkinsons disease patients.(Zarow, Lyness, Mortimer, & Chui, 2003) Indeed, the periaqueductal grey and the serotonergic raphe nucleus

magnus, as well as supraspinal regions heavily involved in providing descending inhibitory and facilitatory input to the nociceptive afferent signals, are located in the region of the brainstem that is known to undergo extensive neurodegenerative changes in the early stages of Parkinsons disease.(Hawkes, Del Tredici, & Braak, 2010)

2.5 Pain mechanisms in Parkinsons disease

2.5.1 The basal ganglia

The basal ganglia are comprised of the striatum (caudate and putamen), nucleus accumbens, the external and internal segment of the globus pallidus, the subthalamic nucleus and the substantia nigra (Figure 2.1).(Yelnik, 2008)

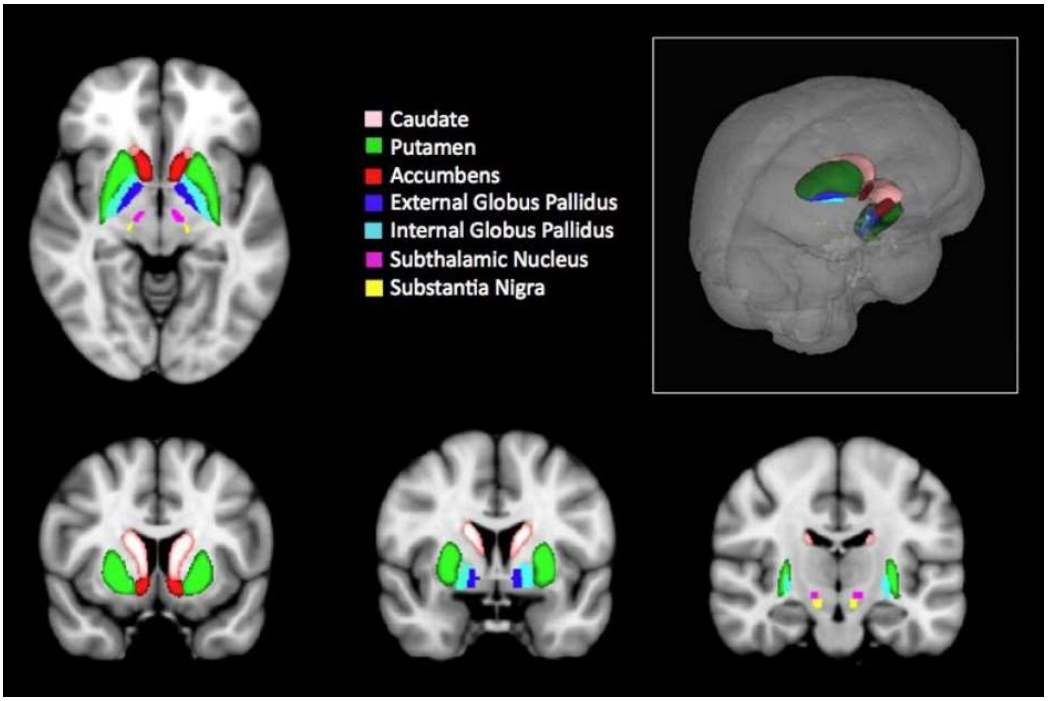


Figure 2.1 The basal ganglia. 3D representation of the basal ganglia in the human brain.
Brain section form FMRI Software Library http://www.fmrib.ox.ac.uk/fsl/

Cortical connections to the basal ganglia subserve the cognitive, affective and motor elements, projecting into the central basal ganglia (caudate and precommissural putamen) for procedural and working memory, ventral basal

ganglia (nucleus accumbens) for roles in reward and reinforcement, and dorsolateral portion of the striatum (postcommissural putamen) for control of movement, respectively.(Lavoie, Coˆte, & Parent, 1992; Selemon & Goldman-Rakic, 1985)

The cortical connections serving these anatomically and functionally distinct elements traverse specific regions of the striatum, ultimately projecting to the internal segment of the globus pallidus and substantia nigra pars reticulata, which are the output nuclei of the basal ganglia.(Graybiel, 1984) The output of the basal ganglia converge on to the thalamus before being projected back to the cortical areas of origin, thus creating a loop.(Carpenter, Nakano, & Kim, 1976; Ilinsky, Jouandet, & Goldman‐Rakic, 1985)

For the loop involved in motor control, 2 distinct pathways exist in the striatum, namely direct and indirect pathways. The direct pathway exerts an excitatory influence whereas the indirect exerts an inhibitory influence on motoric function.(Pollack, 2001) Over activity of the indirect pathway results in the motor symptoms in Parkinsons disease and enhanced activity of the direct pathway results in the hyperkinetic movements typically seen in Huntingtons disease.(DeLong, 1990)

These loops were initially thought to be a closed circuit and work in parallel with each other, remaining segregated functionally and structurally from one another.(Alexander & Crutcher, 1990; Alexander, Crutcher, & DeLong, 1991) Injury to these closed circuit loops results in selective disturbance that corresponds to the elements that is served.

However, recent research now point towards a framework in which the basal ganglia circuits are comprised of not only a closed loop circuit but also open-ended connections that allow all the different closed loop circuits to interact with each other.(Haber, 2003; Joel & Weiner, 1994) Tracing studies in monkeys demonstrated a dopaminergic interface between different striatal regions that

allow an hierarchical information flow for the cognitive, limbic and motor elements via the ventral midbrain.(Haber, Fudge, & McFarland, 2000) Using diffusion tractography analysis, a group of researchers were able to show *in vivo* segregated and overlapping connections from cortical sites to basal ganglia in healthy human subjects.(Draganski et al., 2008) Arguably, this model would be able to explain the constellation of cognitive, behavioural and motoric symptoms in early Huntingtons disease and early Parkinsons disease when the pathology is fairly limited in the brain.(Joel, 2001)

Colder applied predictive coding theory in regards to the function of the basal ganglia in regulating movement.(Colder, 2015) In predictive coding theory, the brain is continuously updating models of the environment, including our own body.(Clark, 2013) Importantly, our perception at any given time is coloured by large parts of the pre-formed models (accumulated from previous experiences), and not derived solely on incoming sensory stimuli. Higher-level neurons impose prediction of incoming sensory stimuli on lower order sensory neurons in a continuous manner. A comparison is made between the prediction model and incoming sensory stimuli and any discrepancy is termed a prediction error.(Colder, 2011) The hypothesis suggests that the basal ganglia performs a function that chooses multiple possible neural networks representing prediction of movements, which also includes the sensory prediction associated with the movements. The default objective is to minimize the prediction error. Movement and incoming sensation stimuli are closely interlinked and influences the action selection that best minimizes prediction error.

Thus, the basal ganglia are ideally placed as an organ that is capable of multi-sensory integration.(Chudler, Sugiyama, & Dong, 1995; Nagy, Eördegh, Paróczy, Márkus, & Benedek, 2006) This is important for certain behavioural function carried out by the basal ganglia, such as goal directed behaviour that requires not only the execution of the movement but also the initial processes in planning the movement which involves integrating elements of motivation, emotion and cognition. Further, animal studies have also shown that neurons in the basal ganglia are responsive to visual, auditory and somatosensory stimuli.(Márkus,

Eödegh, Paróczy, Benedek, & Nagy, 2008) This is relevant to pain perception as the response to acute or chronic pain involves integration of sensory, emotional, cognitive and motor influences.

A maladaptive neuroplasticity of the multisensory integration of the basal ganglia may be responsible for dystonic phenomena such as 'writers' cramp'. It has been suggested that loops within the basal ganglia e.g. motor loops, contain motor subroutine for the execution of learned task e.g. writing, blowing a trumpet which is integrated with sensory expectation information for feedback control.(Kaji, Shibasaki, & Kimura, 1995) It is possible that dystonia with *geste-antagoniste* occurs following a dysfunctional motor subroutine that has gone awry (possibly due to overuse). The sensory trick represents the sensory expectation of a completely different motor subroutine that becomes activated, thus attenuating the dystonia.(Kaji, 2001)

Lim et al compared pain threshold and tolerance between 3 groups of Parkinsons disease patient (fluctuators, dyskinetics and stable responders) and healthy controls.(Lim et al., 2008) Interestingly, the patients with dyskinesia attained a greater improvement in their cold pain threshold and tolerance following levodopa as compared to patients belonging to the other 2 groups. It is thought that dyskinesia is a manifestation of a maladaptive neuroplastic response of the basal ganglia as a consequence of phasic dopaminergic stimulation. The authors argued that the underlying aberrant neuroplasticity might be mediating both dyskinesia and pain processing abnormalities. Additionally, the response of levodopa towards pain sensitivity in the dyskinesia group suggests that the mechanism of sensitization could be under dopaminergic influence.

Evidence for the involvement of the basal ganglia in pain processing can be derived from several pre-clinical studies. Electrophysiological studies in rats show activation of various basal ganglia nuclei e.g. globus pallidus, caudate, putamen, upon noxious stimuli.(Bernard, Huang, & Besson, 1992; Chudler, 1998) Micro-injection of various chemicals e.g. somatostatin, apomorphine, as well as

chemical or surgical lesioning into the basal ganglia has been shown to modulate behavioural pain response in rats.(Chudler & Lu, 2008; M. Lin, Wu, Chandra, & Tsay, 1981; Saadé, Atweh, Bahuth, & Jabbur, 1997; Saadé, Shbeir, Atweh, & Jabbur, 1996; Takeda et al., 2005; Tashev, Belcheva, Milenov, & Belcheva, 2001) Tracer studies in rats show that ascending nociceptive neurons originating in the dorsal horn of the spinal cord terminating in various subcortical structures, including the globus pallidus.(Braz, Nassar, Wood, & Basbaum, 2005)

2.5.2 Dopamine

In Parkinsons disease, it has been proposed that dopamine depletion causes dysfunctional pain processing and altered pain perception. Population studies have shown that Parkinsons disease patients report more pain as compared to age-matched controls.(Beiske et al., 2009)

This dysfunction in pain processing is partly amenable to dopamine replacement therapy. Brefel-Courbon et al showed that using heat-evoked pain, the pain threshold of Parkinsons disease patients increased (able to tolerate more pain) following levodopa administration.(Brefel-Courbon et al., 2005) Similarly, Schetasky et al showed that Parkinsons disease patients had lower heat pain and laser pin-prick thresholds as compared to controls, which was attenuated following levodopa administration. (Schestatsky et al., 2007) Finally, Gerdelat et al showed that the nociceptive flexion reflex in Parkinsons disease patients was increased following levodopa administration. (Gerdelat-Mas et al., 2007) The nociceptive flexion reflex is a neurophysiological tool to objectively record an individuals' pain experience based on the measurement of the spinal reflex.(Skljarevski & Ramadan, 2002) It is a reliable and objective tool that can be used in a clinical setting and also in research to study central sensitization and chronic pain.(Arendt-Nielsen, Brennum, Sindrup, & Bak, 1994; Willer, 1977) A recently published systematic review and meta-analysis has shown that Parkinsons disease patients, tested in the medication OFF state had increased pain sensitivity across multiple modalities as compared to healthy controls.(Sung, Vijiaratnam, Chan, Farrell, & Evans, 2018a) Further, the

difference in pain sensitivity between the 2 groups became less apparent when the patients were tested in the ON state, thus implicating dopamine deficient states as a possible contributory factor in the pathogenesis of hyperalgesia.

Nevertheless, there have also been studies that showed that dopamine replacement therapy does not appear to be helpful in pain. Dellapina et al showed that subjective and objective pain threshold were not altered in Parkinsons disease patients following apomorphine infusion.(Dellapina et al., 2011) This finding suggests that other mechanisms are at play in the genesis of dysfunctional pain processing in Parkinsons disease and most likely extra-dopaminergic in nature.

2.5.3 Neuropathological influences on pain pathways in Parkinsons disease

The histopathological hallmark of Parkinsons disease is deposition of abnormal aggregates of alpha-synuclein protein, called Lewy bodies. The deposition of Lewy bodies in the substantia nigra is thought to give rise to abnormal motor symptoms characteristic of Parkinsons disease such as bradykinesia, resting tremor and rigidity.

In 2003, Heiko Braak et al argued that the appearance of motor symptoms in Parkinsons disease is preceded by an abnormal deposition of Lewy bodies in other parts of the brain.(Heiko Braak et al., 2003) The Braak hypothesis has 6 stages, with deposition of Lewy bodies occurring rostro-caudally as the disease progresses. Motor symptoms occur at the mid-stage state (stage 3 and 4) (Figure 2.2).

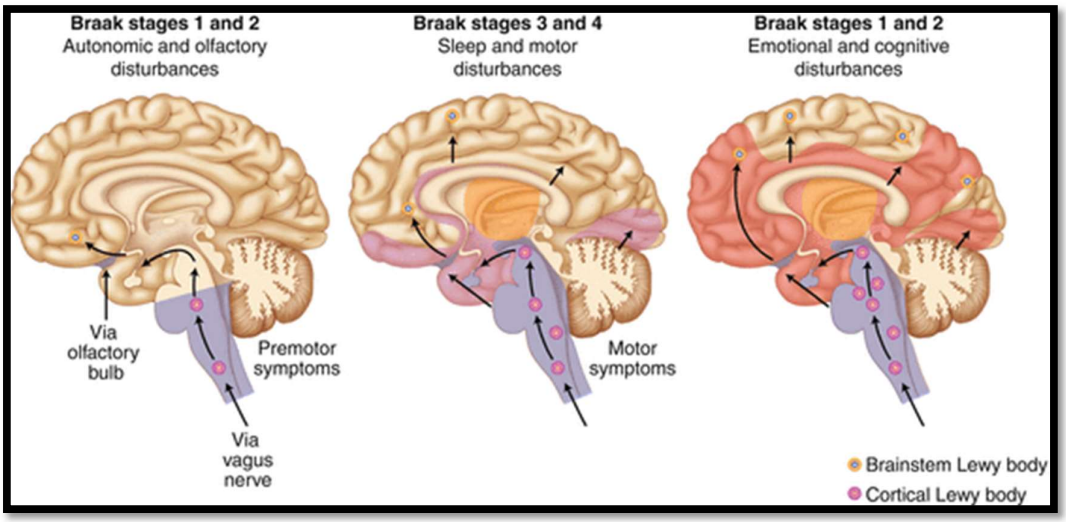


Figure 2.2 The Braak staging of Parkinsons disease (from Jellinger K.A. (2014) Neuropathology of Parkinson's Disease. In: Thomas M. (eds) Inflammation in Parkinson's Disease. Springer, Cham).

At Braak stage 1, Lewy body deposition starts at the lower brain stem and olfactory system and may occur approximately 10 years before the manifestation of motor symptoms.

At Braak Stage 2, Lewy body deposition progress to the medullary structures and affects structures involved in the medial pain pathway, namely, serotonergic raphe nuclei, periaqueductal grey and noradrenergic locus coeruleus. A disturbance in these areas could cause dysfunctional pain processing and increased pain sensation.(Scherder, Wolters, Polman, Sergeant, & Swaab, 2005) This may explain why non-motor symptoms such as depression and pain occur at the pre-motor stage of Parkinsons disease.(Tysnes, Müller, & Larsen, 2010)

However, the scheme proposed by Braak et al is not without its critics and recent pathological findings have highlighted some of its inconsistencies. The Braak hypothesis is especially problematic in regards to the pre-motor stage and early motor stage of Parkinsons disease.

In an autopsy study of patients diagnosed in life with Parkinsons disease, Kalatzaikis et al found that 7% had sparing of the dorsal motor nucleus of the

vagus nerve, the purported site of entry for alpha-synuclein according to the Braak hypothesis, despite the presence of alpha-synuclein in other higher centres of the brain.(Kalaitzakis, Graeber, Gentleman, & Pearce, 2008) Several autopsy studies have shown the presence of widespread Lewy body deposition in the brain in subjects who were never documented to have any symptoms of parkinsonism or dementia during their lifetime.(Parkkinen, Pirttilä, & Alafuzoff, 2008)

It has been observed that Parkinsons disease patients that adhere to the Braak hypothesis of disease progression tended to be young and had a reduced tendency to develop problems with dementia.(Rietdijk, Perez-Pardo, Garssen, van Wezel, & Kraneveld, 2017) In those patients, it is plausible to assume that the pathogenesis of pain is heavily interlinked with the dysfunction of brainstem structures as ascribed by Braak Stage 1-2.

Whether the Parkinsons disease patients that transgress the Braak hypothesis develop pain in a different pattern, or indeed develop pain at all, is a question that presently does not have an answer.

2.5.4 Relevant neurotransmitters for pain beyond dopamine

The role of dopamine in the symptomatology of Parkinsons disease is beyond dispute, especially in regards to development of motor symptoms. Nevertheless, other neurotransmitter systems have been shown to be involved in the pathophysiology of Parkinsons disease. Furthermore, the disturbance in the interaction between different neurotransmitters with dopamine is also considered to be an important factor in regards to the manifestation of non-motor symptoms in Parkinsons disease. (Ahlskog, 2007) Specific interactions and consequent imbalances between serotonin, noradrenaline and dopamine are thought to play an important role in the pathogenesis of depression. (Nutt, 2008) In Parkinsons disease, REM sleep disorder is associated with increased cholinergic and a corresponding decreased dopaminergic activity.(Askenasy, 2001) In animal studies, the genesis of REM sleep is thought to involve

mechanisms that implicate glutamatergic-GABAergic interactions.(Luppi et al., 2006)

It is therefore reasonable to state that when considering factors contributing to pain in Parkinsons disease, attention must also be placed on the role of different neurotransmitters, especially the ones involved in nociception and pain pathway mechanisms. It also must be appreciated that the state of dopamine deficiency adds a further layer of complexity in trying to disentangle the role of different neurotransmitters in the development of pain in Parkinsons disease.

2.5.4.1 Glutamate

Glutamate is the primary excitatory neurotransmitter in the peripheral and central nervous system and transmits nociceptive signals across synapses by binding with glutamate receptors post-synaptically; there are 3 types of glutamate ionotropic receptors (NMDA, AMPA, kainite) and 8 glutamate metabotropic receptors (mGluR1-8).(Meldrum, 2000) Activation of these receptors induces an action potential that propagates the nociceptive signal through ascending pathways of the spinal cord to higher brain centres.(Bleakman, Alt, & Nisenbaum, 2006)

Pertaining to pain and nociception, glutamate plays a major role in the phenomenon of central sensitization.(Woolf, 1983) The phosphorylation of NMDA and AMPA receptor induces a translocation from intracellular stores to the synaptic membrane, resulting in an increased sensitivity to the excitatory effects of glutamate.(Ji, Kohno, Moore, & Woolf, 2003) These changes lead to an enhanced level of activation of synaptic transmission in the dorsal horn neurons resulting in activation of the pain pathways by stimuli that are normally subthreshold (allodynia), or an exaggerated response to normally suprathreshold stimuli (hyperalgesia).

Glutamate is associated with direct and indirect pathways in the basal ganglia although its actual role is poorly understood. However, certain structural aspects

have been well established. It is generally accepted that almost all corticofugal fibers use glutamate as the primary neurotransmitter and this also includes corticostriatal and corticothalamic pathways that terminates in the basal ganglia.(Young, Penney, Dauth, Bromberg, & Gilman, 1983) Additionally, the subthalamic nucleus and substatntia nigra pars compacta also receive efferent glutamatergic projections from the cerebral cortex.(Afsharpour, 1985; Usunoff et al., 1982)

In Parkinsons disease the loss of dopamine is thought to cause an increase in glutamatergic activity in the basal ganglia.(Conn, Battaglia, Marino, & Nicoletti, 2005) NMDA and AMPA receptor antagonism is associated with improvement of motor symptoms of PD.(Lange, Kornhuber, & Riederer, 1997) It is possible that selective inhibition of glutamatergic activity may be useful in managing certain symptoms of Parkinsons disease, including pain.(Rodriguez, Obeso, & Olanow, 1998)

Currently, pharmacological agents for pain that harnesses the glutamatergic pathway are primarily experimental. However, ketamine, a NMDA receptor antagonist has been shown to exert an inhibitory influence to the propagation of nociceptive signals in the central nervous system in various chronic pain conditions.(Stubhaug & Breivik, 1997)

2.5.4.2 Gamma Aminobutyric Acid (GABA)

GABA is the main inhibitory neurotransmitter in the central and peripheral nervous system. It is present in the interneurons of the spinal cord, neocortex and the cerebellum and primarily binds to the CNS predominant ionotropic $GABA_A$-receptor or the metabotropic $GABA_B$-receptor.(Watanabe, Maemura, Kanbara, Tamayama, & Hayasaki, 2002) Coupling of GABA to its receptor induces an inhibitory effect either by inflow of extracellular Cl^- into the neurons causing a reduction in membrane potential ($GABA_A$) or inhibition of formation of cyclic adenosine monophosphate ($GABA_B$).(Hyland & Cryan, 2010) Animal studies have shown that GABA neurotransmitter system is also involved in nociception, either

by GABA reuptake inhibition and metabolism, or GABA receptor agonism.(Vaught, Pelley, Costa, Setler, & Enna, 1985) Baclofen, a $GABA_B$-receptor agonist primarily used to treat spasticity has been shown to have anti-nociceptive properties, especially when used intrathecally.(Slonimski, Abram, & Zuniga, 2004) In Parkinsons disease, long term levodopa therapy and nigrostriatal denervation is thought to lead to a decrease in GABAergic activity in the striatal neurons.(Bonnet, 2000) Nevertheless, how these changes in GABAergic neurotransmission effects the symptoms in PD, particularly in relation to pain and nociception is currently unknown.(Barone, 2010)

2.5.4.3 Opioid

The principal neurotransmitter system that is responsible for analgesia is the opioidergic system. Opioid peptides bind to the mu-opioid, delta opioid and K-opioid receptors and cause inhibition of excitatory neurotransmitters, resulting in an overall pain attenuation. Opioid peptides include enkephalin, dynorphin and endorphin. The opioid receptors are widely distributed in the primary afferent neurons and the dendrites of postsynaptic neurons. In the dorsal horns of the spinal cord, endogeonous peptides, enkephalins and dynorphins can be released in the synaptic cleft of the interneurons, inhibiting ascending nociceptive signals.(Yam et al., 2018) This mechanism is triggered by descending inhibitory signals originating from areas in the brain stem, such as the periaquaductal grey.(Budai, Harasawa, & Fields, 1998)

The mechanism of action of analgesic opioid drugs such as morphine and tramadol involve activation of mu opioid receptors in the CNS that inhibit the afferent nociceptive impulse transmission, or within the brainstem and midbrain that activates descending inhibitory pathways or inhibit descending facilitatory pain pathways.(Inturrisi, 2002)

Specifically pertaining to the basal ganglia, there exists interplay between the dopamine and opioidergic system. Animal studies have demonstrated that dopamine antagonism reduces the effect of opioid analgesia whereas dopamine

agonism potentiates the effect of opioid analgesia.(Gupta, Chugh, & Seth, 1989; Morgan & Franklin, 1991) This may be an explanation for increased pain in Parkinsons disease and why certain opioid-based treatment appear ineffective.

2.5.4.4 Noradrenaline

The noradrenergic neurotransmitter pathway is also involved in the inhibition of nociceptive signal, primarily via the descending inhibition pathway originating from several areas within the pontine region of the brain, including the locus coeruleus.(Hentall, Mesigil, Pinzon, & Noga, 2003) These projections descend into the dorsal horn and inhibit pain signalling either by activating post-synaptic α_1 receptors, resulting in the release of GABA and glycine from inhibitory interneurons, or by activating α_{2A} receptors on the primary nociceptor terminals.(Benarroch, 2008)

In addition to the spinal mechanism described above, noradrenergic pain modulation is believed to also occur at supraspinal levels but the findings from studies have been conflicting. α_2 adrenoceptor activation in the striatum, amygdala and the thalamus has been shown to attenuate pain in animal studies.(Ortiz, Heinricher, & Selden, 2007; Pertovaara & Wei, 2008; Zhang, Yang, Guo, Qiao, & Dafny, 1997) Conversely, α_1 adrenoceptor activation, especially in the thalamus appears to produce pain facilitation.(Zhang et al., 1997) This complex picture regarding adrenoceptor activation highlights the fact that the exact net effect of noradrenergic stimulation, especially pertaining to supraspinal structure, is still uncertain and caution should be exercised when interpreting studies on the noradrenergic system in relation to pain.(Pertovaara, 2013)

The noradrenaline neurotransmitter system is highly relevant in Parkinsons disease as the biosynthesis of noradrenaline is the result of conversion of dopamine by dopamine β-monooxygenase. It has been shown that there is a reduction in noradrenaline levels in Parkinsons disease patients as compared to healthy subjects.(Barbic et al., 2007; Rommelfanger & Weinshenker, 2007) Imaging studies using PET showed that Parkinsons disease patients had a lower

uptake of ^{11}C-MeNER, a marker for noradrenaline transporter availability, in the thalamus as compared to healthy volunteers.(Nahimi et al., 2018) Unfortunately, administering L-dopa to Parkinsons disease patients only instigates a mild increase in noradrenaline levels in the brain.(Sharabi, Imrich, Holmes, Pechnik, & Goldstein, 2008)

Drugs that belong to the family of monoamine reuptake inhibitors are considered first-line therapy for the treatment of neuropathic pain i.e. amitriptyline.(Attal et al., 2006; Moulin et al., 2014) Other drugs such as duloxetine and milnacipran, belonging to the class of drugs called serotonin noradrenaline reuptake inhibitors (SNRI) are also thought to exert their anti-nociceptive effect primarily via the noradrenergic neurotransmitter system.

2.5.4.5 Serotonin

The descending serotonergic pathway arises from the medullary raphe nucleus and modulates pain signalling in the dorsal horn.(Hornung, 2003) Unlike the noradrenergic descending pathway, which exerts a primarily inhibitory effect on pain signalling, the corresponding serotonergic descending pathway exerts both facilitatory and inhibitory influence, depending on the type of receptor that is being activated.(Argoff, 2011)

For example, activation of the serotonin 5 HT_{1A} and $5HT_{1B/D}$ results in the inhibition of the spinothalamic projecting neurons and inhibition of neurotransmitter release from primary nociceptive afferents, respectively.(Benarroch, 2008) Conversely, activation of the 5-$HT_{2/3}$ facilitate nociceptive transmission within the spinal cord.(Zeitz et al., 2002)

In Parkinsons disease, the impact of serotonergic deficit has been implicated in the development of depression, fatigue and sleep disturbances.(Ballanger et al., 2012; Hagell & Brundin, 2009; Politis & Niccolini, 2015) In regards to pain in Parkinsons disease, the evidence for serotonergic involvement is limited but may

involve disturbance in the interaction with other neurotransmitters, especially noradrenaline.(Fava, 2003)

As a final note concerning dopaminergic and extra-dopaminergic mechanisms, a systematic review and meta-analysis conducted at our centre concluded that Parkinsons disease patients in the medication OFF state have increased pain sensitivity as compared to when they are in the medication ON state.(Sung, Vijiaratnam, Chan, Farrell, & Evans, 2018c) Nevertheless, considering that levodopa gives rise to various mono-aminergic neurotransmitters along the same biosynthetic pathway, it cannot be concluded whether this influence is attributable to either dopamine or other monoamines such as noradrenaline. The study also concluded that persistent pain in Parkinsons disease was associated with a higher dopaminergic dose. This has profound implication for the management of pain as this presents a seemingly paradoxical scenario. In the first instance, increasing dopaminergic medication may attenuate abnormal pain processing leading to normalization of pain threshold but at the same time, increased exposure arguably raises the risk towards the development of persistent pain amongst Parkinsons disease patients. Finally, the abnormal pain processing can occur anywhere along the neuroaxis and may be a consequence of peripheral sensitization or central sensitization, or both. This emphasizes the importance of pain sensitivity studies with outcome measures that allows the researchers to make this distinction e.g. functional MRI for central sensitization.

2.6 Implications for management

2.6.1 Non-pharmacological

There has been ample evidence of the efficacy of non-pharmacological treatment of chronic pain. A comprehensive systematic review looking at randomized clinical trials for common chronic pain condition has shown that a) exercise, massage and yoga therapies improve pain in the short and medium term, and psychological therapies improve pain in the short, medium and long term in chronic low back pain patients; b) exercise improves knee pain but showed no

clear benefit for hands and hip pain for patients with osteoarthritis; and c) tai-chi and qigong improved pain moderately for fibromyalgia patients in the short term.(Skelly et al., 2020)

Concomitant application of non-pharmacological therapies allows the use of pharmacological agents for chronic pain at optimal doses, reducing the risk for adverse side effects such as gastrointestinal bleeding, confusion and cardiovascular disease.(Towheed et al., 2006) This is especially relevant in the at-risk population such as the elderly with chronic pain and patients with progressive neurodegenerative disorders with chronic pain, such as Parkinsons disease.(Cavalieri, 2005) Acetaminophen (paracetamol) is the safest analgesic and recommended for first-line therapy for chronic pain but effectiveness is poor for osteoarthritis.(Wegman, van der Windt, van Tulder, Stalman, & de Vries, 2004)

In the elderly population, several studies have been performed looking at the effectiveness of non-pharmacological therapy for chronic pain. Statistically significant pain reduction has been demonstrated in randomized controlled trials using acupressure for knee osteoarthritis, qigong for neck pain, hydrotherapy and tai chi for osteoarthritis.(Fransen, Nairn, Winstanley, Lam, & Edmonds, 2007; Li, Harris, Tsodikov, Struble, & Murphy, 2018; von Trott et al., 2009) A study using guided imagery with relaxation, a form of cognitive behavioural therapy to distract and refocus attention of pain has been shown to be effective in the older population for the management of chronic pain.(Baird, Murawski, & Wu, 2010)

A systematic review on various non-pharmacological therapies in elderly patients concluded that it is effective in reducing pain.(Tang, Tse, Leung, & Fotis, 2019) No systematic review has been performed in the Parkinsons disease patient with pain population. The applicability of certain non-pharmacological therapies in the Parkinsons disease population might be problematic due to the limitations imposed by their symptoms e.g. motor deficits interfering with exercise therapy.

2.6.1.1 Physiotherapy and exercise

The role of exercise and physiotherapy in the management of Parkinsons disease has been explored extensively over the past 2 decades. This in part due to the realization of the limitation of pharmacological agents in alleviating certain symptoms of Parkinsons disease.(Fox et al., 2011) Systemic reviews and meta-analysis clearly supports the benefits of exercise and physiotherapy for Parkinsons disease, especially in addressing issues of gait and imbalance.(Mak, Wong-Yu, Shen, & Chung, 2017; Shen, Wong-Yu, & Mak, 2016; Tomlinson et al., 2012) The question on whether exercise and physiotherapy has any role in managing pain in Parkinsons disease is less well researched.

To date, there have been 3 studies that have attempted to provide an answer to this question. In a study comparing Nordic walking, walking and relaxation in Parkinson's disease, the results showed reduced pain intensity in the back and legs in the walking and Nordic walking group as compared to the relaxation group.(Reuter et al., 2011) An open labelled study showed that exercise in Parkinson's disease showed a non-significant reduction in pain of 8% ($p=0.061$) between baseline and study completion.(Rodrigues de Paula, Teixeira‐Salmela, Coelho de Morais Faria, Rocha de Brito, & Cardoso, 2006) Finally, in a study comparing aquatic therapy and physiotherapy, both treatments showed improvements in the VAS scores for pain after 1 month but a greater change was seen in those that underwent aquatic therapy.(de la Cruz Pérez, 2017)

The mechanisms by which exercise and physiotherapy are thought to modify pain are several. In animal models of Parkinsons disease, exercise has been shown to promote neuroplasticity by restoring dendritic spine loss in striatal neurons, reducing levels of pro-inflammatory cytokines and activated microglia, and enhancing antioxidant defences against neurotoxins.(Svensson, Lexell, & Deierborg, 2015; Toy et al., 2014; Zigmond & Smeyne, 2014)

A study on a Parkinsons disease mouse model showed that exercise restores D2 receptors in the dorsal striatum.(Fisher et al., 2004) The same research group tested this hypothesis in Parkinsons disease patients and demonstrated that exercise resulted in an increase striatal dopamine D2 receptor binding potential.(Fisher et al., 2013) The involvement of the D2 receptor is notable as Hagelberg et al demonstrated a link between pain perception and D2 receptor binding potential in human studies with chronic pain.(Hagelberg et al., 2004) Other studies involving Parkinsons disease patients showed that exercise results in an increased level of serum brain-derived neurotropic factor (BDNF) concentration, which protects against dopamine transporter signalling deficits.(Petzinger et al., 2015)

2.6.1.2 Complementary and surgical approaches

There have been some evidence for the use of complementary therapies such as acupuncture and Japanese massage for pain in Parkinson disease but further studies are required to confirm these findings.(Donoyama & Ohkoshi, 2012; Shulman et al., 2002)

Kodama et al published a case report of improvement in off period dystonia following transcranial magnetic stimulation. (Kodama et al., 2011) Botulinum toxin has been used to treat painful OFF-dystonia and showed resolution of pain at 4 months in 20 out of 30 patients.(Pacchetti et al., 1995)

Anecdotal reports of reduced pain symptoms in patients following pallidotomy to relieve symptoms of hypokinesia and rigidity were the earliest indications that surgical approaches may help in the management of pain in Parkinsons disease.(Baron et al., 1996; Laitinen, Bergenheim, & Hariz, 1992) This was confirmed by a prospective study of 21 Parkinsons disease patients that showed significant reduction in overall pain scores at 6 weeks and 1 year following unilateral pallidotomy.(Honey, Stoessl, Tsui, Schulzer, & Calne, 1999)

In recent years, with the increasing adoption of deep brain stimulation surgery as a modality for advance therapy in Parkinsons disease, studies have shown that stimulation of the subthalamic nucleus also produced improvement in pain symptoms.(Loher, Burgunder, Weber, Sommerhalder, & Krauss, 2002; Oshima et al., 2012) Indeed, an 8-year follow up study showed that the improvement in pain following subthalamic nucleus stimulation was long lasting although in some patients, new pain in the form of musculoskeletal pain may subsequently occur.(Jung et al., 2015)

In summary, there is ample evidence that deep brain stimulation surgery (and pallidotomy) is an effective measure for the management of pain in Parkinsons disease. Nevertheless, due to the significant risk and invasive nature, this approach cannot be part of the routine management for pain in Parkinsons disease for most patients.

2.6.2 Pharmacological management

There is currently no established guideline for the management of pain in Parkinsons disease. Presently, pain is managed by a variety of pharmacological agents.

Despite the high prevalence of pain in Parkinsons disease, several cross-sectional studies have shown that analgesics are underused in Parkinsons disease patients with pain, as compared with other chronic pain patient groups.(Christine Brefel-Courbon et al., 2009; Nègre‐Pagès et al., 2008) Lee et al found that for pain in Parkinsons disease, the commonest analgesic used was paracetamol (50.4%), followed by a weak opioid (25.2%) and then NSAIDs (12.2%).(Lee, Walker, Hildreth, & Prentice, 2006)

2.6.2.1 Analgesics and NSAIDs

A study looking at the quality of life of patients with Parkinsons disease did show that there is a positive correlation between better quality of life and the frequency of analgesic intake per week.(Müller, Muhlack, & Woitalla, 2011) There have been no studies specifically investigating the effectiveness of NSAID analgesics for pain in Parkinsons disease.

It has been suggested that pain arising from changes in the musculoskeletal system brought about by the rigidity, dystonia and postural abnormalities from Parkinsons disease may respond better with analgesics and NSAIDs.(Perez-Lloret et al., 2012) The rationale is that these types of pain are thought to be nociceptive in nature and that the pain is a direct consequence of actual or potential damage, which triggers the inflammatory cascade and cytokine release.

2.6.2.2 Opioids

Opioids are effective in managing pain and have been used extensively in other chronic pain conditions, such as pain arising from cancer and osteoarthritis. The usefulness of opioids in the treatment of pain in Parkinsons disease is limited by its effect on the enteric mu-opioid receptors in the gastrointestinal tract, which compounds constipation problems in Parkinsons disease patients. Naloxone, an opioid receptor antagonist, is combined with the opioid oxycodone to minimize this effect.

An open label study using oxycodone naloxone for pain in Parkinsons disease patients showed a statistically significant improvement in pain scores.(Madeo et al., 2015) A phase-2 randomised placebo controlled trial showed a lower 24-hour pain score in the Parkinsons disease patient group given oxycodone-naloxone, as compared to the group given placebo, but the results did not reach statistical significance ($p=0.058$).(Trenkwalder et al., 2015) Moreover, in this study, opioids were significantly associated with worsening nonmotor symptoms of nausea and constipation.

2.6.2.3 Dopaminergic agents

There have not been many studies specifically looking at the effectiveness of levodopa for pain in Parkinsons disease as this type of studies was designed primarily to investigate motor symptom changes; pain usually being a secondary outcome measure or performed as a post-hoc analysis.

Nevertheless, improvements in pain reports following initiation of levodopa therapy have been consistent across several studies.(Fahn, Keiburtz, & Tanner, 2005; Honig et al., 2009) A study looking at pain during ON and OFF periods showed that there was a statistically significant reduction in pain scores following levodopa administration.(Nebe & Ebersbach, 2009) A double blind placebo controlled study showed that levodopa reduced pain scores as measured by VAS after 4 weeks as compared to placebo in patients with pain arising from diabetic peripheral neuropathy.(Ertas, Sagduyu, Arac, Uludag, & Ertekin, 1998)

Dopamine agonist therapy (e.g. apomorphine, pramipexole and rotigotine) has been used to address motor symptoms in Parkinsons disease. Research has now shown that this group of drugs can also be useful for pain in Parkinsons disease, with varying levels of evidence.

Apomorphine has been shown to be useful for pain in Parkinsons disease in one case report and one case series.(Factor, Brown, & Molho, 2000; Frankel, Lees, Kempster, & Stern, 1990) However, a randomized controlled trial did not show any statistically significant difference between apomorphine and placebo on evoked pain threshold in Parkinsons disease patients.(Dellapina et al., 2011)

The use of dopamine agonist pramipexole has been investigated for use in burning mouth syndrome and fibromyalgia, chronic pain conditions with purported dysfunctional pain processing arising from central dopamine abnormalities.(Holman & Myers, 2005; Stuginski-Barbosa, Rodrigues, Bigal, & Speciali, 2008) The only randomized control trial for pramipexole in Parkinsons disease had pain as a secondary measure; the pramipexole group had

statistically significant lower VAS scores compared to the placebo group.(Paolo Barone et al., 2010)

Rascol and colleagues conducted a pilot study exploring the use of rotigotine for pain in Parkinsons disease and showed that there was a trend towards improvement on the Likert pain scale in the rotigotine group as compared to the placebo group, but this did not reach statistical significance (p=0.172).(Rascol et al., 2016)

It is common in clinical practice for pain to not improve despite optimization of dopaminergic medications. Moreover, in cross-sectional studies, higher daily dopaminergic drug doses has been specifically linked to persistent pain.(Sung et al., 2018b) These findings may indicate that a more complex relationship exists between pain and dopaminergic treatment effects, and that pain in Parkinsons disease is likely to be multifactorial in origin, with contribution from central and peripheral mechanisms in varying degrees.(Lim, Farrell, & Evans, 2011)

2.6.2.4 Duloxetine

Duloxetine is serotonin-noradrenaline reuptake inhibitor and was initially formulated to treat depression. The mode of mechanism is thought to be via the modulation of serotonin and noradrenaline tone in the central nervous system.

There have been 2 studies performed looking at the effect of duloxetine in patients with osteoarthritis; both studies showed statistically significant improvement in pain scores following duloxetine, as compared to placebo.(Chappell et al., 2011; Chappell et al., 2009) These findings were also seen in studies involving chronic back pain patients.(Skljarevski, Desaiah, et al., 2010; Skljarevski et al., 2009; Skljarevski, Zhang, et al., 2010)

Longstanding uncontrolled diabetes mellitus may predispose patients to a peripheral neuropathy that can cause chronic pain. To date, there have been 3 well-designed randomized controlled trials that showed statistically significant

improvement in average pain scores in patients with painful diabetic peripheral neuropathy following 12 weeks duration of 60mg/day duloxetine, as compared to placebo.(Goldstein, Lu, Detke, Lee, & Iyengar, 2005; Raskin et al., 2005; Wernicke et al., 2006) These studies also showed that although duloxetine 120mg/day was equally effective as 60mg/day, higher doses of duloxetine were associated with more reports of adverse effects.

In patients with central neuropathic pain following spinal cord injury and stroke, duloxetine was shown to improve mechanical and cold allodynia, as compared to placebo ($p<0.001$; $p<0.019$). However, pain reports using Visual Analogue Scale only showed a positive trend favouring duloxetine over placebo in this group of patients ($p=0.056$).(Vranken et al., 2011)

Another condition that is thought to cause chronic pain stemming from a central neurological cause is fibromyalgia. It has been postulated that there is a defect in the descending pain inhibition pathway thus causing an abnormality in the serotonin-noradrenergic tone.

A multi-center placebo controlled study found that duloxetine, at a target dose of 120mg, showed a statistically significant difference compared to placebo in almost all the psychophysical measures tested, including dolorimetry using an algometer ($p=0.002$).(Arnold et al., 2004). A follow up study however showed that these results did not carry over when the dose of duloxetine was reduced to 60mg per day.(Arnold et al., 2005) This suggests that unlike studies on painful diabetic peripheral neuropathy, the total dosage is an important factor in the effectiveness of duloxetine in fibromyalgia.

Finally, Djaldetti et al looked at pain in Parkinson's disease in an open labeled study of 6 weeks duration using Brief Pain Inventory (BPI) and Short form McGill Pain Questionnaire (SF-MPQ) as the main efficacy outcome measure.(Djaldetti et al., 2007) The study showed that duloxetine significantly reduced pain compared to placebo but quantitative sensory testing assessments using evoked thermal

pain stimulus did not show any statistical difference between treatment and placebo groups.

There have been many theories put forth on the exact mechanism by which duloxetine is able to modulate pain in chronic pain condition. It is speculated that one of the mechanism is by modulating the descending pain inhibition pathway. Lopez-Sola et al looked at the effect of duloxetine on brain activations following experimental thermal pain stimuli in patients with major depressive disorder. The results showed that compared to healthy controls, patients with major depressive disorder had reduced activations in the pregenual anterior cingulate cortex on fMRI, which was restored following 8 weeks of duloxetine.(López-Solà, Pujol, Hernández-Ribas, Harrison, Contreras-Rodríguez, et al., 2010) It is known that the pregenual anterior cingulate cortex has dense projection to the periaqueductal gray region, an area important in the descending pain inhibition pathway. (Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003) Additionally, symptom improvements in patients were correlated with reduced activations in the right prefrontal cortex and pons.

In summary, there has been extensive research on the use of duloxetine in a variety of chronic pain conditions, ranging from pain arising from musculoskeletal pathology i.e. osteoarthritis to pain stemming from chronic neurodegenerative conditions. Studies on pain in Parkinsons disease in general and specifically on duloxetine for pain are limited. Nevertheless, the majority of studies show that duloxetine may have a place as part of the armamentarium for the management of pain in general, and in Parkinsons disease in particular.(Djaldetti, Yust-Katz, Kolianov, Melamed, & Dabby, 2007; Iwaki et al., 2020)

2.7 Neuroimaging in Parkinsons disease and pain

Over the past 30 years there has been an explosion of different neuroimaging modalities that are available for use for Parkinsons disease. There are more than a dozen techniques available in the field of MRI and approximately 100 radioligands available for use in PET and SPECT.(Politis, 2014) However, these are primarily performed in a research setting and very few have been adopted for day-to-day clinical use.

Presently, the use of neuroimaging to confirm the diagnosis of Parkinsons disease is only in the form of a supplementary role; objective clinical findings and the response to levodopa treatment remain the primary methods in confirming a diagnosis.(Reichmann, 2010)

Neuroimaging has provided some insights towards our understanding of non-motor symptoms in Parkinsons disease, specifically relating to the involvement of other neurotransmitter systems and brain regions beyond the basal ganglia.

Although Parkinsons disease patients transplanted with dopamine-rich fetal graft experienced improvement in motor symptoms, this was associated with a corresponding deterioration in serotonergic function in brain areas regulating sleep, arousal, mood and emotion i.e. non-motor symptoms.(Politis et al., 2012)

Depression is a common non-motor symptom in Parkinsons disease and adversely affects the quality of life of patients; PET studies revealed reduced noradrenergic, serotonergic and dopaminergic function in the brain limbic regions.(Boileau et al., 2008; Doder, Rabiner, Turjanski, Lees, & Brooks, 2000; M Politis et al., 2010; Remy, Doder, Lees, Turjanski, & Brooks, 2005)

The literature relating to imaging and pain in Parkinsons disease is limited. A PET study on patients with Parkinsons disease during the OFF condition revealed increased activation in the pain processing regions of the brain (ipsilateral insula and PFC; contralateral ACC) following cold pressor test; the

increased activation was attenuated upon administration of levodopa.(Brefel-Courbon et al., 2005) The same group also demonstrated changes in brain activation within pain processing areas in the brain between Parkinsons disease patients with and without pain.(Brefel-Courbon, Ory-Magne, Thalamas, Payoux, & Rascol, 2013) In a recently published study using brain SPECT with ^{123}I-ioflupane-FP-CIT, subjective pain threshold showed positive correlation with radiotracer binding in the extra-striatal regions but not within the nigrostriatal area.(Dellapina et al., 2019) A study comparing Parkinsons disease patients with and without pain revealed cortical thinning in frontal, prefrontal and insular regions, further advancing this theory.(Polli et al., 2016) Taken together, these findings suggests that pain perception abnormalities not only involve nigrostriatal dopaminergic neuronal loss but also implicates monoaminergic extra-striatal pathways.

Tan et al conducted a fMRI study on pain in Parkinsons disease using a combination of evoked pain stimuli and resting state scan which demonstrated reduced functional connectivity in the putamen during the evoked pain condition and reduced connectivity between the salience network and sensorimotor network, when compared to controls.(Tan et al., 2015) The salience network is a network comprising of the anterior insula and the mid-cingulate cortex and regulates the attention of the organism to external stimuli. Functional imaging studies have demonstrated that giving prior information of impending noxious stimuli activate the insula prior to stimulation and mid-cingulate during stimulation. Importantly, the basal ganglia act as an important bridge between the pain neuro-matrix and the salience network, thus providing another example on how pain perception abnormalities can be dysfunctional in Parkinson disease.

2.8 Hypothesis and goals for this PhD

In summary, pain in Parkinsons disease is a pressing issue and can potentially adversely impact beyond the individual. In the coming years, pain in Parkinsons disease may potentially impose an increasing strain on financial resources. Presently, this condition is poorly managed with different therapies showing inconsistent results.

New alternatives to the management of Parkinsons disease are warranted. Beyond the identification of new therapies, further understanding of the pathophysiological process of pain in Parkinsons disease is equally important. The promising result of duloxetine needs to be confirmed and the mechanism of action needs to be clarified.

Therefore, the primary aims of this thesis were as follows:

1. To improve the understanding of the neurobiology of pain in Parkinsons disease.
2. To provide a framework for the management of pain in Parkinsons disease.

The research questions that we wish to address were:

1. How does duloxetine affect pain in Parkinsons disease?
2. How does duloxetine affect the function of the pain processing areas in Parkinsons disease patients with pain?

Our objectives were:

1. Evaluation of the effects of duloxetine on chronic pain in Parkinsons disease patients
2. Establish whether duloxetine affects pain sensitivity following evoked pain stimulus in Parkinson's disease patients with pain
3. Establish whether changes in pain sensitivity are associated with changes in activation in pain processing areas in the brain.

4. To explore whether chronic persistent pain in Parkinsons disease patients is associated with changes in activation of the default mode network.

In accordance with the thesis aims and research questions, the primary hypotheses were:

1. Following administration of duloxetine, patients with Parkinson's disease with pain will report reduced pain scores.
2. Following administration of duloxetine, Parkinsons disease patients will report reduced pain sensitivity following evoked pain stimulus.
3. Changes in pain sensitivity will be associated with changes in areas of the brain involved in pain processing.
4. Following administration of duloxetine, there will be changes in the pattern of activation of the default mode network.

Chapter 3: Experimental Methods

This chapter describes in general terms, the materials and general procedures used in this thesis. Technical details pertaining to specific MRI procedures will be further elaborated in the methodology section of the corresponding chapters.

3.1 Recruitment

This was a 6-week, single-centre, prospective double-blind placebo-controlled trial carried out at the Royal Melbourne Hospital, Melbourne, Australia. Prospective participants were recruited from patients attending the movement disorder outpatient clinic at the Royal Melbourne Hospital. The local ethics committee provided approval for the research protocol (HREC 2015-145). Written informed consent was obtained from all patients participating in the study. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

3.1.1 Inclusion criteria

- Participants must have a diagnosis of Parkinsons disease as defined by the UK PDS Brain Bank Diagnostic Criteria (Hughes, Daniel, Kilford, & Lees, 1992)
- Participants must be aged between 18 years to 85 years old
- Participants must report daily pain of at least 3 months duration
- Participants must be on stable doses of dopaminergic medication in the preceding 2 months prior to recruitment into the study

3.1.2 Exclusion Criteria

- Participants with a contraindication to undergo an MRI scan
- Participants with dementia (MMSE <24)
- Participants with significant peripheral neuropathy (by clinical examination)
- Participants who are pregnant

- Participants with significant symptoms of depression (Geriatric Depression Scale >10)
- Participants already on an anti-depressant for the past 3 months that would contraindicate the use of duloxetine
- Participants with a known hypersensitivity or a contraindication to duloxetine
- Participants with any other medical condition that might cause acute or chronic pain

3.2 Study drugs

Treatment consisted of either a once daily dose of duloxetine or placebo, taken in the evening. Duloxetine and placebo drugs were matched in appearance. Patients were randomized in blocks of 4 at a 1:1 ratio at baseline using a schedule drawn up by a statistician and provided to the pharmacist to guide dispensing of the study drug to the participants. All the study drug (duloxetine and placebo) were prepared and dispensed by the study pharmacists according to the randomization schedule provided. Both the study investigators and the participants were blinded to the randomization protocol. At baseline (Visit 1), participants were given duloxetine 30 mg or matching placebo. After 2 weeks (Visit 2), the dose was increased to 60mg of duloxetine, or matching placebo and continued for another 4 weeks until study completion (Visit 3; total study duration 6 weeks). All assessments were performed at baseline (Visit 1) and at study completion (Visit 3). All the assessments were performed in the ON state, conducted approximately 30 minutes after the participants' last dose of anti-parkinson medication. Dosages of dopaminergic medication were not adjusted during the study period.

3.3 Efficacy measures

3.3.1 Scale and Questionnaires

3.3.1.1 Short-Form McGill Questionnaire

This is a validated questionnaire developed by the Ronald Melzack.(Melzack, 1987) It has been extensively validated and used widely in chronic pain research. The components include 11 sensory pain descriptors and 5 affective pain descriptors that are rated on an intensity scale (0=none; 1=mild; 2=moderate and 3=severe). The questionnaire also includes a Visual Analogue Scale.

3.3.1.2 King's Parkinsons disease pain scale

This is the first validated scale that is disease specific for pain in Parkinsons disease.(Chaudhuri et al., 2015) The scale comprises of 14 items representing different types of pain. The scoring system captures severity and frequency of each item, with a possible score ranging from 0 to 168 (a higher score signifying greater pain burden).

3.3.1.3 Parkinsons Disease Questionnaire (PDQ)-39

The 39-item questionnaire assesses quality of life measures across 8 dimensions which includes elements relating to relationships, social situation and communications.(Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995) Participants are required to respond according to how often they encounter the problem defined by each item. The score ranges from 0 (never have difficulty) to 100 (always have difficulty), with lower scores signifying better quality of life.

3.3.1.4 Geriatric Depression Scale (Short-Form)

This is a 15-item screening tool to identify presence of depression in the older adults.(Sheikh & Yesavage, 1986) Scores of 0-4 are considered normal; 5-8 indicates mild depression; 9-11 indicates moderate depression; and 12-15 indicates severe depression.

3.3.1.5 Positive Affect and Negative Affective Schedule (PANAS)

This self-report questionnaire comprises of 20-items that measures positive affect and negative affect.(Watson, Clark, & Tellegen, 1988) Each item is rated on a five point Likert scale based on how strongly the participant experiences the described item i.e. 1=not at all, 2=a little, 3=moderately, 4=quite a bit, and 5=extremely. The scoring system is divided into positive affect and negative affect, with each having a score range between 10 (signifying weak affect) to 50 (signifying strong affect).

In addition to the above outcome measure, we also used the Unified Parkinsons Disease Rating Scale (UPDRS) Part III for the assessment of severity of Parkinsons disease.(Fahn & Elton, 1987) The levodopa equivalence dose for all the dopaminergic medication was calculated based on previously established methods, where 100mg of levodopa = 130mg of levodopa in controlled-release form, 70mg of levodopa if also using entacapone, 1mg of pramipexole, 5mg of ropinirole, 3.33mg of rotigotine, 1mg of rasagiline, and 100mg of amantadine.(Smith, 2010)

3.3.2 Pain sensitivity using evoked pressure pain stimulus

Pain is a subjective experience and at any given noxious stimulus, the reports of pain intensity will be different between one subject to another. Psychophysical methods allow the subjective experience of pain to be quantified into a scale that allows comparison between subjects. In this thesis, we chose an evoked pressure pain stimulus as the psychophysical method to investigate the relationship between duloxetine and pain sensitivity in Parkinsons disease.

A mechanical pressure apparatus was used to apply painful or innocuous pressure to the thumbnail of the right hand. The apparatus was designed specifically to be used safely during MRI experiments, and therefore does not contain any ferromagnetic components and its use is validated in pain research utilizing functional MRI techniques.(Cole et al., 2006) The pain evoked by the

apparatus does not persist beyond the period of stimulation, with no reports or observation of injury to the nail bed following its application.

The pressure stimulus is delivered via a 0.5 cm^2 hard rubber circular probe that is positioned over the right thumbnail by a plastic housing and driven hydraulically by a set of pistons. The mechanism of the pistons is activated by a set of calibrated weights placed on a movable table. A set of valves regulate stimulus timing and duration, allowing controlled and repeatable pressure stimulation when used in combination with the calibrated weights. The pressure stimulus was applied using calibrated weights in increments of 0.25kg, which is equal to a pressure of 0.32kg/cm^2.

Short duration (5 seconds) pressure stimuli will be applied in a multiple random staircase method procedure to determine the minimum amount of stimulation required to elicit a report of 0.5/10 and 5.5/10 on the 11-point numerical descriptor scale.(Gracely, Lota, Walter, & Dubner, 1988) For each participant, the pressure threshold required to produce a report 0.5/10 will be recorded as the Just Noticeable Pain (JNP) and the pressure threshold that produced a report of 5.5/10 will be recorded as Moderate Pain (MP).

As preparation, all the participants were shown a demonstration of the workings of the mechanical pressure apparatus. To familiarize with the pressure stimulus, a few stimuli were delivered to the right thumbnail in duration of not more than 5 seconds at a random intensity and the participants were asked to rate the intensity immediately upon the withdrawal of the stimulus. The participants were reminded to report the intensity of the pain and not the intensity of the pressure.

3.3.2.1 Determining pressure threshold using Multiple Random Staircase (MRS)

The Multiple Random Staircase method was chosen to determine the pressure threshold for each participant and is a modification of the Method of Limits. Criticism of the Method of Limits relates to the sequence in which the intensity of

the stimuli is presented, which is based on the response of the preceding stimuli and the possibility of the participants being able to deduce the underlying scheme. For example, a response of no pain would increase the subsequent stimuli and a response of mild pain would reduce the subsequent stimuli. In the Method of Limits, there is a concern that the participants would anticipate the intensity of the stimuli and have a preconceived response formed in their mind even before the stimuli is presented.

The Multiple Random Staircase method consists of 3 separate staircases that are used to titrate the evoked pressure stimulus to elicit a response anchored to an intensity of 0.5/10 (Just Noticeable Pain), 2.5/10 (Mild Pain) and 5.5/10 (Moderate Pain). Each of the staircases was conducted in the simple up-down method, where the amount of pressure to be given is dependent on the response history for that particular staircase. For example, for the staircase of Just Noticeable Pain (0.5/10), if the stimulus received a response of 1/10 or above, the following stimulus would be decreased. If the stimulus received a response of 0/10, the following stimulus will be increased. The step size of the next delivered stimuli is adjusted between 0.25kg/cm^2 to 1kg/cm^2 based on how far the response given by the participant is from the targeted response. Each of the staircase delivered 10 stimuli each and the switch between each staircase is predetermined beforehand and applied in the same sequence to all the participants. The participants were blinded to the sequence of the staircase. The stimulus level required to evoke Just Noticeable Pain and Moderate Pain for each participant was recorded from the average value of 10 stimuli for each staircase.

3.4 Procedures

The study was conducted over 3 visits. The participants were assessed in the ON state. Consequently, all procedures were performed approximately 30 minutes after ingestion of participants' usual anti-parkinsons medication.

Visit 1

Each participant's pressure threshold for Just Noticeable Pain (JNP) and Moderate Pain (MP) was determined using the mechanical pressure apparatus, as previously described in **Section 3.3.2**.

Following this, information about the participants were collected. This included demographic data such as their age, age of onset of Parkinsons disease, gender, ethnicity, as well as the use of scales to obtain information about the severity of their Parkinsons disease, cognitive function, quality of life, and pain experience (as listed above).

Finally, a selected number of participants underwent an MRI scan, conducted at the Murdoch Children's Research Institute, Melbourne. This involved a task-based fMRI and a resting state fMRI.

Images were acquired using a Siemens TRIO 3T MRI scanner. Firstly, a high-resolution T1 weighted structural image was acquired to aid registration of functional images to the Montreal Neurological Institute template brain.

In the task-based fMRI, the participants underwent an evoked pressure pain stimulus paradigm over 2 runs during Blood Oxygen Level Dependant (BOLD) image acquisition. The paradigm consists of fingernail pressure on the right thumb, using the mechanical pressure apparatus applied for 20 seconds, alternating with no stimulus control periods of 30 seconds for a total duration of 6 minutes. Blocks of pressure will be applied at the intensity previously determined to elicit MP, or be innocuous in a pseudorandom order (for further details, please refer to **Section 5.2 Methodology**).

All the participants were asked to rate the intensity of the pain induced by the pressure stimulus during each fingernail pressure. The participants were trained to report the intensity of the pain on a scale of 0 (no pain) to 10 (worst pain imaginable) by holding up how many fingers on the left hand that corresponds to the pain score. For example, for a pain score of 3 out 10, the participants were

asked to raise 3 fingers on their left hand; for a pain score of 8 out of 10, the participants were asked to raise 5 fingers followed by 3 fingers on their left hand. This method was chosen to reduce head and body movement during the MRI scan.

Following this, the participants underwent a resting state fMRI scan. BOLD image acquisition were performed with the participants' eyes closed for a duration of 6 minutes (for further details, please refer to **Section 6.2 Methodology**).

At the end of Visit 1, participants were randomised to receive either duloxetine or placebo. The randomisation process was performed according to a schedule that was prepared beforehand by a statistician. The schedule was given to the dispensing pharmacist in a manner that would ensure the principal investigator (AE) and associate investigator (SA) would be blinded to the randomisation schedule.

Patients randomised to the duloxetine group started at a dose of 30mg for 2 weeks and increased to 60mg thereafter, if tolerated.

Visit 2

This session occurred 2 weeks after Visit 1. Participants were reviewed and questions regarding any side effects of the drugs were asked. Participants tolerating the initial dose had their dose increased to 2 capsules of either duloxetine or placebo (i.e. duloxetine 60mg).

Visit 3

This session occurred 6 weeks after Visit 1. The conduct of this visit was similar to that of Visit 1. Participants who underwent MRI scanning in Visit 1 had another MRI scan using the same paradigm.

At the end of visit, participants were asked to stop all drugs that have been given for the purpose of the study.

3.5 Statistical Analysis

All data were analyzed using IBM SPSS Statistics 22.0 software package. Qualitative and quantitative demographic characteristics were tabulated and tested for normality using *Shapiro-Wilk* test. Results were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR). The *student's t-test* was used to compare the means of two normally distributed data. The *Mann-Whitney U-test* was used to compare between two groups for non-normally distributed data. The analysis of variance was used to evaluate changes in continuous variables over time. A p value of <0.05 was deemed as statistically significant.

3.6 Sample size calculation

In our study the main primary outcome measure would be the Short-Form McGill Pain Questionnaire.

A previous open label study using duloxetine for pain in Parkinson's disease provides information of the following (Djaldetti et al., 2007):

The mean Short-Form McGill Questionnaire score before treatment was 15.1 and the mean after treatment is 9.4, with a standard deviation of 5.9. This gives a targeted difference of 5.7.

The effect size is 0.966 (targeted difference / standard deviation= 5.7/5.9). Therefore, using an α of 0.05 and power of 0.8 gives a sample size of 36 (18 per group).

For the purpose of the whole study, we have decided to have a sample size of 40 participants (20 in each arm). This will provide sufficient power for all the primary outcome measures that we wish to use.

In regards to the functional imaging study, sample size considerations were based on 2 previous default mode network studies in Parkinson's disease and neuropathic pain diabetes, with sample sizes of 14 and 16 participants,

respectively.(Cauda et al., 2009; van Eimeren, Monchi, Ballanger, & Strafella, 2009) We aimed to recruit 8 participants per group for the functional MRI study.

Chapter 4: The effect of duloxetine on clinical pain ratings in Parkinsons disease patients with pain

4.1 Introduction of aims and hypothesis.

Duloxetine is a serotonin-noradrenaline reuptake inhibitor. Initially approved for the treatment of major depression in 2004, duloxetine has since acquired license for use in various chronic pain conditions, including painful diabetic peripheral neuropathy, fibromyalgia, and chronic back pain.(Alev et al., 2017; Lunn, Hughes, & Wiffen, 2014; Schukro et al., 2016) Presently, duloxetine is not licensed for use in Parkinsons disease patients with pain.

Duloxetine inhibits transporters of serotonin and noradrenaline, thus causing an increase in the concentration of these neurotransmitters in-vivo. In pain, the mechanism of action of duloxetine is speculated to be related to its action on the descending pain inhibition pathway.(Iyengar, Webster, Hemrick-Luecke, Xu, & Simmons, 2004; Mixcoatl‐Zecuatl & Jolivalt, 2011)

In a paper published in 2007, a study conducted in an open label design showed that 6-weeks administration of duloxetine in Parkinsons disease patients with pain reduced pain scores, as determined by the sensory portion of the Short-Form McGill Questionnaire.(Djaldetti et al., 2007)

Guided by this study, we conducted a 6-week double blind placebo-controlled trial of duloxetine in Parkinsons disease patients with pain. Our research question is whether duloxetine affects clinical pain scores in Parkinsons disease patients with pain. This can be achieved by comparing the pain ratings of Parkinsons disease patients with pain before and after treatment with either duloxetine or placebo.

4.2 Methodology

Participants were recruited from patients attending the movement disorder clinic at the Royal Melbourne Hospital. The inclusion and exclusion criteria are outlined in **Chapter 3** (Section 3.1.1 and 3.1.2).

The total score of the Short-Form McGill Pain Questionnaire was chosen as the primary outcome measure.

Secondary outcome measures included the total score of the following scales:

- The affective component of the Short-Form McGill Pain Questionnaire
- The sensory component of the Short-Form McGill Pain Questionnaire
- Visual Analogue Scale
- King's Parkinsons Disease Pain scale
- Parkinsons Disease Questionnaire (PDQ)-39
- Geriatric Depression Scale (GDS)
- Positive Affect and Negative Affect Schedule (PANAS)

A more detailed explanation of the properties of each questionnaire and scales is described in **Chapter 3** (Section 3.3.1).

Other information collected include:

- Demographic data e.g. age, gender
- Information pertaining to Parkinsons disease e.g. duration, UPDRS Part III score
- Analgesic medication used
- Dopaminergic medication used

4.3 Results

A total of 21 participants were enrolled into the study, comprising 11 males and 10 females. One male participant withdrew from the study due to an adverse drug reaction (nausea) 1 week into the study, and one female participant did not return for the study completion visit due to scheduling conflicts (participant underwent a surgical procedure unrelated to the study drug). In those that completed the study, 5 participants prescribed duloxetine reported non-debilitating symptoms of drowsiness that did not impact on their daily activities. Participants prescribed placebo reported no serious adverse events or side-effects throughout the study duration.

Of the 19 participants that completed the study, 9 participants were randomised to have duloxetine, comprising 6 females and 3 males. 10 participants were randomised to the placebo arm, comprising 4 females and 6 males.

The baseline demographic data is shown in Table 4.1. There were no statistically significant differences in baseline demographic and clinical data at baseline between groups. The participants were on stable doses of dopaminergic medications in the preceding 3 months prior to recruitment into the study and no subsequent adjustments to the dosage was made for the duration of the study.

Table 4.1 Baseline demographic data

	Placebo (n=10)	Duloxetine (n=9)	p value
Age (years)	69.10 (7.95)	68.89 (8.10)	0.955
PD duration (years)	6.20 (3.58)	5.33 (2.92)	0.569
H&Y, median (IQR)	2.00 (1.00)	2.00 (0.50)	0.604
MMSE median (IQR)	30.00 (2.00)	30.00 (2.00)	1.000
LEDD (mg/day)	774.40(542.60)	640.11 (329.03)	0.529
UPDRS median(IQR)	32.50 (29.50)	40.00 (14.50)	0.156

Data is expressed as mean (SD) unless otherwise stated.
IQR, Inter-quartile range; PD, Parkinsons disease; H&Y, Hoehn and Yahr; MMSE, Mini-mental state examination; LEDD, Levodopa equivalence daily dosage; GDS, Geriatric depression scale; UPDRS, Unified Parkinsons disease rating scale Part III.

The baseline pain scores were shown to be normally distributed as assessed using Shapiro-Wilk test ($p>0.05$) except for the sensory component, affective component and the total scores of the Short-Form McGill Pain Questionnaire in the placebo group (Shapiro-Wilk p=0.016, 0.019 and 0.001, respectively), as well as the affective component of Short-Form McGill Pain Questionnaire in the duloxetine group (Shapiro-Wilk p=0.027).

A breakdown of the different types of pain experienced by the participants is presented in Appendix I.

Before treatment, there were no statistically significant differences in the pain scores and other outcome measures between groups (Table 4.2).

Table 4.2 Baseline pain scores

	Placebo (n=10)	Duloxetine (n=9)	p value
SFM-sens; median (IQR)	7.00 (7.00)	10.00 (7.00)	0.113
SFM-affect; median (IQR)	2.00 (4.00)	3.00 (3.00)	0.156
SFM-total; median (IQR)	8.50 (6.25)	11.00 (10.50)	0.243
VAS	4.51 (2.93)	5.53 (2.25)	0.415
KPPS	21.10 (12.56)	25.33 (11.73)	0.459
PDQ -39	17.30 (6.16)	20.57 (6.96)	0.133
GDS	8.40(4.99)	7.44 (3.36)	0.635
PANAS	14.20 (12.58)	24.56 (10.09)	0.059

Data is expressed as mean (SD) unless stated otherwise.
IQR, Inter-quartile range; VAS, Visual Analogue Scale; SFM-sens, sensory component Short-Form McGill Questionnaire; SFM-affect, affective component Short-Form McGill Questionnaire; SFM-total, total score Short-Form McGill Questionnaire; KPPS, King's Parkinson Disease Pain Scale; PDQ-39, Parkinsons Disease Questionnaire-39; GDS, Geriatric Depression Scale; PANAS, Positive Affect and Negative Affect Schedule.

4.3.1 Analgesic use

The analgesic use in the 19 participants was analysed. The types of analgesia were divided into paracetamol, NSAIDs and opioids. Our results showed that 7 out of 19 (36%) participants were not on any regular analgesic medication. The most common class of analgesic in our cohort, used either singly or in combination with another type of analgesic, were NSAIDs (7 out of 19; 36%), followed by paracetamol (6 out of 19; 31%); only 1 (5.2%) participant was on an opioid medication (tramadol). Of the 12 participants that were taking any analgesic medications, 10 participants were on a single type of analgesic (4 participants on paracetamol, 5 participants on NSAID's and 1 participant on an opioid) and the remainder 2 participants were taking paracetamol and NSAIDs in combination.

4.3.2 Changes in outcome measure scores

Table 4.3 summarizes the changes in the various outcome measure scores before and after treatment.

Table 4.3 Outcome measures before and after treatment

		Before Treatment	After Treatment	p value
SFM-sens	Placebo	8.60 (6.54)	8.90 (5.92)	0.227
	Duloxetine	10.67 (3.74)	8.00 (4.15)	
SFM-affect	Placebo	2.60 (3.10)	2.80 (3.36)	0.049*
	Duloxetine	3.44 (1.60)	1.56 (1.67)	
SFM-total	Placebo	11.20 (9.00)	12.50 (10.69)	0.114
	Duloxetine	13.22 (5.97)	9.56 (5.73)	
VAS	Placebo	4.51 (2.93)	5.11 (1.97)	0.302
	Duloxetine	5.53 (2.25)	4.79 (1.93)	
KPPS	Placebo	21.10 (12.56)	15.40 (9.91)	0.406
	Duloxetine	25.33 (11.73)	23.11 (10.60)	
PDQ-39	Placebo	21.22 (17.21)	21.41 (15.45)	0.796
	Duloxetine	21.59 (4.59)	22.68 (10.88)	
GDS	Placebo	8.40 (4.99)	10.60 (5.17)	0.265
	Duloxetine	7.44 (3.36)	7.67 (2.92)	
PANAS	Placebo	14.20 (12.58)	11.60 (11.41)	0.883
	Duloxetine	24.56 (10.09)	21.22 (8.58)	

All scores are mean (SD); *, $p<0.05$.

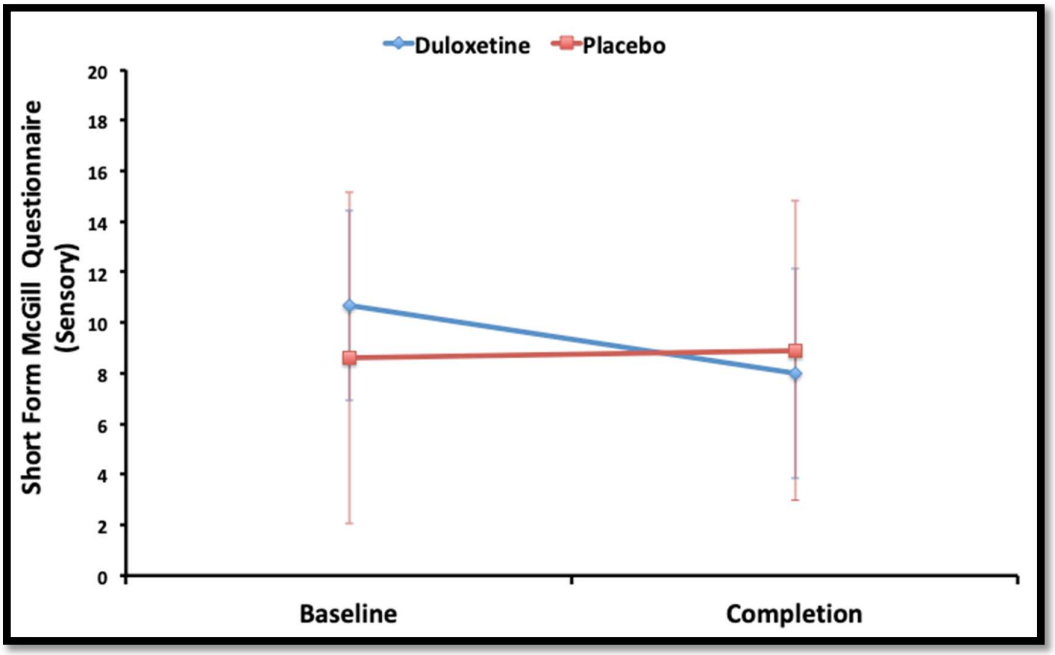
VAS, Visual Analogue Scale; SFM-sens, sensory component Short Form McGill Questionnaire; SFM-affect, affective component Short Form McGill Questionnaire; SFM-total, total score Short Form McGill Questionnaire; KPPS, King's Parkinsons Disease Pain Scale; PDQ-39, Parkinsons Disease Questionnaire-39; GDS, Geriatric Depression Scale; PANAS, Positive Affect and Negative Affect Schedule.

Sensory component of the Short-Form McGill Questionnaire

The scores of sensory component of the Short-Form McGill Questionnaire (SFM-sens) were normally distributed on both visits in the duloxetine group ($p>0.05$) but were not normally distributed in visit 1 and visit 2 in the placebo groups ($p=0.016$ and $p=0.017$, respectively) as determined by the Shapiro-Wilk test.

There was no statistically significant interaction between treatment and time on the sensory component of the Short-Form McGill Questionnaire scores $F(1, 17)=1.58$, $p=0.227$, partial $\eta^2=0.085$ (Figure 4.1). Post hoc analysis did not show any statistically significant main effects on time $F(1, 17)=0.10$, $p=0.331$, partial $\eta^2=0.056$ and treatment $F(1, 17)=0.76$, $p=0.787$, partial $\eta^2=0.004$.

Figure 4.1 Sensory component of Short-Form McGill Questionnaire before and after treatment

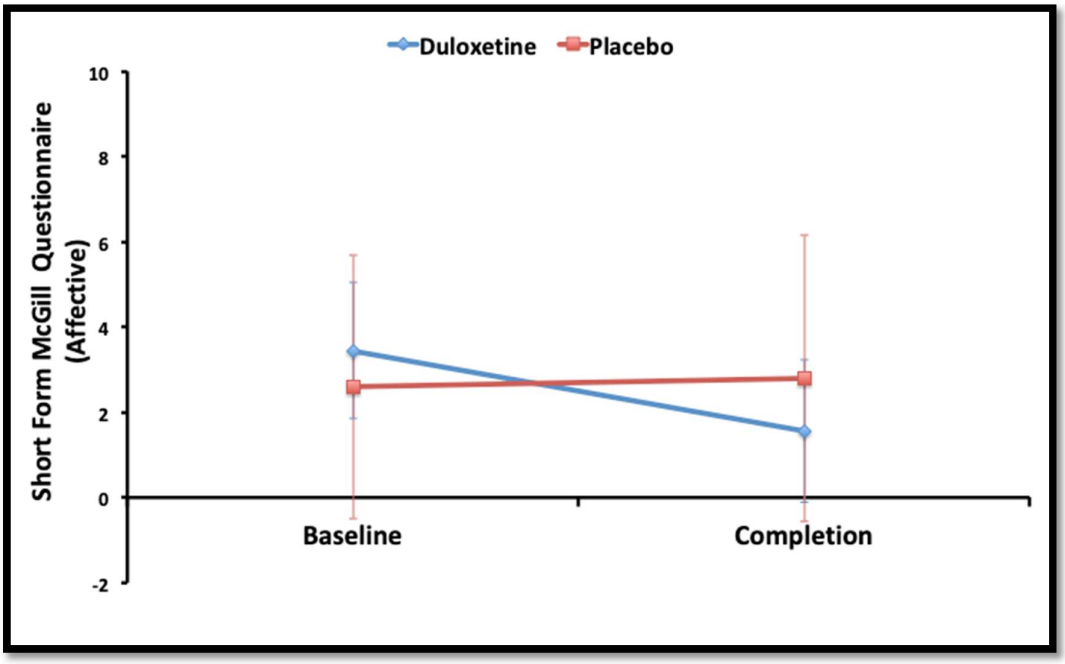


Affective component of Short-Form McGill Questionnaire

The scores of the affective component of the Short-Form McGill Questionnaire of the placebo group were not normally distributed for both visits (p=0.019 and p=0.033, respectively), and the duloxetine group scores were not normally distributed in the first visit (p=0.027) but normally distributed in the second visit (p=0.136), as determined by the Shapiro-Wilk test.

There was a statistically significant interaction between treatment and time on the affective component of the Short-Form McGill Questionnaire scores $F(1,17)=4.36$, $p=0.049$, partial $\eta^2=0.204$ (Figure 4.2). Post-hoc simple main effects were performed. There were no statistically significant difference in the scores between the duloxetine group and placebo at study completion $F(1,17)=1.01$, $p=0.330$, partial $\eta^2=0.056$. However, there was a statistically significant effect of time on the scores for the duloxetine group $F(1,8)=15.21$ $p=0.005$, partial $\eta^2=0.655$ but not for the placebo group $F(1,9)=0.06$ $p=0.817$, partial $\eta^2=0.006$.

Figure 4.2 Affective component of the Short-Form McGill Questionnaire before and after treatment.

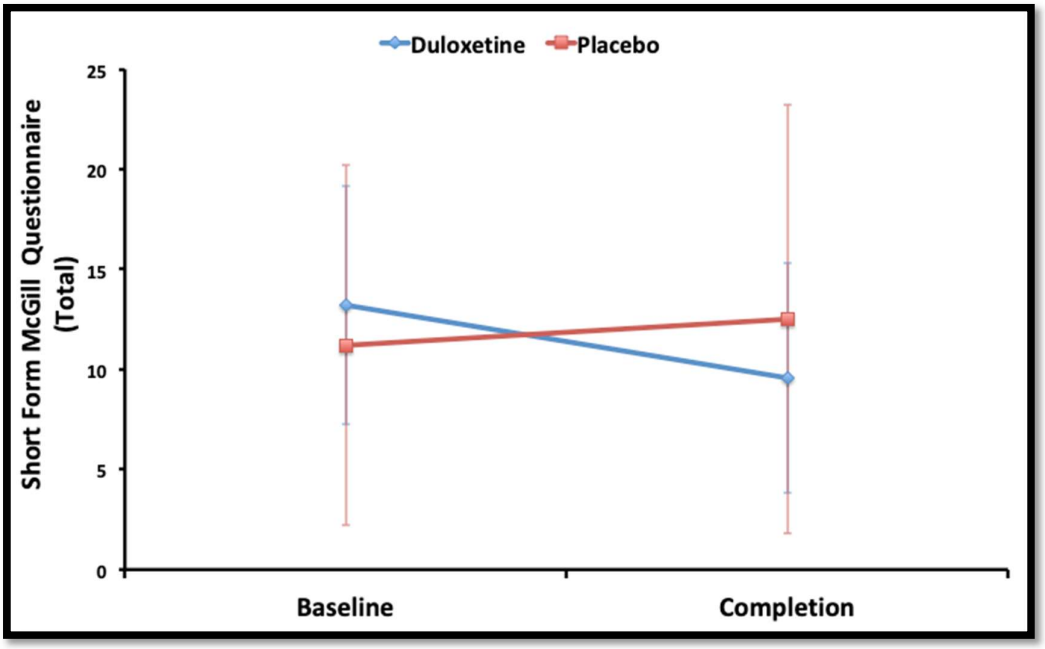


The total scores of the Short-Form McGill Questionnaire

The total scores of the Short-From McGill Questionnaire were normally distributed for the duloxetine group for both visits ($p>0.05$) but not normally distributed for the placebo group for visit 1 and 2 ($p=0.001$ and $p=0.002$, respectively), as determined by the Shapiro-Wilk test.

There was no statistically significant interaction between treatment and time on the total scores of the Short-From McGill Questionnaire $F(1,17)=2.78$, $p=0.114$, partial $\eta^2=0.141$ (Figure 4.3). Post-hoc analysis did not show any statistically significant main effects on time $F(1,17)=0.63$, $p=0.438$, partial $\eta^2=0.036$ and treatment $F(1,17)=0.02$, $p=0.896$, partial $\eta^2=0.001$.

Figure 4.3 The total scores of the Short-Form McGill Questionnaire before and after treatment.

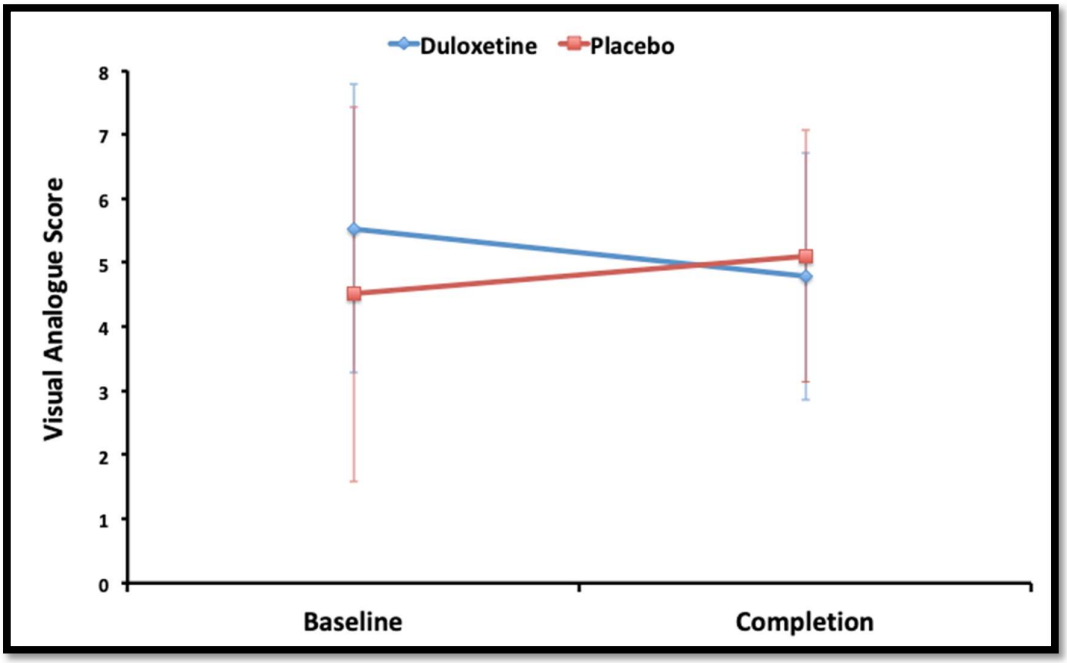


Visual Analogue Scale

Visual Analogue Scale scores were normally distributed as determined by the Shapiro-Wilk test ($p>0.05$).

There was no statistically significant interaction between treatment and time on Visual Analogue Scale scores $F(1, 17)=1.13$, $p= 0.302$, partial $\eta^2=0.062$ (Figure 4.4). Post-hoc analysis showed no statistically significant difference in main effects of time $F(1, 17)=0.01$, $p= 0.911$, partial $\eta^2=0.001$ and treatment $F(1, 17)=0.16$, $p=0.697$, partial $\eta^2=0.009$.

Figure 4.4 Visual Analogue Scale before and after treatment



King's Parkinson's Disease Pain Scale (KPPS)

The King's Parkinsons Disease Pain Scale scores were normally distributed for both groups on both visits ($p>0.05$), as determined by the Shapiro-Wilk test.

There was no statistically significant interaction between treatment and time on the King's Parkinsons Disease Pain Scale scores $F(1,17)=0.73$, $p=0.406$, partial $\eta^2=0.041$. Post-hoc analysis did not show any statistically significant main effects on time $F(1,17)=3.78$, $p=0.069$, partial $\eta^2=0.181$ and treatment $F(1,17)=1.58$, $p=0.225$, partial $\eta^2=0.085$.

Parkinson's Disease Questionnaire (PDQ)-39

The Parkinson's Disease Questionnaire-39 scores were normally distributed for the duloxetine group for both visits ($p>0.05$) but not normally distributed for the placebo group for visit 1 and 2 ($p<0.001$ and $p=0.002$, respectively), as determined by the Shapiro-Wilk test.

There was no statistically significant interaction between treatment and time on the PDQ-39 scores $F(1,17)=0.07$, $p=0.796$, partial $\eta^2=0.004$. Post-hoc analysis did not show any statistically significant main effects on time $F(1,17)=0.14$, $p=0.714$, partial $\eta^2=0.008$ and treatment $F(1,17)=0.02$, $p=0.890$, partial $\eta^2=0.001$.

Geriatric Depression Scale (GDS)

The Geriatric Depression Scale scores were normally distributed for both groups on both visits ($p>0.05$), as determined by the Shapiro-Wilk test.

There was no statistically significant interaction between treatment and time on the Geriatric Depression Scale scores $F(1,17)=1.33$, $p=0.265$, partial $\eta^2=0.072$. Post-hoc analysis did not show any statistically significant main effects on time $F(1,17)=1.99$, $p=0.176$, partial $\eta^2=0.105$ and treatment $F(1,17)=1.21$, $p=0.287$, partial $\eta^2=0.066$.

Positive Affect and Negative Affect Schedule (PANAS)

The Positive Affect and Negative Affect Scale scores were normally distributed for both groups on both visits ($p>0.05$), as determined by the Shapiro-Wilk test.

There was no statistically significant interaction between treatment and time on the Positive and Negative Affective Scale scores $F(1,17)=0.02$, $p=0.883$, partial $\eta^2=0.01$. Post-hoc analysis did not show any statistically significant main effects on time $F(1,17)=1.46$, $p=0.244$, partial $\eta^2=0.079$. There was a statistically significant main effects on treatment with $F(1,17)=5.31$, $p=0.034$, partial $\eta^2=0.238$.

Post-hoc linear regression analysis for the affective component of the Short-Form McGill Questionnaire

A linear regression analysis was run to understand the relationship between the scores of the affective component of the Short-Form McGill Questionnaire with the scores of GDS and PANAS at study completion for all the participants.

A simple linear regression was calculated to predict the score of the affective component of the Short-Form McGill Questionnaire based on the score of the GDS at study completion. A non-significant regression was found $F(1, 17)= 3.110$, $p=0.096$ with an R^2 of 0.155. Participants' predicted score of the affective component of the Short-Form McGill Questionnaire is equal to -0.009+0.241. Participants' score of the affective component of the Short-Form McGill Questionnaire increased 0.241 units for each 1-unit increase of the GDS score.

A simple linear regression was calculated to predict the score of the affective component of the Short-Form McGill Questionnaire based on the PANAS score at study completion. A non-significant regression was found $F(1,17)=2.723$, $p=0.117$ with an R^2 of 0.138. Participants' predicted score of the affective component of the Short-Form McGill Questionnaire is equal to 3.676-0.091. Participants' score of the affective component of the Short-Form McGill

Questionnaire decreased by 0.091 units for each 1-unit increase of the PANAS score.

Multiple linear regression analysis was not performed as initial examination of the data revealed violations in the independence of observations as assessed by Durbin-Watson statistic of 3.232.

4.4 Discussion

The important findings in this study can be summarised as follows;

1. In Parkinsons disease patients with pain, treatment of duloxetine for a duration of 6 weeks reduced the pain symptoms as measured by the affective component of the Short-Form McGill Questionnaire.

2. Although not statistically significant, other pain measures such as the sensory component and total scores of Short-Form McGill Questionnaire, as well as the Visual Analogue Scale showed a trend towards improvement in pain symptoms following 6 weeks of duloxetine.

The results regarding patterns of analgesic medication use in our cohort were informative. Slightly more than a third of our cohort (36%) were not on any regular analgesic medication regime. This is notable considering participants in both treatment groups could be considered to be experiencing at least moderate pain in the context of their mean VAS scores at baseline visit (4.51 and 5.53 in the placebo and duloxetine group, respectively).(Boonstra, Preuper, Balk, & Stewart, 2014; Collins, Moore, & McQuay, 1997) This observation is in keeping with the literature reporting that chronic pain is poorly recognised and under-treated.(Green, Wheeler, LaPorte, Marchant, & Guerrero, 2002)

Interestingly, out of 19, only one participant was prescribed an opioid drug for the management of pain. Several reasons may account for the low rate of opioid prescription in our cohort. Factors relating to inadequate training in opioid prescribing and a misplaced concern regarding addiction have been identified as

reasons for the under-utilisation of opioid medication in pain management.(Lin, Alfandre, & Moore, 2007) Additionally, opioid use inhibits bowel movement and compounds the symptom of constipation commonly reported in Parkinsons disease patients. Prolonged-released formulation of the opioid oxycodone with naloxone has been used to try to minimize this effect although a recent study showed that these patients still complain of some degree of drug-induced constipation.(Trenkwalder et al., 2015)

Common side-effects attributable to duloxetine involve the gastrointestinal system (nausea, dry mouth and constipation) and the nervous system (drowsiness, headache and dizziness).(Wernicke, Gahimer, Yalcin, Wulster-Radcliffe, & Viktrup, 2005) The incidence of nausea and drowsiness in clinical trials involving patients with major depressive disorder have been quoted to be approximately 20% and 7.1%, respectively.(Hudson et al., 2005) The high incidence of drowsiness in our study may be related to the demographic of our participants who belong in the older age group (mean age 68.89 years) and the use concomitant anti-parkinsons medication that can cause drowsiness.

The most important finding of this study relates to results as assessed by the Short-Form McGill Questionnaire. We found a statistically significant interaction between treatment and time in the affective component of the Short-Form McGill Questionnaire. Post-hoc analysis of simple main effects of time showed that there was a statistically significant reduction in the scores between baseline and study completion in the duloxetine group that was not observed in the placebo group.

As described in Chapter 1, the sensory and the affective dimension of pain involve 2 distinct, albeit highly interlinked and overlapping systems. Briefly, the affective dimension of pain is subserved by the medial pain pathways involving brainstem structures with ascending projection to the insula, anterior cingulate cortex and the limbic regions of the brain.(Willis Jr, Zhang, Honda, & Giesler Jr, 2001; Willis & Westlund, 1997) The sensory dimension of pain is subserved by the lateral pain pathway and is comprised of the lateral thalamus with

projections to the insula and parietal operculum, as well as the primary and secondary somatosensory cortex.(Scherder, Sergeant, & Swaab, 2003)

Our findings of duloxetine improving scores related to the affective dimension of pain in non-depressed Parkinsons disease patients has some neuropathological basis. Studies using functional MRI techniques have shown changes in affective pain scores associated with activation in the anterior cingulate cortex, which is part of the limbic system.(Rainville, 2002) In Parkinsons disease, heavy deposition of Lewy body pathology in higher order neurons of the medial pain pathway, specifically in the amygdala, insular cortices and the anterior cingulate cortex have been characteristic in mid-stage Parkinsons disease based on autopsy findings.(Braak et al., 1994; Braak, Braak, Yilmazer, Schultz, & Jansen, 1995) In a study looking at the thalamus, the deposition of Lewy body appears to be more severe in the regions belonging to the medial pain pathway (central lateral, central medial, paracentral, limitans suprageniculate complex).(Brefel-Courbon et al., 2013) In contrast, with respect to the lateral pain pathway and the sensory dimension of pain, the lateral part of the thalamus shows relatively little impairment in Parkinsons disease.(Rüb et al., 2002; Scherder et al., 2005) Finally, subthalamic nucleus stimulation has been known to improve lateral discriminative pain symptoms although a prospective study using an affective pain questionnaire showed that affective pain symptoms also improved, presumably by modulating projections from the thalamus to areas involved in the medial pain pathway, such as the anterior cingulate cortex.(Pellaprat et al., 2014)

Our findings may suggest that duloxetine may be most effective in Parkinsons disease patients suffering from symptoms arising from the affective dimension of pain. Furthermore, the improved pain scores in the affective dimension of pain raises the question of whether duloxetine, in addition to its purported action localised in the brain stem region (i.e locus coeruleus, pontine tegmentum) involved in the descending inhibition pathway, may potentially be acting on other areas of the brain, specifically the limbic regions and others higher-order regions of the medial pain pathway.(Rempe et al., 2014; Rempe et al., 2015)

The sensory pain component of the Short-Form McGill questionnaire and the total score of the Short-Form McGill questionnaire (sensory and affective component) did not show any statistically significant interaction between treatment and time, with a p value of 0.227 and 0.114, respectively. However, a closer inspection of the results shows that there was a trend towards improvement of the scores i.e. less pain between baseline and study completion visits for both outcome measures in the duloxetine group (sensory pain mean scores 10.67 to 8.00; total mean scores 13.22 to 9.56). Conversely, in the placebo groups, there was a trend towards worsening of the scores i.e. more pain between baseline and study completion for both questionnaires. The magnitude of the changes in the Short-Form McGill found in this study appear to be in line with the open labelled study by Djaldetti *et al* that showed improvement in scores of the sensory component of the Short-Form McGill Questionnaire following 6 weeks of duloxetine.(Djaldetti et al., 2007) The affective pain component of the Short-Form McGill questionnaire was not selected as one of the outcome measures in their study.

A more clinically relevant approach in the judgement of the efficacy of investigative drug therapy is by determining whether the treatment results in clinically discernible change from the perspective of patients.(Rowbotham, 2001) This can assessed by comparing the results of a specific pain outcome measure against an external criterion that measures patients' perspective of clinical improvement. e.g. patients' global impression of change (PGIC).(Farrar, Young Jr, LaMoreaux, Werth, & Poole, 2001; Grotle, Brox, & Vøllestad, 2004) A study that explored the clinically meaningful improvement in a cohort of chronic pain patients with rheumatic and musculoskeletal pain indicated that a change of >5 (out of a total score of 45) in the total score of the Short-Form McGill Questionnaire represent clinically meaningful change.(Strand, Ljunggren, Bogen, Ask, & Johnsen, 2008) By this measure, both the duloxetine and placebo groups in our study did not experience clinically meaningful improvement (duloxetine, 13.22 to 9.56; placebo, 11.20 to 12.50) Inspection of the individual scores revealed that 3 participants in the duloxetine group and 2 participants in the placebo group experienced clinically meaningful improvement based on the total

score Short-Form McGill Questionnaire (see Appendix II). There is no consensus regarding the accepted score for the sensory component and affective component of the Short-Form McGill questionnaire that represent clinically meaningful change due to the lack of satisfactory discrimination.(Strand et al., 2008)

In our study, we found that in all outcome measures e.g. VAS, Short-Form McGill Questionnaires, there was a trend towards improvement in the pain in the participants prescribed duloxetine. More compellingly, the participants in the placebo group generally had a worsening in the outcome scores over a period of 6 weeks. A consistent trend across all outcome measures with worsening of pain scores in the placebo group and improvement in the duloxetine group provides food for thought. At the very least, our results may suggest that in comparison to duloxetine, inaction in the treatment of pain in Parkinsons disease may potentially lead to a deterioration in their pain symptoms over time. Our findings may suggest that sentiments encouraging behaviour to 'ignore the pain' or to 'work through the pain' in the setting of chronic persistent pain may be counter-productive and harmful.

In Parkinsons disease, pain is significantly associated with depression scores, even after adjusting for clinical severity.(Ehrt et al., 2009) In advanced disease, Parkinsons disease patients with pain were more likely depressed as compared to those without pain.(Valkovic et al., 2015) Perahia et al reported that the mechanism of duloxetine in pain is due to a direct analgesic effect and not a by-product of reduced depression scores.(Perahia, Pritchett, Desaiah, & Raskin, 2006) Similarly, a pooled analysis of 4 randomised controlled trials in patients with fibromyalgia used logistic regression analysis to conclude that duloxetine produced a substantial direct antinociceptive effect and the change in mood only provided a modest indirect effect on pain symptoms.(Marangell et al., 2011) It is tempting to conclude that our results provide further evidence that the analgesic effect of duloxetine is independent of its antidepressant properties. The univariate analysis showed that there was a significant interaction between treatment and time in the affective component of the Short-Form McGill

Questionnaire but no statistically significant interaction between treatment and time in the corresponding univariate analysis of GDS and PANAS scores. A linear regression analysis conducted to predict the relationship between the affective component of the Short-Form McGill Questionnaire at study completion with GDS and PANAS scores resulted in a non-significant finding with a p value of 0.096 and 0.117, respectively. Nevertheless, our findings must be intrepreted with caution as the sample size of the study was small and may be underpowered to detect desired differences.

We did not see any significant interaction between time and treatment on Parkinsons Disease Questionnaire (PDQ)-39. This is somewhat surprising as numerous studies have shown the detrimental impact of pain on the quality of life of Parkinsons disease patients.(Schrag et al., 2000; Valkovic et al., 2015) A longitudinal study assessing the quality of life of Parkinson disease patients over a 4-year period showed a clear association between increasing pain scores and a poorer quality of life.(Karlsen, Tandberg, Årsland, & Larsen, 2000) One possible explanation for our finding is that the improvements in the affective component of pain, although significant was not adequate enough in magnitude to effect any statistically significant change in the quality of life of the participants following 6 weeks of duloxetine, as measured by the PDQ-39 questionnaire. An alternative explanation would be that the 6-week treatment duration was too short to allow improvements in the negative repercussions of persistent pain such as quality of life.

Similarly, we did not find any significant interaction between treatment and time on the Kings Parkinsons Disease Pain scale. The Kings Parkinsons Disease Pain scale comprises of seven different domains, namely musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, orofacial pain, discolouration, and radicular pain.(Chaudhuri et al., 2015) The scale addresses localisation, intensity and frequency of pain, as well as its relationship with motor fluctuation or musculoskeletal pain. In our study, we did not find any significant interaction between treatment and time using this scale. The statistically non-significant findings in our study could be explained by the

possibility that the Kings Parkinsons Disease Pain scale may be more sensitive in detecting pain symptoms in the sensory discriminative dimension of pain and pain symptoms that are dopamine responsive, and less sensitive to pain symptoms arising from the affective pain dimension. Arguably, this may also explain the finding of a recently published randomised double blind placebo controlled trial exploring the use of duloxetine 40mg once a day in Parkinsons disease patients with pain that reported no statistically significant difference between groups as measured by the Visual Analogue Scale, which is a generic uni-dimensional pain scale. (Iwaki et al., 2020)

The small sample size is the primary weakness of this study and may be contributed by several factors. In an effort to ensure our findings were robust, Parkinsons disease patients with significant peripheral neuropathy were excluded from the study. The rationale being that the presence of peripheral neuropathy may produce some bias into the results. This may have inadvertently excluded a few potential patients from being recruited into the study. A systematic review showed that the prevalence of large fiber neuropathy is 16.3% in Parkinsons disease patients.(Zis, Grünewald, Chaudhuri, & Hadjivassiliou, 2017)

Another factor that may have contributed to the poor recruitment relates to participants' longstanding medication. Depression and pain are closely interlinked.(Ehrt et al., 2009; Valkovic et al., 2015) We observed that a considerable number of Parkinsons disease patients were already prescribed an anti-depressant that prevented their participation in the study.

The factor that possibly exerted the biggest impact on the small sample size relates to study funding. The study was partially funded by the Government of Malaysia. Due to events beyond our control, funding for the PhD degree was restricted to only 3 years instead of 4 years and this severely affected the recruitment of participants.

Arguably, the small sample size may have an impact on the validity of our study and caution should be exercised when making inferences of our findings.

Outcome measures that did not reach the threshold for discovery (e.g. GDS, PANAS, PDQ-39) may simply signify that the study was under-powered to detect underlying effects of treatment and absence of evidence should not be construed as evidence of absence.

As for the outcome measures that did reach the threshold for discovery i.e. the affective component of the Short-Form McGill Questionnaire may indicate that the effect size may be larger than previously thought although the likelihood of an overestimation of the effect size and low reproducibility of the results are issues that needs to be considered.(Button et al., 2013)

Our findings relating to affective pain may be spurious. However, the improving trend observed in other pain outcome measures (e.g. sensory component and total score of the Short-Form McGill Questionnaire, VAS) in participants prescribed duloxetine with a corresponding worsening trend in those prescribed placebo has scientific basis and is consistent with findings from previous studies.(Djaldetti et al., 2007; Iwaki et al., 2020) It is possible that with a bigger sample size, duloxetine may show a statistically significant improvement in pain scores in the aforementioned outcomes.

It is difficult to assume generalizability but our finding nevertheless provides food for thought and adds to the body of literature of pain in Parkinsons disease. Further studies with a bigger sample size is required to confirm our findings.

4.5 Conclusion

We showed that duloxetine at a dose of 60mg for at least 4 weeks reduced ratings related to the affective dimension of pain in Parkinsons disease patients with pain. The changes in pain ratings did not occur in the corresponding group of patients given placebo.

It is possible that duloxetine acts on the medial pain pathway including the limbic regions of the brain in addition to established mechanism of modulation of the descending pain inhibition pathway.

Further research, particularly in functional brain imaging is required to provide further clarity to these questions.

Chapter 5: Pain sensitivity and task-based functional MRI in Parkinsons disease patients with pain

5.1 Introduction of aims and hypothesis

Changes in pain sensitivity in Parkinsons disease were first described by Urakami et al in 1990, who reported a reduced pain threshold following evoked ischaemic stimuli that was associated with a reduction in cerebrospinal fluid serotonin concentration in Parkinsons disease patients with pain.(Urakami et al., 1990)

Several systemic reviews and meta-analyses have been performed that add to the body of knowledge relating to changes in pain sensitivity in Parkinsons disease. Two meta-analysis concluded that Parkinsons disease patients had increased sensitivity to noxious stimuli when tested in the OFF state, when compared to healthy controls. (Sung et al., 2018a; Thompson et al., 2017) In another meta-analysis, Sung et al concluded Parkinsons disease patients with pain have an increased pain sensitivity in comparison to patients that do not have pain.(Sung et al., 2018c)

Duloxetine is a serotonin noradrenaline reuptake inhibitor and has been shown to be helpful in Parkinsons disease patients with pain.(Djaldetti et al., 2007). The modulation of noradrenergic and serotonergic tone on the descending inhibitory pathways of the spinal cord has been proposed to be one of the mechanism of action of duloxetine for analgesia.(Fields, 1999) Nevertheless, the exact mechanism by which duloxetine can reduce pain symptoms in Parkinsons disease is still unknown.

In healthy subjects, duloxetine has been found to attenuate activity in brain regions that regulate affect (anterior cingulate cortex, thalamus, insula, amygdala).(van Marle et al., 2011) The same research group also explored the effects of duloxetine on emotion related memory as well as reward processing in healthy subjects. In the emotion-related memory fMRI study, duloxetine

decreased the activity in the putamen and middle frontal gyrus, an area that is involved in successful memory formation of emotionally salient items, following a paradigm that was designed to induce formation of sad memories.(Tendolkar, Van Wingen, Urner, Verkes, & Fernández, 2011) This circuitry is correlated with emotional memory formation and retrieval in the region of the brain involved in affective state and its regulation.(Phillips, Drevets, Rauch, & Lane, 2003) In depressed patients, over-activity of this circuit can lead to negative learning schemes resulting in persistence of depression.(Hamilton & Gotlib, 2008) In the reward processing study, duloxetine was shown to modulate the activity of the ventral striatum in healthy volunteers following a memory incentive task.(Ossewaarde et al., 2011) The ventral striatum belongs to the mesolimbic dopamine reward system and regulates reward responsiveness; dysfunction in this locus may contribute to symptoms of anhedonia and apathy in depressed patients.

A resting state fMRI study on healthy subjects demonstrated that duloxetine reduced the connectivity of the default mode network in healthy volunteers.(Van Wingen et al., 2014) Relevantly, the default mode network has been shown to be altered in a variety chronic pain states e.g. fibromyalgia, burning mouth syndrome and complex regional pain syndrome.(Ichesco et al., 2016; Khan, Keaser, Meiller, & Seminowicz, 2014; Kim et al., 2017)

To our knowledge, there are no functional imaging studies looking at the effects of duloxetine in Parkinsons disease. In this area, studies have been mainly performed on patients with depression. Nonetheless, the findings may still provide a relevant clinical model of persistent pain in Parkinsons disease. The neuropathology of Parkinsons disease differentially affects the medial pain system which is involved in the affective-motivational and cognitive-evaluative dimension of pain.(Scherder et al., 2005) These regions overlap with areas of the brain involved in regulating emotion and affective states.(Apkarian, Bushnell, Treede, & Zubieta, 2005; López-Solà, Pujol, Hernández-Ribas, Harrison, Ortiz, et al., 2010; Wiech, Ploner, & Tracey, 2008) A study has shown that the variance in pain measures in Parkinsons disease patients were primarily determined by

anxiety and depression, further emphasizing the fact that pain and affective states are closely interlinked.(Engels, Weeda, Vlaar, Weinstein, & Scherder, 2016)

Duloxetine in major depression has been shown to augment connectivity in the anterior default mode network, while reducing connectivity within the subgenual cingulate was predictive of clinical antidepressant response.(Fu et al., 2015) Several other studies on resting state fMRI in patients with depression showed symptom improvement following duloxetine that was associated with changes in functional connectivity of the limbic and striatal regions of the brain.(An et al., 2019; Lai & Wu, 2012; Wang et al., 2019b)

A voxel-based morphometry fMRI study showed that compared to controls, patients with depression had grey matter density deficits in the limbic regions, which was reversed followings duloxetine at study completion.(Lai & Hsu, 2011) Duloxetine has been shown to relieve mood symptoms as well as somatic symptom in major depressive disorders.(Gupta, Nihalani, & Masand, 2007) In patients with depression, an fMRI study using thermal noxious stimuli showed that duloxetine reduced activations in the pregenual anterior cingulate cortex, right prefrontal cortex and pons. More importantly, these changes occurred at 1 week of administration of duloxetine, when the antidepressant effect of duloxetine was presumed to be modest.(López-Solà, Pujol, Hernández-Ribas, Harrison, Contreras-Rodríguez, et al., 2010)

Studies using the resting state functional connection networks approach in patients with complex regional pain syndrome have consistently demonstrated reduced functional connectivity in the default mode network and an increased amygdala-centered functional connectivity with cortical and subcortical regions and (Kim et al., 2017)

The primary aim of this study was to investigate the effect of the treatment with duloxetine on pain sensitivity using evoked pressure stimulus in Parkinsons disease patients with pain. This was achieved by comparing the pain sensitivity

thresholds of Parkinsons disease patients with pain before and after taking duloxetine or placebo. We hypothesised that the pain sensitivity threshold will be reduced in the participants taking duloxetine but not in the placebo group.

A secondary aim of this study was to explore whether changes in pain sensitivity following evoked pressure stimulus was associated with any changes in brain activation on functional MRI scans. This was achieved by comparing brain activation maps at baseline and at study completion in participants taking either duloxetine or placebo. We hypothesised that pain sensitivity changes will be associated with changes in the brain activation patterns in areas of the brain involved in pain processing.

5.2 Methodology

Participants were recruited from Parkinsons disease patients attending the movement disorder clinic at the Royal Melbourne Hospital. The Human Research Ethics Committee of Melbourne Health provided ethics approval to conduct the study. The inclusion and exclusion criteria are outlined in Section 3.1.1 and 3.1.2.

5.2.1 Pain sensitivity using evoked pressure pain stimulus

In this study, the Just Noticeable Pain (JNP) and Moderate Pain (MP) thresholds were used as the primary outcome measure. A full description of the procedure to determine the Just Noticeable Pain and Moderate Pain thresholds for each participant is described in Section 3.3.2.

Briefly;

- Just Noticeable Pain (JNP) threshold is the minimum intensity of pressure (kg/cm^2) to evoke a pain intensity report of 0.5/10 on the 11-point numerical descriptor scale.
- Moderate Pain (MP) threshold is the minimum intensity of pressure (kg/cm^2) to evoke a pain intensity report of 5.5/10 on the 11-point numerical descriptor scale.

5.2.2 Task-based functional MRI outcomes

In the functional MRI study, selected participants agreeing to the above pain sensitivity study were invited to undergo functional MRI scans at baseline and at study completion.

The outcome measures were regional BOLD signal changes associated with the application of phasic pressure stimulus applied to the right thumbnail.

Anatomical T1 weighted images were acquired for registration purposes (TR=1900ms, TE=2.63ms, FA=9^{O}, 208 sagittal slices, 320x320 matrix, 0.84mm^3 isotropic voxels). BOLD contrast functional images were acquired using an echo-planar imaging sequence (TR=2000ms, TE=35ms, FA=90^{O}, 32 axial slices 4.5mm thick, 64x64 matrix, 3.28mm^2 in-plane resolution).

During each session, functional MRI Blood Oxygen Level Dependent (BOLD) data were collected over 2 runs, with each run lasting for 6 minutes. Each run consists of 3 innocuous stimuli and 3 moderate pain stimuli, each lasting for 20 seconds, with a period of no stimuli lasting for 30 seconds as a control in a pseudo-random order. The order of stimuli was standardized for all the participants for all the sessions (Figure 5.1 and Figure 5.2).

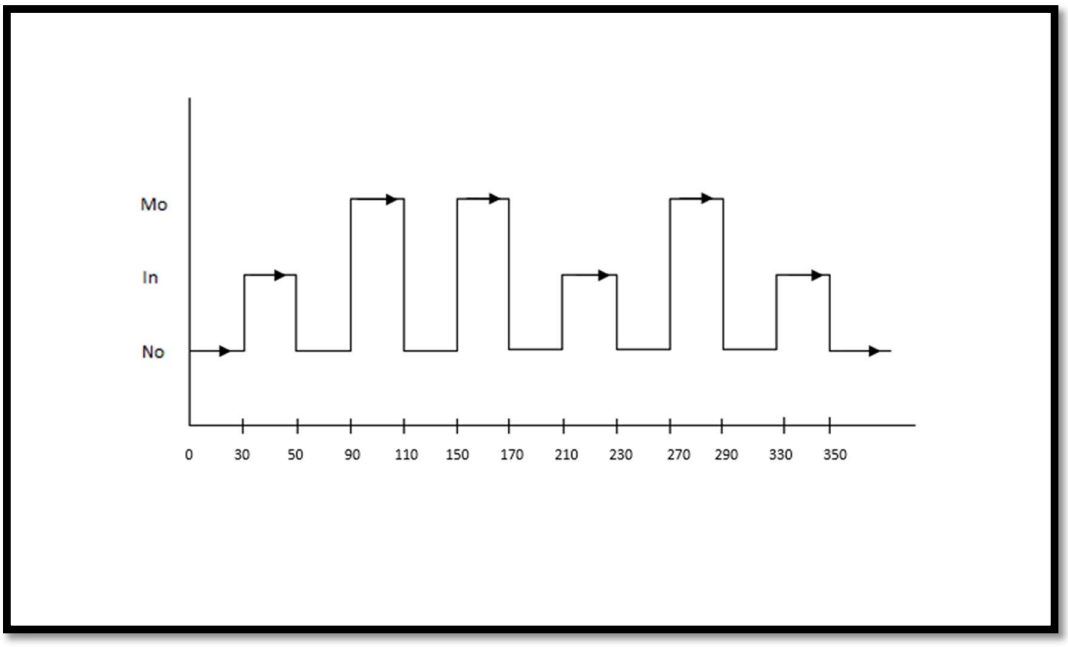


Figure 5.1 Protocol for presenting stimulus during BOLD scanning for RUN 1. X-axis, time in seconds; No, No stimulus; In, Innocuous stimuli; Mo, Moderate pain stimuli

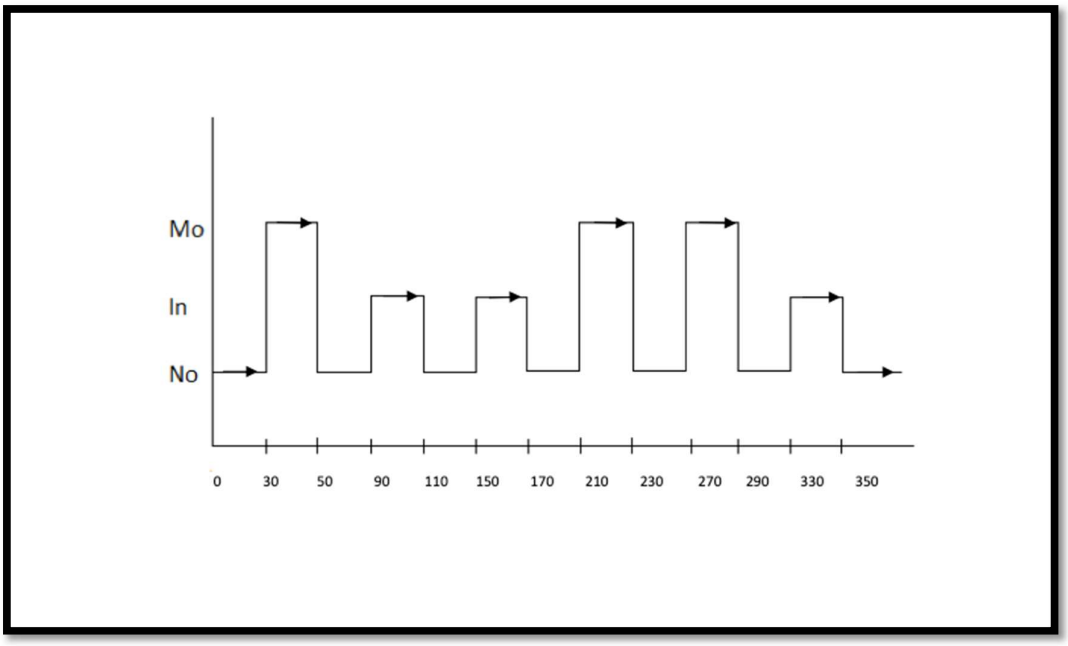


Figure 5.2 Protocol for presenting stimulus during BOLD scanning for RUN 2. X-axis, time in seconds; No, No stimulus; In, Innocuous stimuli; Mo, Moderate pain stimuli

Pre-processing of BOLD images included brain extraction using BET(Smith, 2002), motion correction procedure using MCFLIRT(Jenkinson, Bannister, Brady, & Smith, 2002), high pass filtering and spatial smoothing with a 6mm FWHM Gaussian kernel. For the motion correction procedure, the image at mid-time point of the series was used as the reference against which the other images were aligned. Participants displaying excessive head motion, defined as any translational displacement of over 1 voxel were excluded from the analysis.

The registration process involved co-registration of the middle image of the time series to the skull-stripped T1 image of the participants' brain using Boundary-Based registration (BBR) as implemented in FLIRT.(Jenkinson et al., 2002) The T1 was then warped to the Montreal Neurological Institute (MNI) template using an affine registration with 12 degrees-of-freedom (DOF). The resulting matrices were multiplied to produce a matrix for transformation of images in the native functional space to the MNI template.

The timing of onsets and durations for innocuous stimuli, moderate pain and rating were used to generate regressors, which were convolved with a gamma hemodynamic function. The regressors and their temporal derivatives were incorporated in a General Linear Model (GLM) for the first level analysis. Contrasts were performed for each main condition and the difference between innocuous stimuli and moderate pain blocks. The statistical parametric map was transformed to the standard MNI space using the matrix calculated in the preprocessing stage to allow further analysis at group level using FLAME. (Beckmann, Jenkinson, & Smith, 2003). A second-level fixed effects analysis was performed to combine the four first level analysis results, with contrasts constructed for baseline, completion, baseline and completion, baseline greater than completion, and completion greater than baseline. For group level analysis, mixed effects analysis was performed using FLAME 1+2 across all participants. Resulting group statistical parametric maps were used to identify activated regions using a voxel inclusion of $z > 2.3$ and cluster corrected threshold $p < 0.05$ according to the FEAT implementation of the random field theory.(Worsley, Evans, Marrett, & Neelin, 1992)

5.2.3 Procedures

The study procedure is as per described in Section 3.4. Briefly, the study was conducted over 3 visits, lasting for 6 weeks between the first and last visit. The procedures performed at each visit is as follows:

- Visit 1 (baseline): Collection of demographic data and determination of pain thresholds following evoked pressure stimulus for each participant. Selected participants underwent functional MRI scans for the pilot functional MRI study. Following this, participants were randomised to either duloxetine 30mg per day or matching placebo.
- Visit 2: Up-titration of duloxetine to 60mg per day or matching placebo.
- Visit 3 (study completion): Determination of pain thresholds following evoked pressure stimulus for each participant. Functional MRI scans were repeated for the participants that underwent baseline scans. Following this, all the participants were asked to stop all study drugs.

MRI scans were performed at the Murdoch Children's Research Institute, using a Siemens TRIO 3 Tesla MRI scanner.

5.3 Results

5.3.1 Pain sensitivity on evoked pressure stimulus

For the pain sensitivity study, the same participants that enrolled in the study in Chapter 4 also agreed to participate in this study. In brief, 19 participants completed the study, with 9 participants randomised to receive duloxetine and 10 participants randomised to the placebo arm.

The baseline demographic data is as per described in **Chapter 4** (Table 4.1). There was no statistically significant difference in the demographic data at baseline and at study completion between participants in both treatment groups.

5.3.1.1 Just Noticeable Pain (JNP)

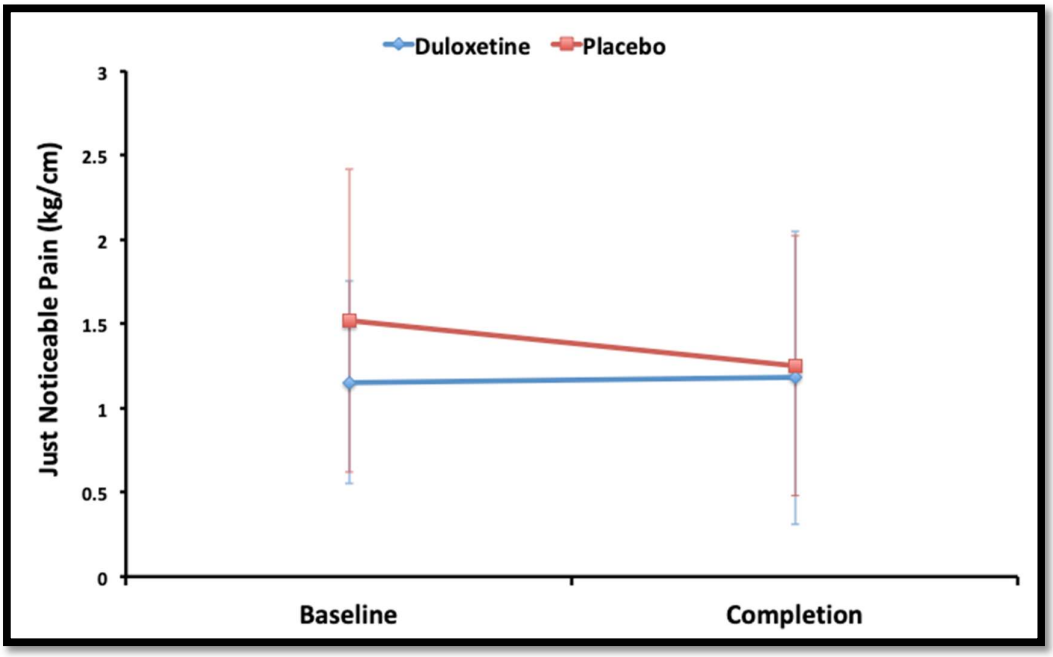
The Just Noticeable Pain threshold data were normally distributed as determined by the Shapiro-Wilk test, except for the Just Noticeable Pain threshold data at 6 weeks (study completion) in the duloxetine group (Shapiro-Wilk; p=0.033).

There was no statistically significant interaction between treatment and time on JNP threshold, $F(1, 17)=1.10$, $p=0.310$, partial $\eta^2=0.061$ (Table 5.1). Post-hoc analysis exploring main effects showed no statistically significant difference in main effects of time, $F(1, 17)=0.67$, $p= 0.423$ partial $\eta^2=0.038$ and no statistically significant difference in main effects of treatment, $F(1, 17)=0.42$, $p= 0.527$ partial $\eta^2=0.024$ (Figure 5.3).

Table 5.1 Just Noticeable Pain (JNP) thresholds between treatment and time

	Baseline JNP	6 week JNP	p value
Placebo	1.52 (0.90)	1.25 (0.77)	0.310
Duloxetine	1.15 (0.60)	1.18 (0.87)	

Figure 5.3 Just Noticeable Pain thresholds at baseline and study completion



5.3.1.2 Moderate Pain (MP)

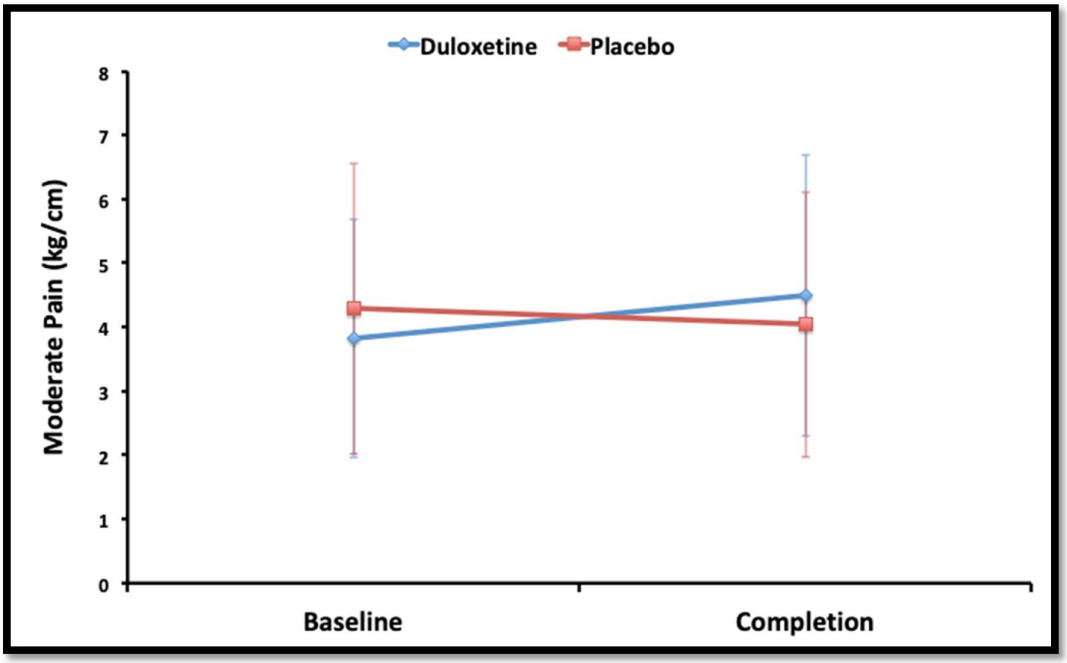
The Moderate Pain threshold data were normally distributed as determined by the Shapiro-Wilk test ($p>0.05$).

There were no statistically significant interaction between treatment and time on MP threshold, $F(1, 17)=2.98$, $p= 0.102$ partial $\eta^2=0.149$ (Table 5.2). Post-hoc analysis exploring main effects showed not statistically significant difference in main effects of time, $F(1, 17)=0.61$, $p= 0.447$ partial $\eta^2=0.034$ and no statistically significant difference in main effects of treatment $F(1, 17)=0.00$, $p= 0.996$ partial $\eta^2=0.000$ (Figure 5.4).

Table 5.2 Moderate Pain (MP) thresholds between treatment and time

	Baseline MP	6 week MP	p value
Placebo	4.29 (2.27)	4.04 (2.07)	0.102
Duloxetine	3.82(1.86)	4.49 (2.19)	

Figure 5.4 Moderate Pain thresholds at baseline and study completion



5.3.2 Task-based functional MRI

Of the 19 participants that were enrolled in the pain sensitivity study above, 13 participants agreed to participate in the task-based functional MRI scan study.

Twelve participants completed the baseline and study completion functional MRI scans. One participant withdrew due to an adverse reaction to the study drug (nausea). Analysis was performed on the remainder of the 12 participants. There were 7 participants from the placebo group, comprising of 3 females and 4 males. The duloxetine group comprised of 3 females and 2 males.

5.3.2.1 Demographic and baseline clinical data of the functional MRI study

There was no statistically significant difference in the demographic profile at baseline between the participants in the duloxetine and placebo group (Table 5.3).

Table 5.3 Demographics and clinical features of participants in the fMRI study

	Placebo (n=7)	Duloxetine (n=5)	p value
Age (years)	67.86 (7.19)	67.00 (10.27)	0.868
PD duration (years)	7.29 (3.73)	6.40 (3.36)	0.682
H&Y, median(IQR)	2.00 (1.00)	2.00 (1.00)	1.000
MMSE ,median (IQR)	30.00 (3.00)	29.00 (3.00)	0.639
LEDD (mg/day)	944.86 (564.58)	731.20 (317.80)	0.466
GDS, median (IQR)	6.00 (8.00)	7.00 (5.00)	0.639
UPDRS	36.57(16.83)	38.60 (5.63)	0.803

Data is expressed as mean (SD) unless otherwise stated.
H&Y, Hoehn and Yahr, MMSE, Mini-Mental State Examination; LEDD, Levodopa equivalence daily dose; GDS, Geriatric Depression scale; UPDRS, Unified Parkinson Disease Rating Scale.

Similarly, the clinical pain scores and pain threshold at baseline between the participants given duloxetine and placebo were also not statistically significantly different (Table 5.4).

Table 5.4 Baseline pain scores and psychophysical tests in the fMRI study

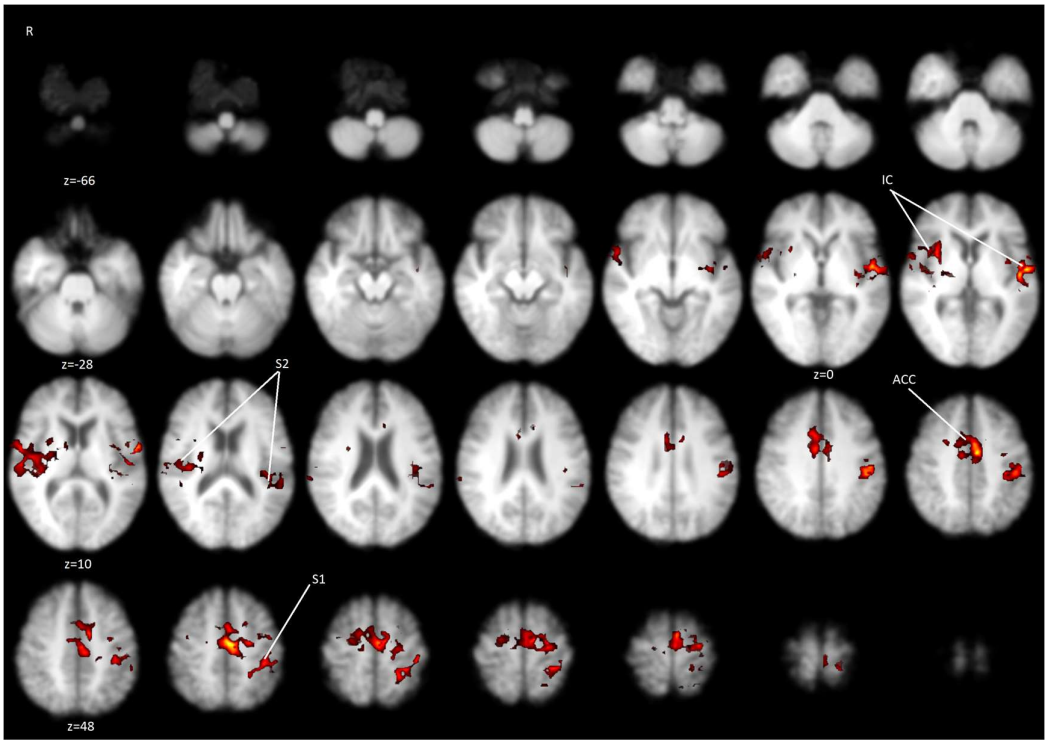
	Placebo (n=7)	Duloxetine (n=5)	p value
SFM-sens	7.43 (3.15)	11.20(4.86)	0.132
SFM-affect	2.29 (1.70)	4.20 (1.79)	0.089
VAS	3.94 (2.73)	5.20 (2.30)	0.425
JNP	1.80 (0.75)	1.51 (0.55)	0.481
MP	5.41 (1.51)	4.93 (1.56)	0.601

Data is expressed as mean (SD).
SFM-sens, sensory component of Short-Form McGill Pain questionnaire; SFM-affect, affective component of Short-Form McGill questionnaire, VAS, Visual Analogue Scale; JNP, Just Noticeable Pain threshold; MP, Moderate Pain threshold.

5.3.2.2 BOLD data before treatment

In the duloxetine group, moderate pain evoked stimulus before treatment showed robust activation in the areas of the brain that are involved in pain processing (Figure 5.5). These include the left primary somatosensory cortex (S1) and bilateral secondary somatosensory cortex (S2), areas of the brain belonging to the lateral pain pathway. Additionally, areas belonging to the medial pain pathway were also activated, namely the bilateral insular cortex and the anterior cingulate cortex.

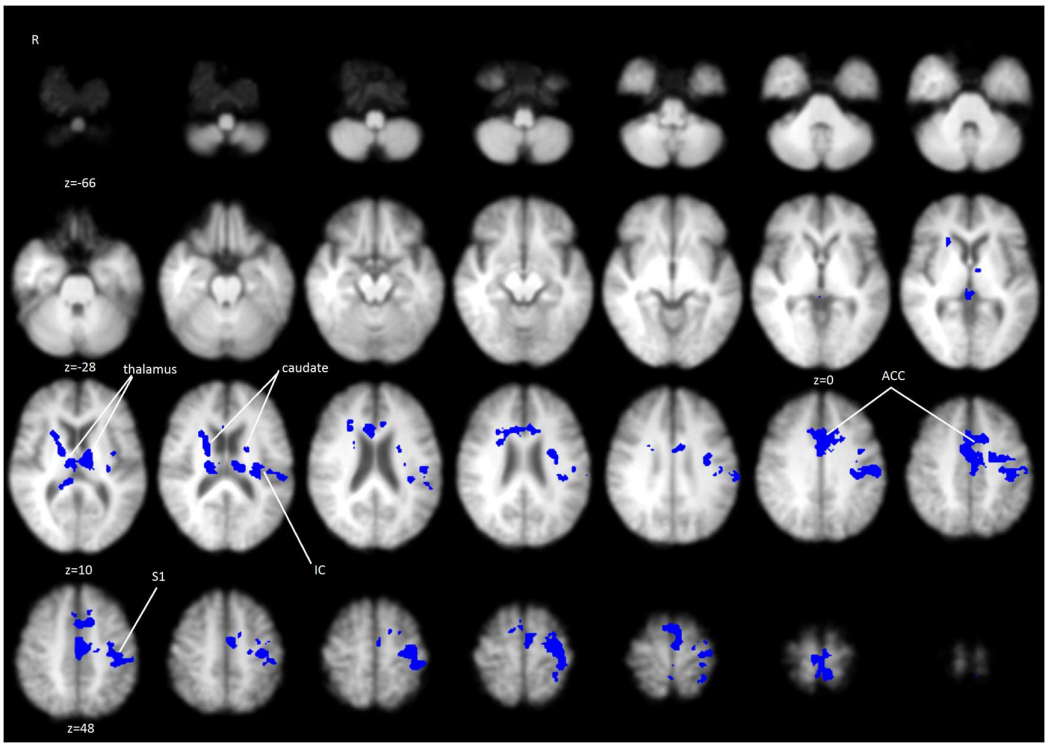
Figure 5.5 Moderate pain pressure in the duloxetine group before treatment



2.3 7.4 (Cluster threshold >2.3; p=0.05)
The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space. S1, primary somatosensory cortex; IC, insular cortex; S2, secondary somatosensory cortex; ACC, anterior cingulate cortex.

In the placebo group, moderate pain evoked stimulus before treatment revealed activation in the left primary somatosensory cortex (S1) belonging to the lateral pain pathway, as well as activation in the areas belonging to the medial pain pathway, namely the bilateral thalamus, bilateral caudate, left insular cortex and the anterior cingulate cortex (Figure 5.6).

Figure 5.6 Moderate pain pressure in the placebo group before treatment

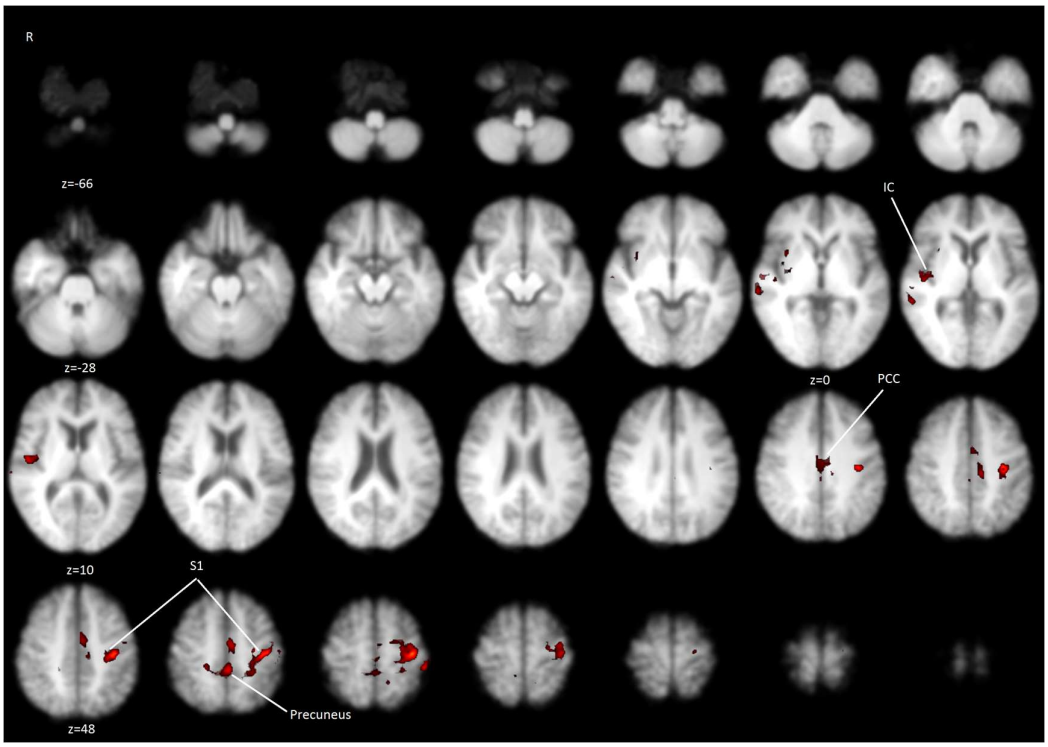


2.3 7.4 (Cluster threshold >2.3; p=0.05)
The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space. ACC, Anterior cingulate cortex; Caudate, caudate nucleus; IC, insular cortex; S1, primary somatosensory cortex.

5.3.2.3 BOLD data after treatment

In the duloxetine group, moderate pain evoked pressure stimulus after treatment revealed activation in the left primary somatosensory cortex (S1), precuneus, posterior cingulate cortex and the right insular cortex (Figure 5.7).

Figure 5.7 Moderate pain pressure in the duloxetine group after treatment



2.3 5.2 (Cluster threshold >2.3; p=0.05)
The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space. IC, Insular cortex; PCC, posterior cingulate cortex; S1, primary somatosensory cortex.

In the placebo group, moderate pain evoked pain stimulus after treatment revealed no areas of the brain that survived the activation threshold that was set at cluster threshold Z>2.3; p=0.05.

5.3.2.4 Differences in brain activation between the visits

At the statistical level of cluster threshold of Z>2.3 with p=0.05, no areas of the brain survived the threshold in the completion>baseline contrast and the baseline>completion contrast in both treatment groups.

5.4 Discussion

The most important findings in this study can be summarised as follows:

- Although not statistically significant, the Moderate Pain threshold showed an increasing trend (reduced pain sensitivity) following administration of duloxetine.
- In the placebo group, the evoked pressure stimulus for Just Noticeable Pain and Moderate Pain thresholds showed a non-statistically significant worsening trend (increased pain sensitivity) between baseline and study completion visits.
- No statistically significant interaction between treatment and time was observed in the task based functional MRI study between the duloxetine and placebo group

5.4.1 Pain sensitivity thresholds on evoked pressure stimulus

The findings relating to the Just Noticeable Pain and Moderate Pain thresholds following evoked pressure stimulus did not show any interaction between treatment (placebo, duloxetine) and time (baseline, study completion) that approached statistical significance.

Although there has been a considerable amount of research conducted over the years investigating pain sensitivity in Parkinsons disease, studies looking at changes in pain sensitivity in Parkinsons following duloxetine are scarce.

To our knowledge, the only other research that investigated changes in pain sensitivity in Parkinsons disease patients was an open labelled study that used heat pain threshold as the evoked pain stimulus and also found no statistically significant difference in pain sensitivity following 6 weeks of duloxetine.(Djaldetti et al., 2007)

Several studies explored the effect of duloxetine on pain sensitivity following evoked pressure pain stimulus in various chronic pain conditions. In a study on

stroke patients and patients with spinal cord injuries, no statistically significant change was observed in pain sensitivity following duloxetine, despite significant improvement in self reports of pain. (Vranken et al., 2011)

In patients with fibromyalgia, 2 double-blind placebo-controlled trial revealed similar outcomes, with duloxetine at a dose of 60mg once a day showing a statistically significant improvement in pain intensity reports but no significant change in pressure thresholds.(Arnold et al., 2005; Russell et al., 2008)

Making comparisons with studies on pain sensitivities following duloxetine in other chronic pain conditions is problematic as the pathophysiological substrate for the development of pain would presumably be different to that of Parkinsons disease.

The type of stimulus used to evoke pain is an important consideration in studies in investigating pain sensitivity. Different stimuli elicit responses from different types of peripheral afferent fibres during the transduction of nociceptive signals. For example, heat pain thresholds preferentially rely on the function of the C peripheral afferent fibres, whereas laser, cold and electrical evoked stimuli activate the Aδ peripheral afferent fibres. Pressure stimulus can activate both Aδ and C peripheral afferent fibers.

Furthermore, even within the same chronic pain condition, the exact pathophysiological mechanism of chronic pain can be different and several. For example, dynamic mechanical allodynia arises from a dysfunction of wide dynamic range neurons in the dorsal horn that miscode the non-noxious stimulus as nociceptive. In contrast, mechanical hyperalgesia is a form of neural plasticity due to peripheral sensitisation and central sensitisation of nociceptive sensitive Aδ and C afferent fibres. In Parkinsons disease, and indeed in various other chronic pain conditions, the symptom of chronic pain can be a manifestation of different underlying pathophysiological pain generating mechanism.

Arguably, all these factors may contribute to the contradictory findings observed in studies investigating pain sensitivity in chronic pain conditions. This compounds the difficulty in interpreting the underlying trends relating to pain sensitivities from different studies using different stimulus to evoke pain and in different chronic pain conditions.

Whilst our study at face value appears to be in agreement with previous research showing that duloxetine does not alter pain sensitivity thresholds in chronic pain conditions and in Parkinsons disease, it is difficult to make a definitive conclusion.

A compounding factor is the small sample size of the study. It is possible that a similar study with a bigger sample size would produce a more conclusive finding with statistically significant results, considering that the changes in the Moderate Pain threshold demonstrated an improving trend.

Although not statistically significant, the Moderate Pain threshold for the participants on duloxetine was observed to undergo an improving trend (i.e. reduced pain sensitivity) between baseline and study completion visits. Similarly, an improving trend was also observed in the duloxetine group for the Just Noticeable Pain threshold, although the changes were substantially more modest.

In contrast, the participants in the placebo group showed worsening trend in both outcomes, suggesting increased pain sensitivity at study completion.

Studies on pain thresholds following evoked stimulus have theorized that the Just Noticeable Pain threshold (i.e. pain threshold) is representative of the sensory-discriminative dimension of pain, and the Moderate Pain threshold (i.e. pain tolerance) reflects the affective-motivational dimension of pain. (Benedetti et al., 1999; Jensen-Dahm et al., 2014)

Our study raises the question of whether the analgesic properties of duloxetine in Parkinsons disease patients with pain are more reactive towards pain arising from the affective-motivational dimension than it is towards the sensory-discriminative dimension of pain.

In Alzheimers disease, pain sensitivity studies have shown a more pronounced dysfunction in pain tolerance (affective-motivational dimension) as compared to pain thresholds (sensory-discriminative dimension).(Benedetti et al., 1999; Jensen-Dahm et al., 2014) This may be a reflection of a more extensive pathological dysfunction in Alzheimer's disease involving the regions of the brain that belong to the medial pain pathways that subserves the affective-motivational dimension of pain, in particular the amygdala and the hippocampus, as compared to the lateral pain pathways that subserves the sensory-discriminative dimension of pain.(McKhann et al., 1984; Scherder et al., 2003) However, a study by Cole et al that tests this hypothesis found no evidence of reduced activation in the regions of the medial pain pathways in response to painful pressure in patients with Alzheimer's disease as compared to controls, indicating that the affective-motivational dimension of pain was not selectively diminished.(Cole et al., 2006)

Nevertheless, a similar pattern of preferential neurodegeneration in areas belonging to the medial pain pathway over the areas belonging to lateral pain pathway is also seen in Parkinsons disease.(Boecker et al., 1999; Rüb et al., 2002; E. Scherder et al., 2005) Nuclei such as amygdala, hippocampus and the anterior cingulate cortex belong to the medial pain pathway and provide important afferent projections to the descending modulation pathway located in the brainstem e.g. periaqueductal grey, locus coeruleus and the raphe nuclei (refer to Section 1.6.2 Projection into the PAG). Disruption of these connections due to Lewy body deposition and neurodegeneration in Parkinsons disease may explain our finding of the reduced pain tolerance (Moderate Pain threshold) seen in our study and provide the possible mechanistic explanation of how duloxetine might be exerting its effect.

5.4.2 Task-based functional MRI

We were hoping to link any changes seen in the pain sensitivity study to changes in functional MRI scan.

Single-session brain activation maps in the duloxetine and placebo group showed patterns consistent with the pain neuromatrix at baseline. In the study completion scan, only the duloxetine group was observed to have activation in the pain neuromatrix, whereas the placebo group did not.

No areas of the brain survived the activation threshold in the between group contrast (duloxetine vs placebo) and the between sessions contrast (baseline vs study completion).

In some ways, our results are not surprising. Although the changes in pain sensitivity relating to the Just Noticeable Pain and Moderate Pain thresholds showed an improving trend in the duloxetine group, the changes did not approach any statistical significance. Thus, the effect size may not be big enough to effect any changes that could be detected by changes in the brain activation in the functional MRI study.

Further, only a selection of the participants was invited to undergo the functional MRI study, further compounding the issue.

5.5 Conclusion

This study is a negative study that is primarily handicapped by a small sample size. Nevertheless, our finding of an improving trend in the Moderate Pain threshold (representing pain tolerance) following duloxetine administration provides food for thought.

Our study may indicate that the action of duloxetine is differentially effective in different dimensions of pain. Further studies with a bigger sample size are required to confirm our findings.

Chapter 6: A pilot study on default mode network changes in Parkinsons disease patients with pain following duloxetine

6.1 Introduction of aims and hypothesis

Resting state network describes a collection of distributed brain regions that show signal changes that correlate across time, which suggests functional connectivity between the regions. These networks are observed when the person is awake and at rest i.e. not cognitively engaged, and can be detected using functional MRI techniques. The phenomenon of resting state networks was first described by Biswal et al, with many studies replicating the results over the years and has since gained widespread acceptance amongst the scientific community.(Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995)

There are several functional brain networks that exist during resting state. Foremost is the default mode network, discovered by Raichle et al.(Raichle et al., 2001) Generally accepted components of the default mode network include the posterior cingulate cortex, median prefrontal cortex and inferior parietal lobule. (Buckner, Andrews‐Hanna, & Schacter, 2008)

Default mode network abnormalities have been demonstrated in various medical conditions. Studies on subjects with autism spectrum disorder revealed abnormalities in the activity and connectivity of the default mode network, as compared to controls. (Cherkassky, Kana, Keller, & Just, 2006; Kennedy, Redcay, & Courchesne, 2006) Over-activity in different components of the default mode network resulting in diminished focused external attention has been an underlying theme in patients with schizophrenia.(Garrity et al., 2007; Harrison, Yücel, Pujol, & Pantelis, 2007; Zhou et al., 2007)

In Alzheimer's disease, hypo-metabolism and brain atrophy have been shown to have an increase predilection for areas generally associated with the default mode network.(Buckner et al., 2005)

The activity of the default mode network has also been implicated in pain-related processing. The level of default mode network activation prior to an evoked stimulus has been shown to influence the level of pain reported by study subjects.(Mayhew, Hylands-White, Porcaro, Derbyshire, & Bagshaw, 2013) "Mind-wandering" away from pain and an associated decrease in pain sensitivity is associated with an enhanced functional connectivity between the default mode network and the periaqueductal grey, a key region of the brain implicated in descending modulation of nociceptive inputs.(Kucyi, Salomons, & Davis, 2013)

In chronic back pain patients and patients with painful diabetic neuropathy, the majority of research has shown either reduced activation or connectivity of the default mode network.(Baliki, Geha, Apkarian, & Chialvo, 2008; Cauda et al., 2009; Malinen et al., 2010; Tagliazucchi, Balenzuela, Fraiman, & Chialvo, 2010) Conversely, in fibromyalgia patients, a condition associated with chronic pain, a study showed that there was an increase in connectivity between the default mode network with the right executive attention network when compared to controls. (Napadow et al., 2010)

The histopathological substrate for Parkinsons disease is the deposition of Lewy bodies in the central nervous system that adopts a rostro-caudal progression, as proposed by Braak and colleagues.(Braak et al., 2003) At Braak stage 3 and 4, the pathology becomes widespread and involves subcortical nuclei and cortical brain regions. It is thus reasonable to speculate that the inevitable progression of the disease would ultimately affect brain areas that constitute the default mode network.

There have been several studies investigating the default mode network in Parkinsons disease. A state of dopamine depletion in the caudate nucleus which disrupts an important connection to the medial prefrontal cortex (a component of the default mode network) has been proposed to be a possible mechanism that leads to the dysfunction of the default mode network in Parkinsons disease.(van Eimeren et al., 2009) Comparisons with healthy subjects has shown that Parkinsons disease patients have reduced connectivity between the

disparate brain areas that make up the default mode network.(Tessitore et al., 2012) Finally, the dysfunction of the default mode network appears to be restored in Parkinsons disease patients following levodopa administration.(Delaveau et al., 2010; Krajcovicova, Mikl, Marecek, & Rektorova, 2012)

Interestingly, Parkinsons disease patients with visual hallucinations have been shown to have increased connectivity between the default mode network with the right middle frontal gyrus and bilateral posterior cingulate gyrus, as compared to Parkinsons disease patients without visual hallucinations.(Yao et al., 2014) This may suggest not only the level of activation or deactivation of the default mode network that is important, but the connectivity of the default mode network, both intrinsically within the network and extrinsically to other regions of the brain may also play a role in the symptom development of Parkinsons disease.

It has become increasingly clear over the years that pain is an important feature in Parkinsons disease. We also know that the cause of pain in Parkinsons disease can be multifactorial. It is possible that the dysfunction in the default mode network may also play a role in the development of pain in Parkinsons disease. Furthermore, considering its role in the management in various chronic pain conditions, we also wanted to explore whether duloxetine influences any changes in the default mode network that may contribute to improvement in pain symptoms in Parkinsons disease patients.

In this context, we conducted a pilot randomised controlled trial in Parkinsons disease patients with pain. We wanted to test our hypothesis that duloxetine would induce changes in the areas of the default mode network. This can be achieved by comparing the default mode network activation brain pattern at baseline and at study completion in Parkinsons disease patients with pain given either duloxetine or placebo. Additionally, with the statistical brain maps obtained from this study, a sample size calculation procedure can be performed

to determine the appropriate sample size for the purpose of a future study to confirm our findings.

6.2 Methodology

Participants were recruited from Parkinsons disease patients attending movement disorder clinic at the Royal Melbourne Hospital. The Human Research Ethic Committee of Melbourne Health provided ethics approval to conduct the study. The inclusion and exclusion criteria are as per outlined in **Chapter 3** (Section 3.1.1 and 3.1.2). As this was a pilot study, a selection of participants involved in experiment described in **Chapter 4** was invited to participate in this study.

The primary outcome measure was the regional BOLD activation changes at baseline resting scan and at completion study scan at 6 weeks.

6.2.1 Procedures

The procedures underwent by the participants is as per described in **Chapter 3** (Section 3.4). The study was conducted over 3 visits. The study duration was 6 weeks. Briefly, the procedures performed are as follows:

- Visit 1 (baseline): Collection of demographic data followed MRI scan to acquire structural and functional images at baseline, followed by randomization to either duloxetine 30mg or matching placebo.
- Visit 2: Up-titration of duloxetine to 60mg or matching placebo.
- Visit 3 (study completion): Participants underwent MRI scan to acquire functional images. Following the scan, all the participants were asked to stop all study drugs.

6.2.2 MRI scan

MRI derived BOLD images were used to compare brain responses at rest between treatment groups. Participants were instructed to lie in a dimly lit room with their eyes closed, thinking of nothing in particular and to not fall asleep.

Images were acquired using a Siemens TRIO 3 Tesla whole body scanner at the Murdoch Children's Research Institute, Melbourne, Australia.

Anatomical T1 weighted images were acquired for registration purposes (TR=1900ms, TE=2.63ms, FA=90^0, 208 sagittal slices, 320x320 matrix, 0.84mm^3 isotropic voxels). BOLD contrast functional images were acquired using an echo-planar imaging sequence (TR=750ms, TE=33ms, FA=85^0, 60 axial slices 2.5mm thick, 64x64 matrix, 2.45mm^2 in-plane resolution).

6.2.3 Pre-processing

The functional MRI data were analyzed using FEAT (FMRI Expert Analysis Tool) Version 6.0, part of FSL (FMRIB's Software Library).(Smith et al., 2004) Pre-processing of BOLD images included brain extraction using BET(Smith, 2002), motion correction (Jenkinson & Smith, 2001), high pass filtering and spatial smoothing with a 6mm FWHM Gaussian kernel. Functional MRI volumes were registered to the individual's structural scan and standard space images using FMRIB's Linear Image Registration Tool (FLIRT).(Jenkinson et al., 2002)

6.2.4 Resting-state functional activation

6.2.4.1 Nuisance signal regression.

In order to increase the signal to noise ratio, eight covariates of no interest (nuisance variable) were identified for inclusion in our analyses. Specifically, these nuisance variables were white matter, cerebrospinal fluid and the 6 motion parameters time series for each individual. The white matter and cerebrospinal

time series were extracted by first segmenting each individual's high resolution structural scan (T1 sequence) to acquire the white matter and cerebrospinal fluid mask using FSL's Auto Segmentation Tool (FAST) segmentation.(Zhang, Brady, & Smith, 2001) The resulting segmented white matter and cerebrospinal fluid mask were then co-registered to each individual functional scan using the *applyxfm* command in the FMRIB's Linear Image Registration Tool (FLIRT) application.(Jenkinson et al., 2002) The masks were thresholded to ensure that it was comparable to the original volume in the individual's functional space. These thresholded masks were then applied to each individual time series and a mean time series was calculated by averaging across all voxels within the mask.

6.2.4.2 Seed description

Based on a priori hypothesis, we created a seed region of interest (ROI) for the posterior cingulate cortex. The posterior cingulate cortex was chosen as a seed due to its importance in the default mode network.(Fox et al., 2005) The seed ROI was defined in standard MNI (Montreal Neurological Institute) space and identified using the Harvard-Oxford Cortical and Subcortical probabilistic atlas. An irregular shaped seed ROI was created, confining within voxels with at least 50% probability of being in the target region. The seed ROI was transformed from standard MNI space to the individual functional space of each participant's fMRI data using the FMRIB's Linear Image Registration Tool (FLIRT) within the FSL application.(Jenkinson et al., 2002)

6.2.4.3 Time series extraction and higher level analysis

Extraction of the time series within the seed region for each individual subject was performed using the application *FSLMEANTS* available within FSL, after having pre-processed the raw functional MRI data. The extracted time series was used as a regressor, without any convolution, in a general linear model using the FMRIB data processing application FEAT. These analyses produced separate individual participant-level correlation maps of all voxels positively correlated with the seed. The FMRIB's Local Analysis of Mixed Effects (FLAME) was used to

perform higher-level analysis.(Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004) Group averages and differences between the treatment groups (duloxetine and placebo) were tested using the General Linear Model (GLM). The Z statistic images were thresholded using cluster determined by Z>2.3 and Z>1.6. A whole brain family-wise error-corrected cluster significance threshold of p=0.05 was applied to the supra-threshold clusters.

6.2.5 Sample size calculation using fMRIpower

A functional MRI sample size calculation was conducted using the MATLAB-based fMRIpow*er* software package.(Mumford & Nichols, 2008) The software estimates power for detecting cortical activations in a pre-specified ROI assuming that the future study adopts the same design with similar scanner noise characteristics as the pilot study. Firstly, the whole brain z-statistics map that resulted in any difference in activation was chosen and entered into fMRIpower. Next, we used the default whole brain Automatic Anatomical Labelling (AAL) atlas as the region of interest (ROI) mask, supplied within the fMRIpower software package. The alpha value for type I error of 0.05 was chosen before performing the analysis.

6.3 Results

Thirteen Parkinsons disease patients with pain gave informed consent to participate in the study. These patients were also involved in the task-based functional MRI scan study described in **Chapter 5** (Section 5.3.2)

One participant withdrew due to an adverse reaction (nausea) to the study drug midway into the study. Analysis was performed on the remainder twelve participants that completed the study.

Of the 12 participants that completed the study, 5 participants were randomised to have duloxetine, comprising 3 females and 2 males. Seven participants were randomised to the placebo arm, comprising 3 females and 4 males.

There was no statistically significant difference in the demographic profile at baseline between the participants in the duloxetine and placebo group. (please refer to **Chapter 5**: Table 5.3)

Similarly, the clinical pain scores and pain threshold between the participants given duloxetine and placebo were also not statistically significantly different. (please refer to **Chapter 5**: Table 5.4)

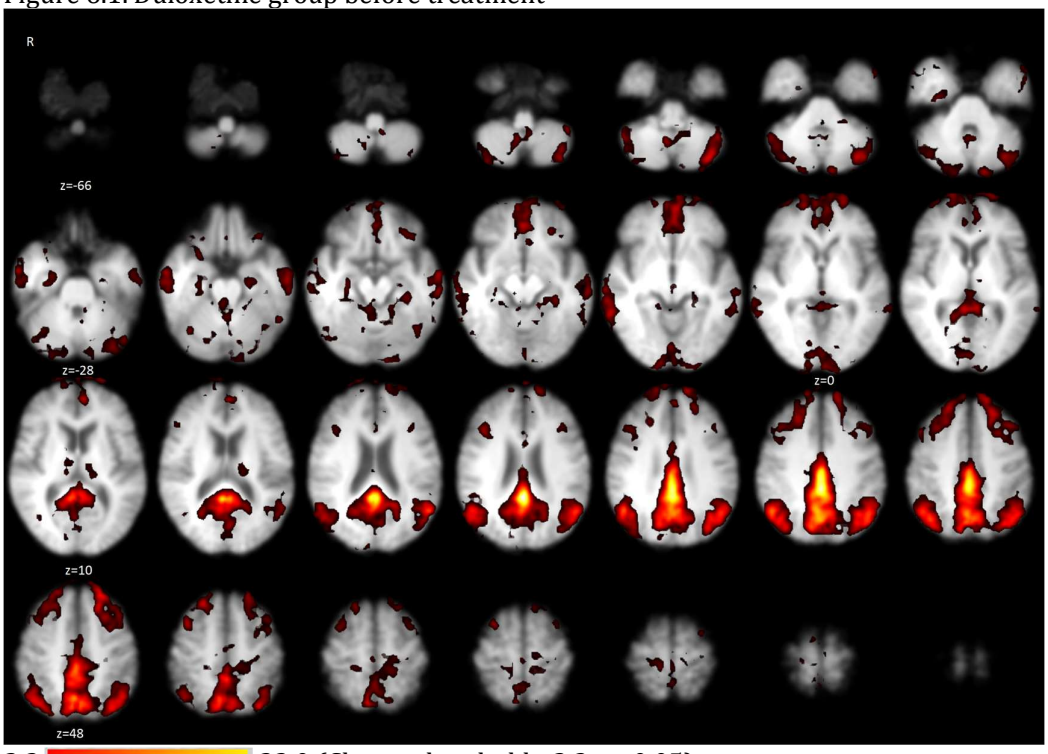
6.3.1 Functional connectivity

Seed based correlation analysis was employed to characterize their associated functional systems at rest.

6.3.1.1 Before treatment

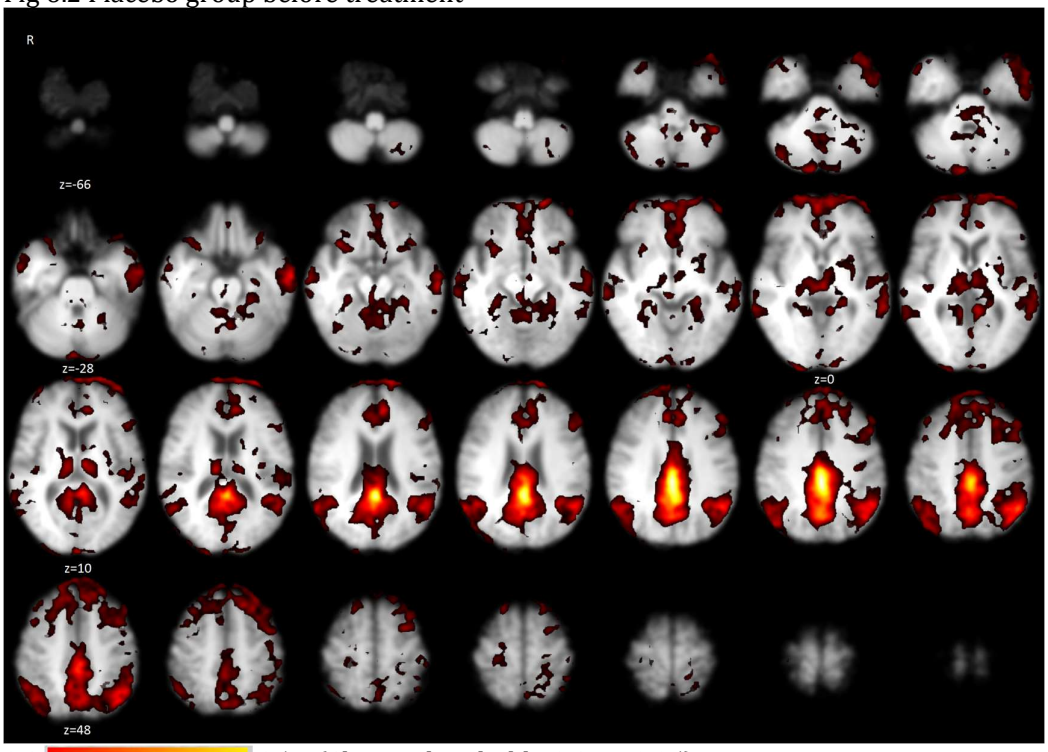
Seed based resting state functional connectivity at baseline in the duloxetine and the placebo groups are presented in Figure 6.1 and Figure 6.2. The connectivity patterns between the duloxetine and placebo group were largely comparable at baseline. (Figures 6.3, 6.4, and 6.5) The main brain regions undergoing activation include bilateral inferior parietal lobe and the medial prefrontal cortex, known components of the default mode network.

Figure 6.1. Duloxetine group before treatment



2.3 23.0 (Cluster threshold >2.3; p=0.05)
The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space.

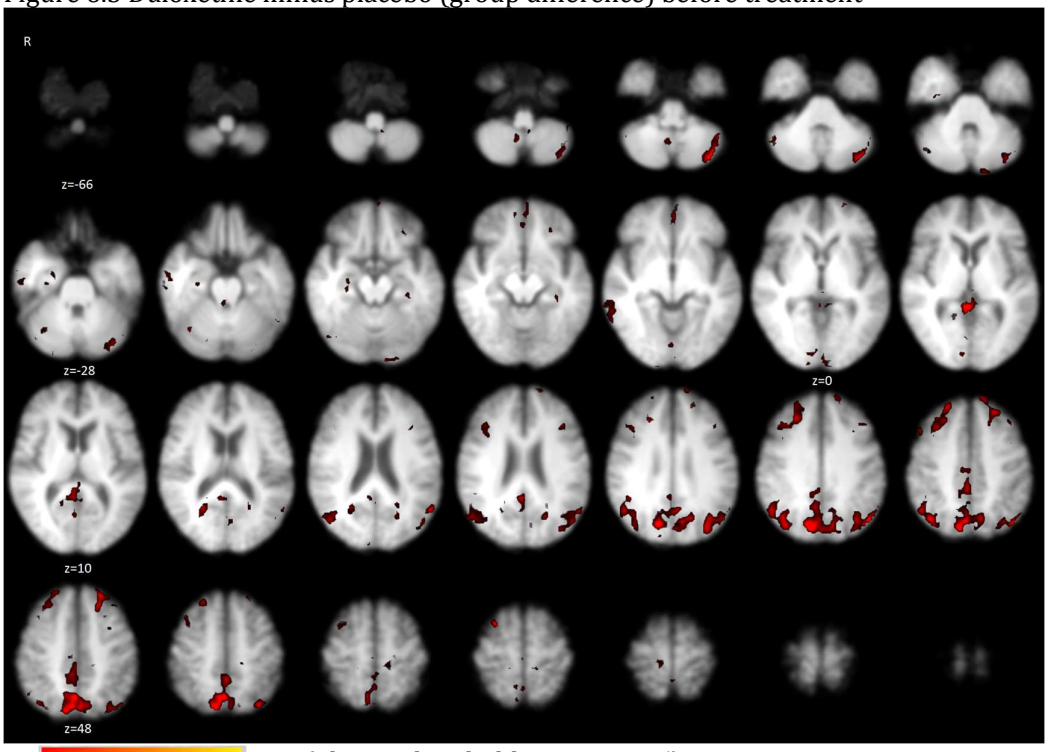
Fig 6.2 Placebo group before treatment



2.3 25.4 (Cluster threshold >2.3; p=0.05)

The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space.

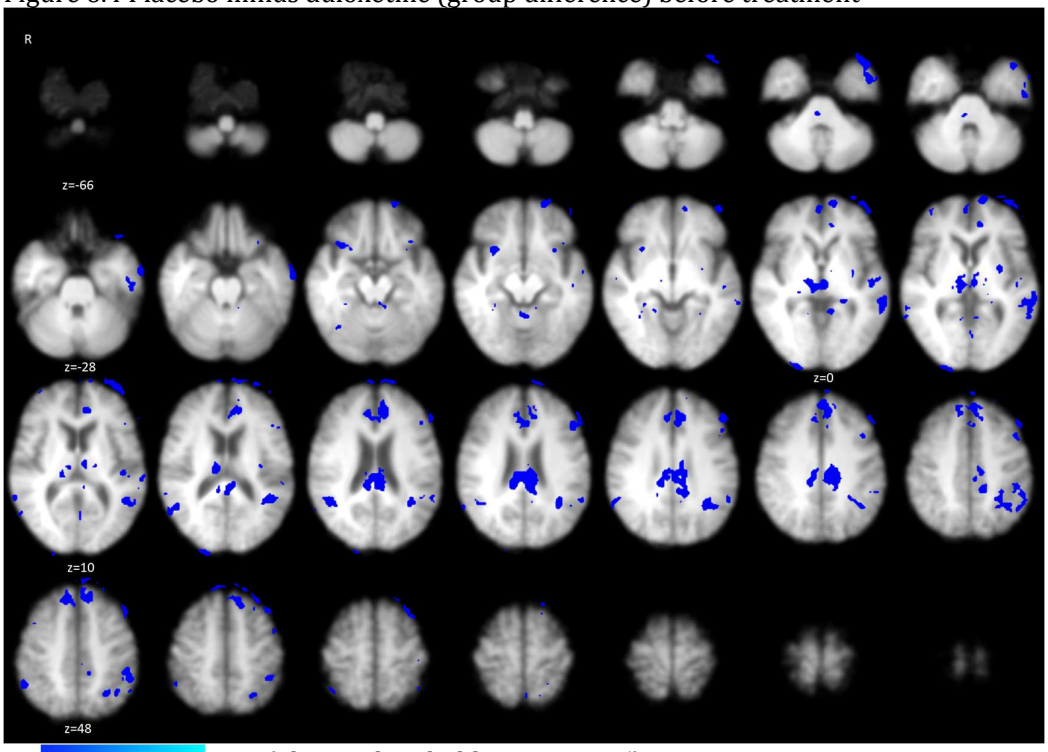
Figure 6.3 Duloxetine minus placebo (group difference) before treatment



2.3 29.6 (Cluster threshold >2.3; p=0.05)

The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space.

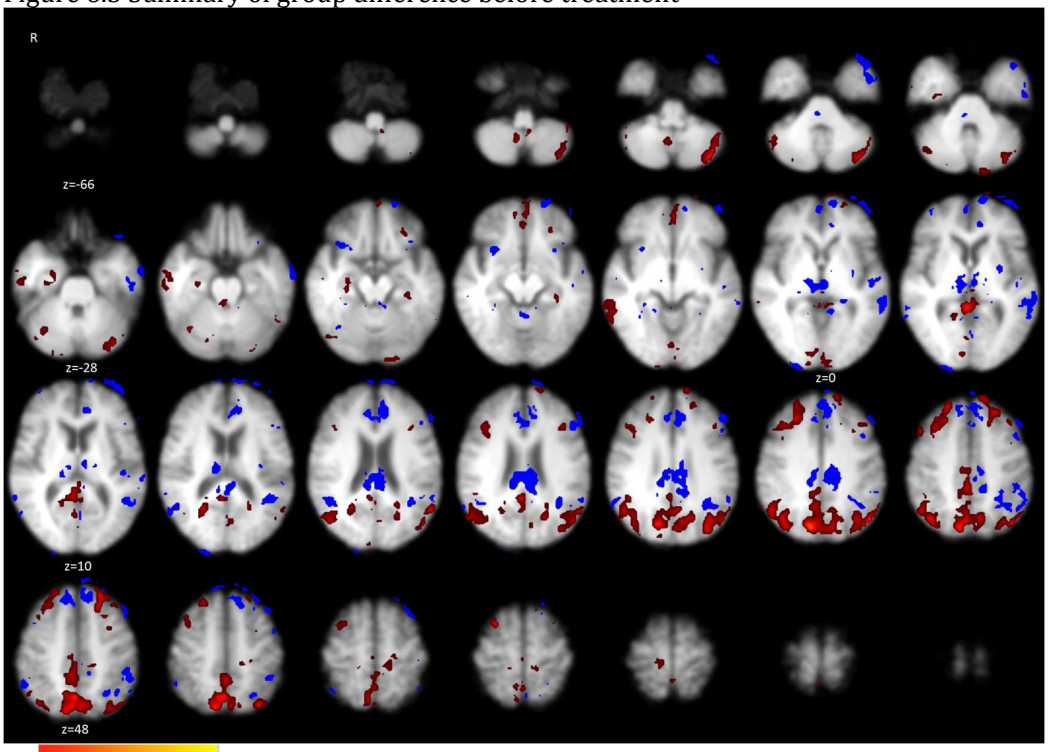
Figure 6.4 Placebo minus duloxetine (group difference) before treatment



2.3 29.6 (Cluster threshold >2.3; p=0.05)

The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space.

Figure 6.5 Summary of group difference before treatment



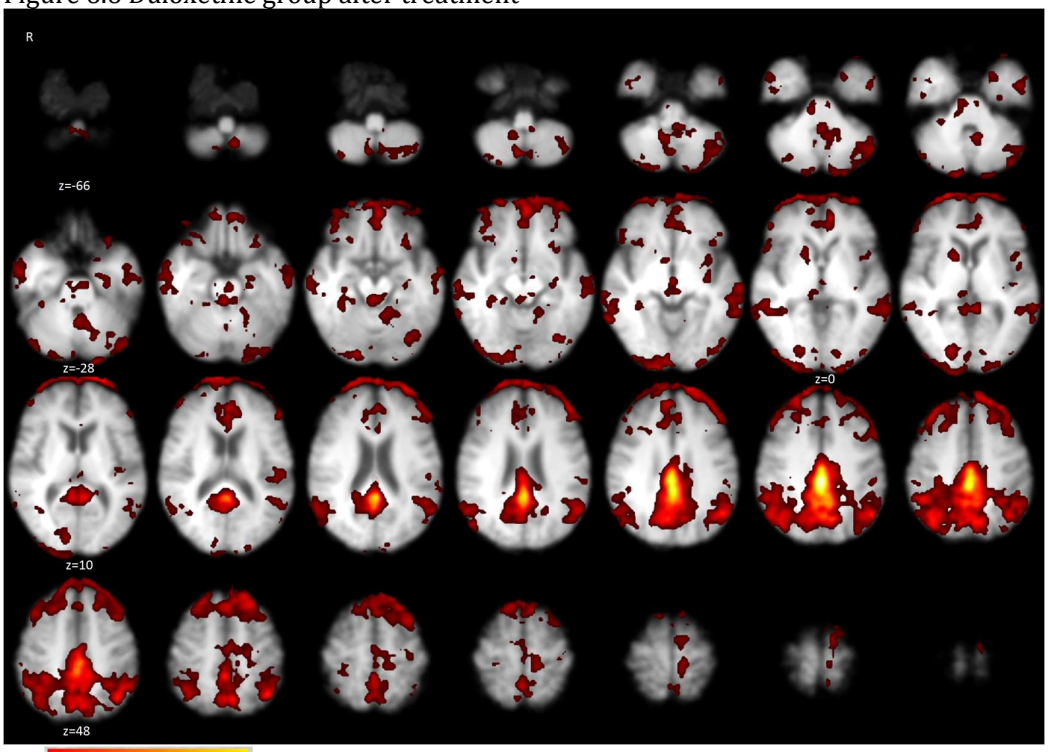
2.3 29.6 (Duloxetine minus placebo; Cluster threshold Z>2.3; p=0.05)
2.3 29.6 (Placebo minus duloxetine; Cluster threshold Z>2.3; p=0.05)
The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space.

6.3.1.2 After treatment

Seed based correlation resting state functional connectivity in the duloxetine and placebo group at study completion are presented in Figure 6.6 and Figure 6.7.

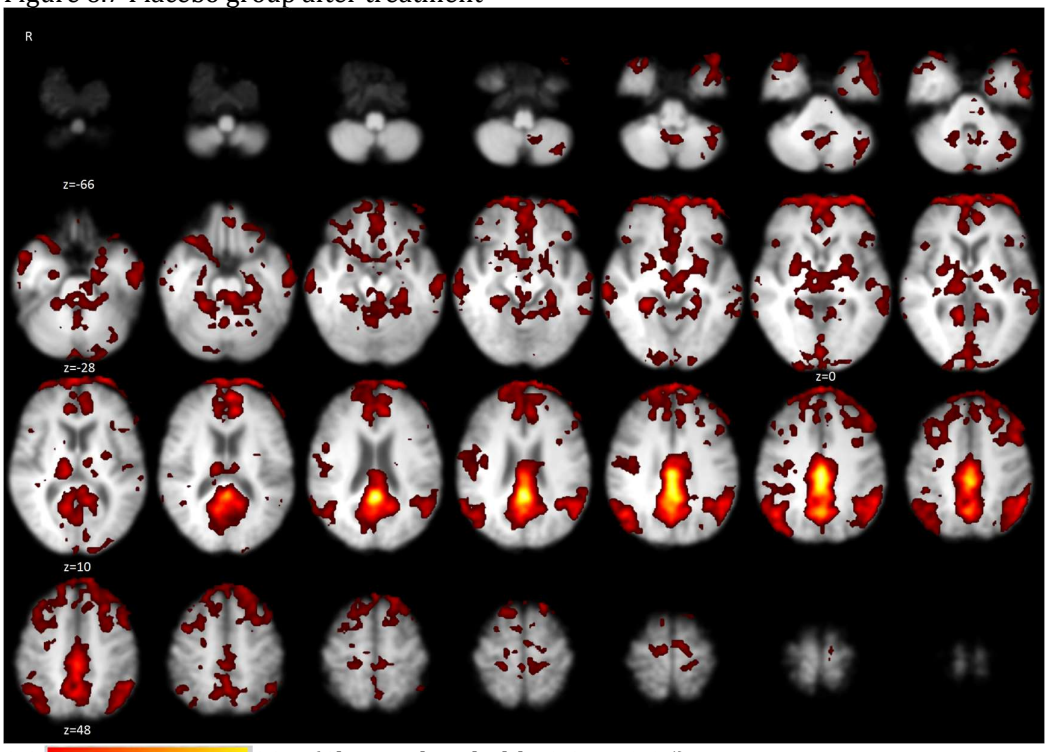
The difference in the connectivity patterns between the duloxetine and placebo groups are displayed in Figures 6.8, 6.9 and 6.10.

Figure 6.6 Duloxetine group after treatment



2.3 24.6 (Cluster threshold >2.3; p=0.05)
The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space.

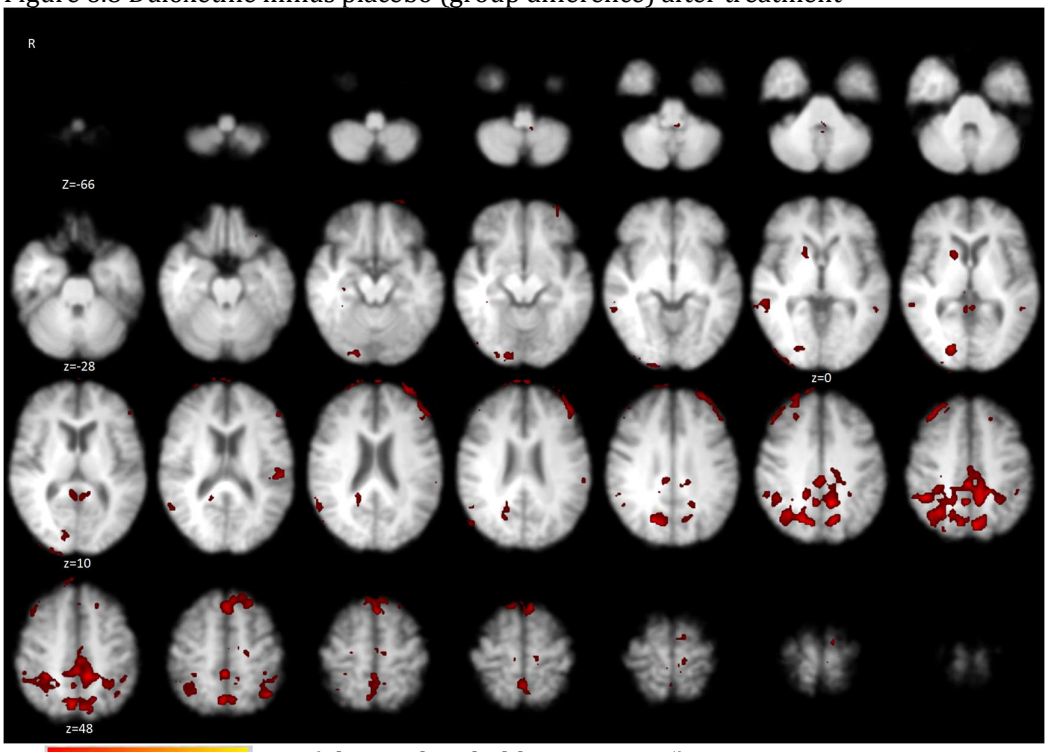
Figure 6.7 Placebo group after treatment



2.3 23.6 (Cluster threshold >2.3; p=0.05)

The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space.

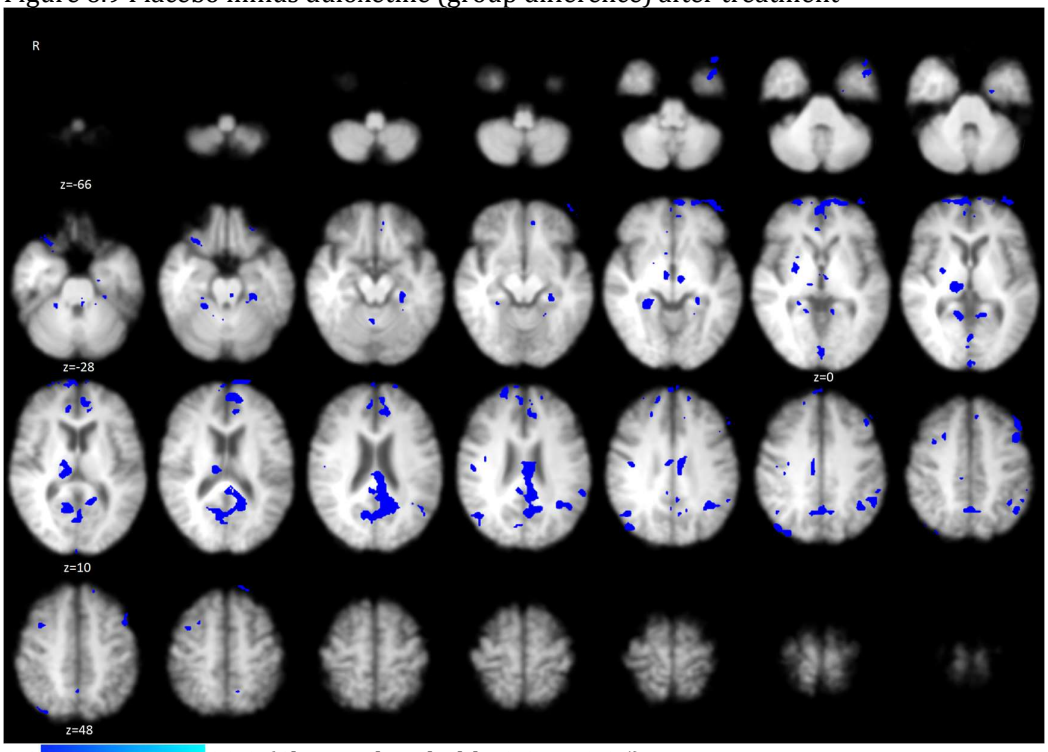
Figure 6.8 Duloxetine minus placebo (group difference) after treatment



2.3 29.9 (Cluster threshold >2.3; p=0.05)

The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space.

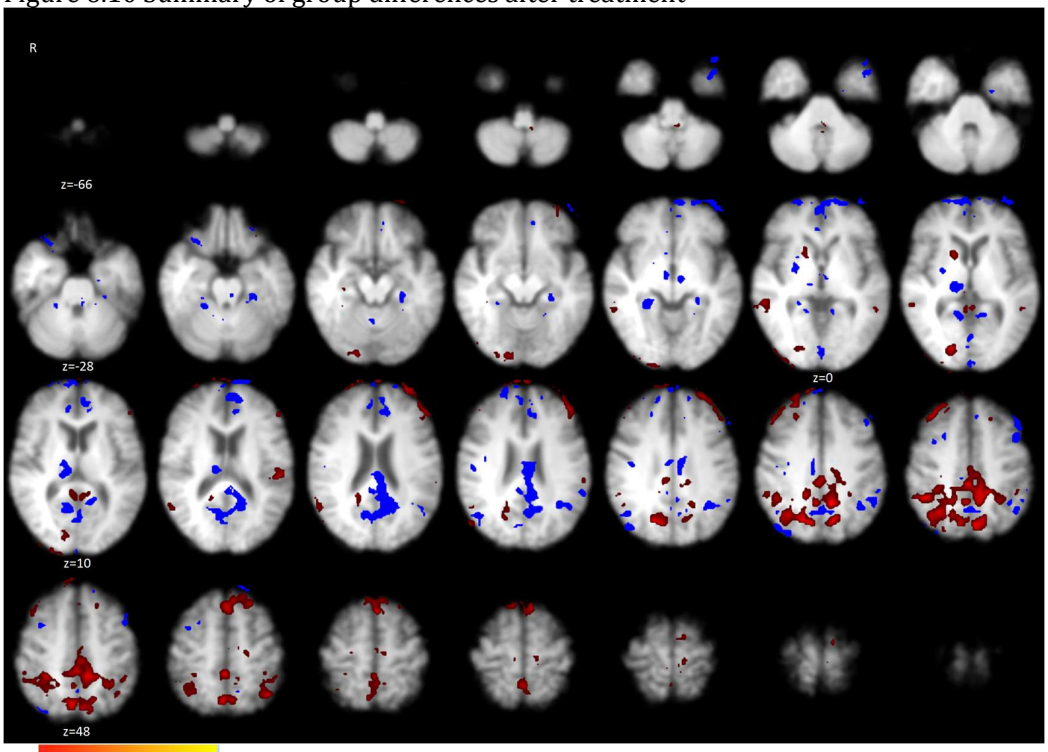
Figure 6.9 Placebo minus duloxetine (group difference) after treatment



2.3 29.9 (Cluster threshold >2.3; p=0.05)

The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space.

Figure 6.10 Summary of group differences after treatment



2.3  29.9 (Duloxetine minus placebo; Cluster threshold Z>2.3; p=0.05)

2.3  29.9 (Placebo minus duloxetine; Cluster threshold Z>2.3; p=0.05)

The statistical maps are presented axially on the average of all participants T_1-weighted anatomical image normalised into standard space. The z value corresponds to the slice location in MNI space.

6.3.1.3 Duloxetine group differences before and after treatment

Seed-based correlation resting state functional connectivity difference in the duloxetine group at baseline and completion was performed.

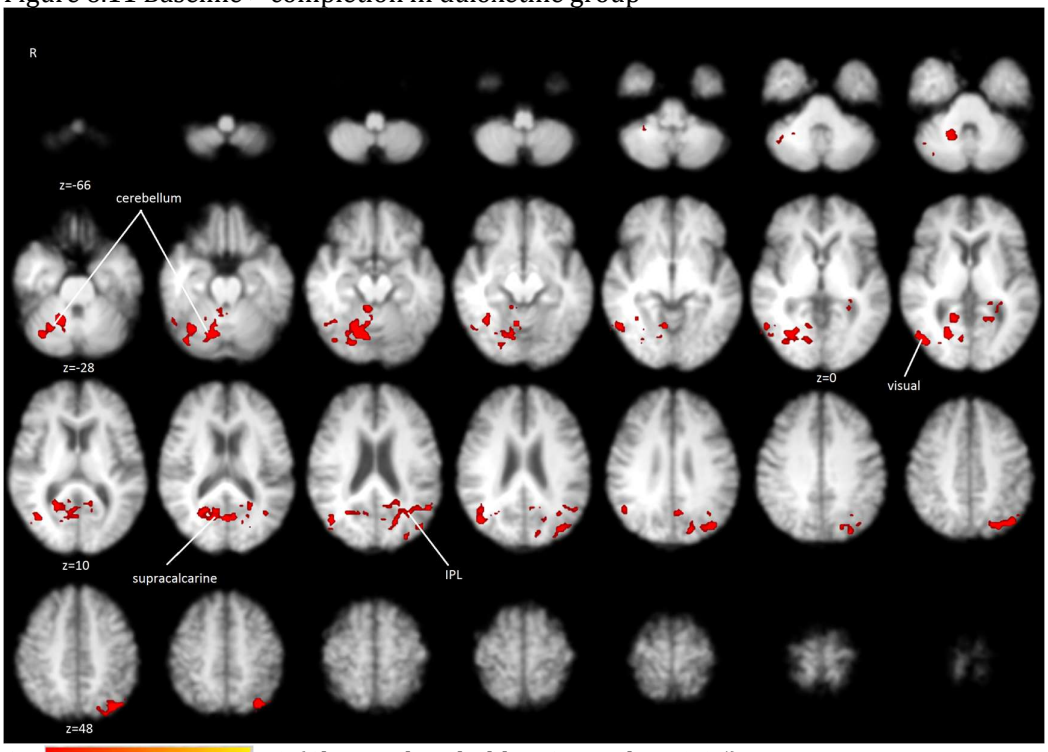
For both baseline>completion and completion>baseline contrasts for the duloxetine group, no voxel survived the threshold when the analysis was set at cluster threshold Z>2.3, p=0.05. Consequently, further analysis was performed at a lower threshold of Z>1.6 and p=0.05.

The results show that in the baseline>completion contrast at cluster threshold z>1.6, p=0.05, Parkinsons disease patients in the duloxetine group had increased functional connectivity between the posterior cingulate cortex with the right cerebellum and the left inferior parietal lobe. (Figure 6.11)

No voxel survived the threshold of Z>1.6, p=0.05 in the completion>baseline contrast in the duloxetine group.

A summary of the brain areas that showed activations in the duloxetine group is shown in Table 6.1.

Figure 6.11 Baseline > completion in duloxetine group



1.6 6.2 (Cluster threshold Z>1.6 with p=0.05)

The statistical maps are presented axially with z values indicating slice location in MNI space and displayed on the average of all subjects T1 weighted anatomical image normalised into standard space. IPL, inferior parietal lobule; IC, insular cortex; Visual; visual cortex.

Table 6.1 Summary of regions showing activation in the baseline>completion contrast in the duloxetine group.

		Peak Voxel Coordinate			Z score
Region	Volume	x	y	z	
Visual cortex V5 Right	4931	46	-76	4	3.4
Supracalcarine cortex		2	-70	14	3.36
Cerebellar Lobule VI Right		12	-70	-16	3.24
Lateral Occipital Cortex Right, inferior		42	-76	-20	3.2
Lateral Occipital Cortex Right, superior		46	-72	24	3.17
Cerebellar Lobule VI Right		12	-70	-20	3.1
Inferior Parietal Lobe Left		-42	-60	24	1.8
Cerebellar Lobule I-IV Right		2	-47	-20	2.8

Coordinates of the maximally activated voxels in each region are provided in MNI space. All activations were at cluster level significance z>1.6, p=0.05.

6.3.1.4 Placebo group differences before and after treatment

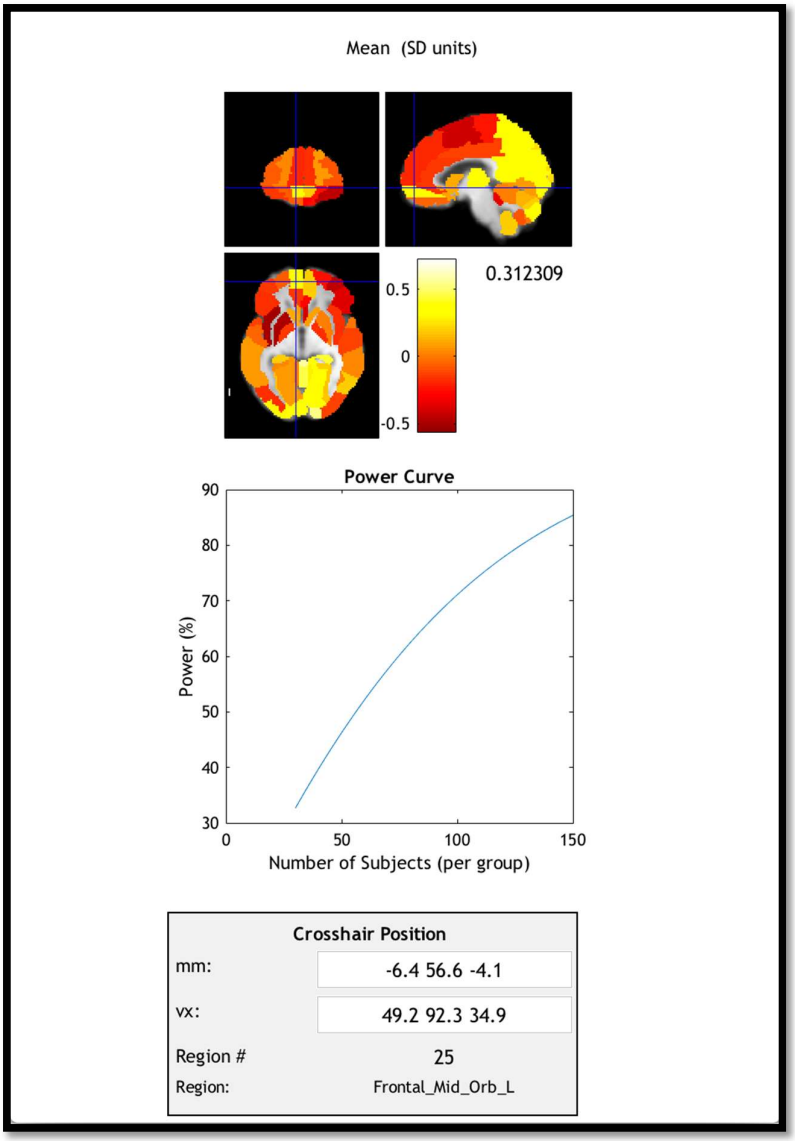
In the group of Parkinons disease patients given placebo, neither the baseline>completion nor the completion>baseline contrast showed any difference in functional connectivity patterns at the statistical analysis set at cluster threshold Z>2.3, p=0.05 and Z>1.6, p =0.05.

6.3.2 Sample size calculation using fMRIpower

The whole brain Z-statistics map of the duloxetine group was chosen on account of the map showing activation differences between different contrasts.

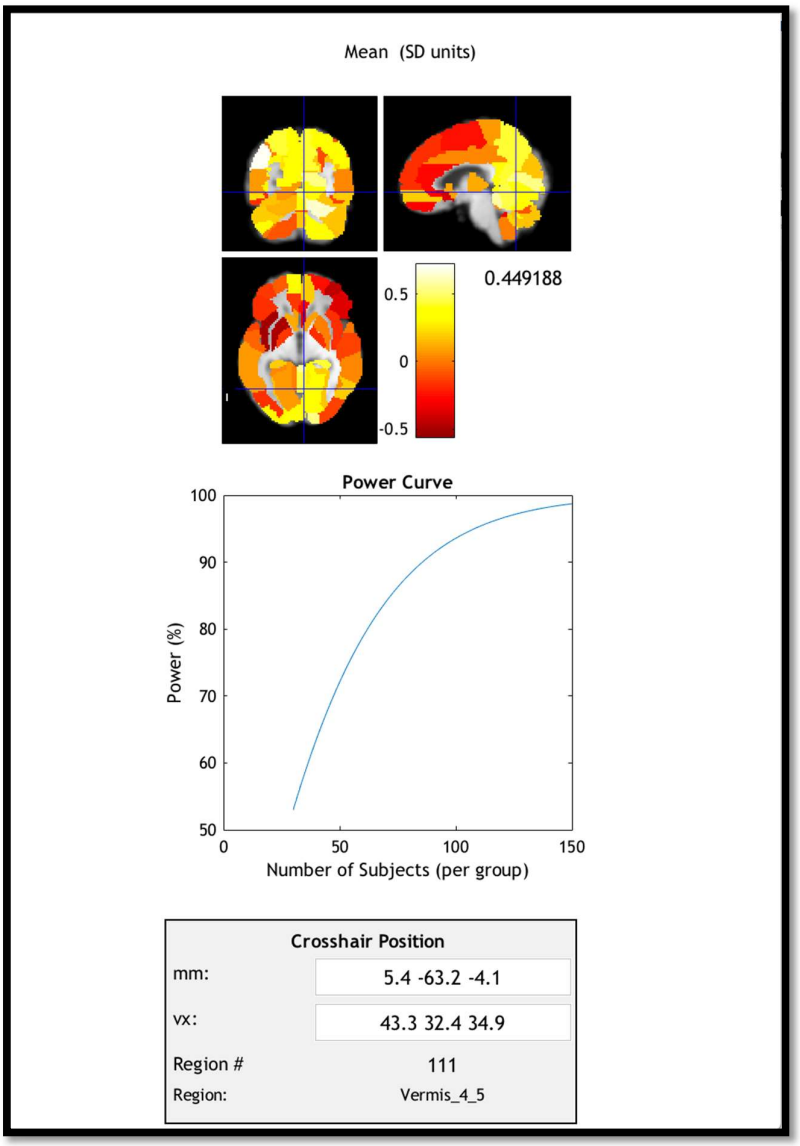
The results of the sample size calculation showed that for the area of the left frontal orbitofrontal cortex, a sample size of approximately 130 subjects per group would provide 80% power with an effect size of 0.31 (Figure 6.12).

Figure 6.12 Power curve and sample size for the left orbitofrontal cortex



For the area of the vermis, our sample size calculation revealed that a sample size of 60 subjects per group is required to detect 80% power with an effect size of 0.45 (Figure 6.13).

Figure 6.13 Power curve and sample size calculation for the vermis



Finally, for the area of the cerebellum, our sample size calculation revealed that a sample size of approximately 130 subjects per group is required to detect 80% power with an effect size of 0.3. (Figures 6.14 and 6.15)

Figure 6.14 Power curve and sample size for the calculation for the left cerebellum

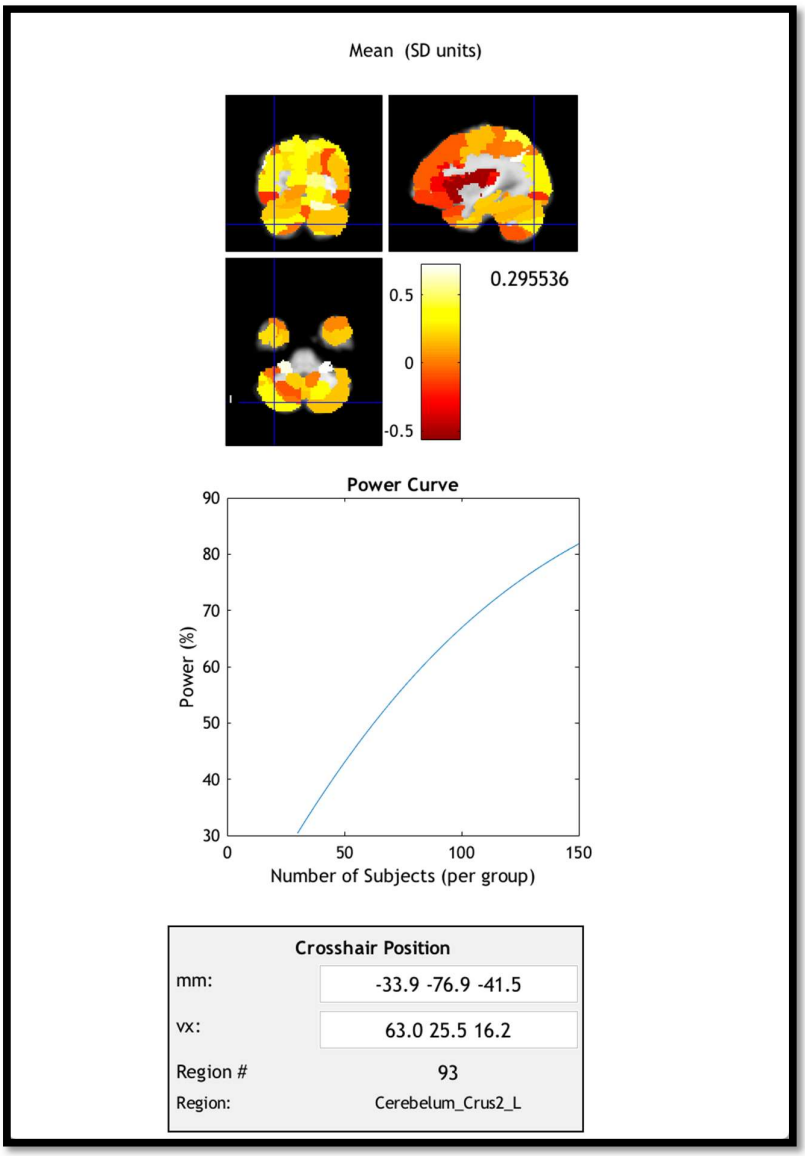
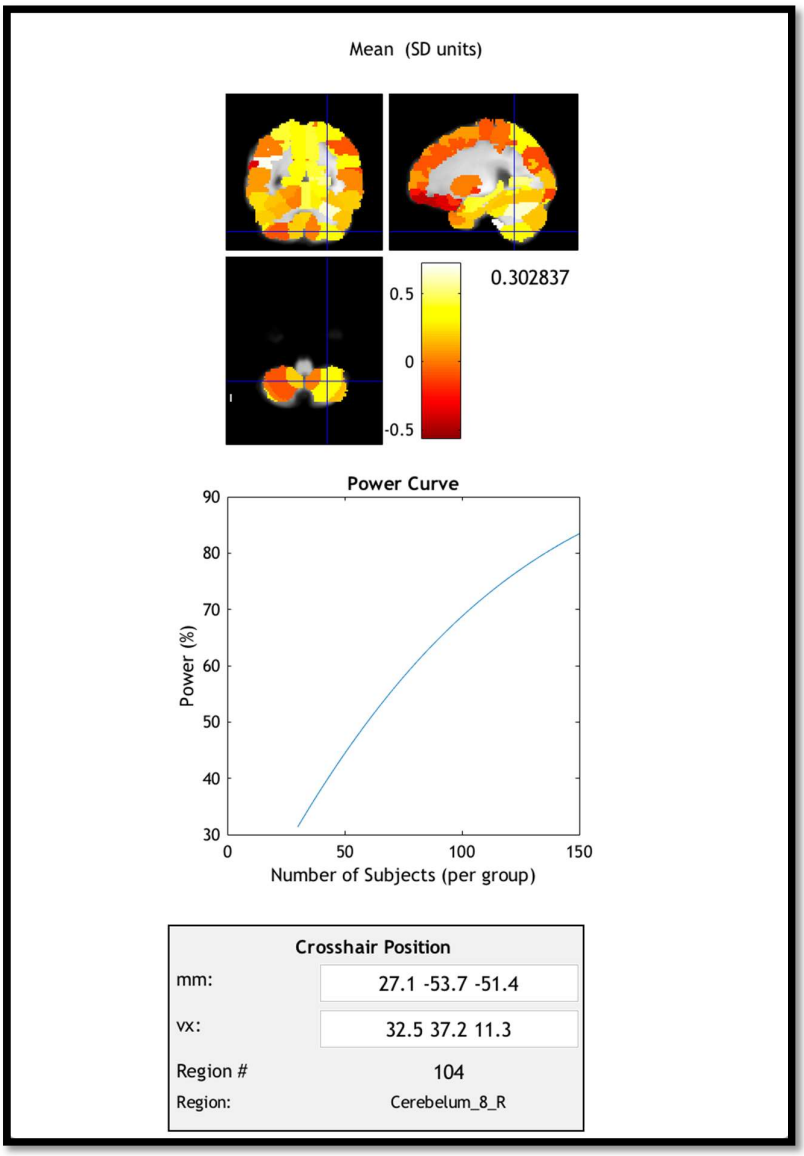


Figure 6.15 Power curve and sample size calculation for the right cerebellum.



6.4 Discussion

The most salient findings in this study can be summarized as follows:

1. Following 6 weeks of duloxetine, Parkinsons disease patients with pain had a trend towards a reduction in functional connectivity between the posterior cingulate cortex with the right cerebellum and the left inferior parietal lobe.

2. Parkinsons disease patients with pain on the placebo treatment arm did not show any difference in the activation of the default mode network at baseline and at study completion.

3. The sample size required for any future studies on Parkinsons disease patients with pain adopting the same methodological design would require at least 60 participants per group in order to achieve statistical power of 80%.

6.4.1 Functional connectivity changes

This experiment was primarily designed as a pilot study to determine the appropriate sample size of future functional MRI studies in Parkinsons disease patients with pain. Consequently, the statistical analysis of the functional MRI data was conducted at the traditional statistical cluster threshold level of $Z>2.3$, $p=0.05$; as well as at a more liberal statistical cluster threshold level of $Z>1.6$, $p=0.05$.

At the traditional statistical cluster threshold of $Z>2.3$, $p=0.05$, there were no difference in the functional connectivity of the default mode network in both treatment arms (duloxetine and placebo) between baseline and study completion functional brain MRI resting state scans.

At the liberal statistical cluster threshold of Z>1.6, p=0.05, no difference in the default mode network activation pattern were observed between baseline and study completion scans in the placebo group.

However, in the duloxetine group, the statistical brain maps showed differences in the activation patterns in the baseline>completion contrast.

6.4.1.1 Baseline>completion contrast in the duloxetine group

We found that there was a trend towards a reduction in functional connectivity between the default mode network with the right cerebellum, the left inferior parietal lobe and the right visual cortex following 6 weeks of duloxetine administration.

Studies have shown that beyond motoric functions, the cerebellum is heavily involved in pain processing. For example, studies in rats showed that pain stimulation induced changes in the posterior cerebellar vermis.(Saab & Willis, 2003) Numerous experiments have shown that electrical or chemical stimulation of the cerebellum influences the nociceptive responses in animals.(Dey & Ray, 1982; Saab & Willis, 2002; Siegel & Wepsic, 1974) Studies on patients with cerebellar infarction showed increased perception of evoked heat and pressure stimuli as compared to healthy subjects. (Ruscheweyh et al., 2014) In a meta-analysis looking at pain related activation of neuroimaging data, the cerebellum was found to have functional connectivity with areas traditionally involved in pain processing, including bilateral insula.(Duerden & Albanese, 2013) The cerebellum also has connections with areas of the brain in pain modulation, particularly the dorsolateral prefrontal cortex, periaquaductal grey and the rostral ventromedial medulla in the brainstem.(Mendlin, Martín, Rueter, & Jacobs, 1996; Middleton & Strick, 2001; Willis & Westlund, 1997)

Relevantly, a functional MRI study showed that fibromyalgia patients with high pain catastrophisation scores had increased activation of the cerebellum and other brain regions involved in the processing of the affective-evaluative

dimension of pain.(Gracely et al., 2004) The phenomenon of pain catastrophisation leads to increases in pain perception via rumination regarding pain, pessimism about health related outcomes and magnification of pain-related symptoms.(Edwards, Bingham III, Bathon, & Haythornthwaite, 2006) Our finding of a trend towards a reduction in the functional activity of the cerebellum with the default mode network following duloxetine raises the question of whether the action of duloxetine on chronic pain occurs via the attenuation of pain catastrophisation features.

Additionally, we also observed a trend towards a reduction in functional connectivity between the default mode network and the left inferior parietal lobe following 6 weeks of duloxetine. We found no studies pertaining to duloxetine and pain that implicate the function of the inferior parietal lobe. It is possible therefore that the changes observed may be attributable to another action separate from pain. Duloxetine, in addition to its action on chronic pain is also used for depression. The changes relating to the connectivity of the inferior parietal lobe may be implicating the action of duloxetine on mood and affect. Echoing this, a study on patients with major depressive disorder showed reduced connectivity of the default mode network with the inferior parietal lobe following duloxetine, although the authors in the paper gave no mechanistic explanation to why this is. (Wang et al., 2019a)

Similarly, we found no studies implicating the visual cortex in chronic pain. The closest relevant study relates to reduced phosphene levels in the visual cortex V5 following transcranial magnetic stimulation in migraine patients with aura.(Battelli, Black, & Wray, 2002)

6.4.2 Sample size calculation using fMRIpower

The primary aim of the experiment is to perform a pilot study in order to determine the sample size required for future studies on Parkinsons disease patients with pain using a 2 intervention arm framework.

A frequent criticisms directed towards functional MRI studies are the small sample sizes. This has important implications relating to issues of study replicability. The primary obstacle in embarking on fMRI studies with a large sample size is financial.

Conversely, an argument against too large a sample size also exists.(Friston, 2012) This is primarily due to the fact that an over-sampled study would cause a small treatment effect to result in a statistically significant result.

Studies have shown that a sample size of N=100 in a task based functional MRI study might still have issues relating to replicability.(Turner, Paul, Miller, & Barbey, 2018)

Steps have been taken to address this problem. Several techniques are now available to assist in the determination of an appropriate sample size in functional MRI studies. This includes the applications fMRIpower and neuropowertools.(Durnez et al., 2016; Mumford & Nichols, 2008)

Using the computer application fMRIpower, we found that for a future study adopting the same design methodology, a sample size of at least 60 participants per group would be required to provide a statistical power of 80%.

Comparatively, other fMRI studies have shown statistical significant responses with a much lower sample size number. This has several implications.

Firstly, the finding of our sample size calculation may represent a small treatment effect and the responses were relatively nuanced. Indeed, activation

responses following treatment of duloxetine were only detected when the statistical significance threshold was applied at the relatively liberal threshold of $z>1.6$, $p=0.05$.

In our pilot study, we performed a resting state whole brain connectivity analysis with the posterior cingulate cortex as the seed. The sample size calculation was performed with the thinking that any future study would adopt the same methodological approach. Our finding of a large sample size might suggest that performing a resting state whole brain connectivity analysis may not be the most efficient way in detecting treatment effects following duloxetine in Parkinsons disease patients with pain.

The fMRIpower computer application performs power calculations based on pre-specified region of interest (ROI).(Mumford & Nichols, 2008) The relatively large sample size calculation may relate to the selection of region of interest (ROI) as we adopted an unbiased whole brain ROI approach to perform power calculation on our pilot data. We hope this will result in a more appropriate estimation of the sample size required to detect the effects in functional MRI.(Mumford, 2012) We did not perform sample size calculation analysis with the ROI restricted to only the brain regions that showed activation response in the pilot data, specifically the right cerebellum, and the left inferior parietal lobe. Although this would potentially result in a smaller sample size estimation for a future fMRI study, this approach would have resulted in a bias due to an overestimation of the effect size driven by noise in the data.(Kriegeskorte, Simmons, Bellgowan, & Baker, 2009; Vul, Harris, Winkielman, & Pashler, 2009; Yarkoni, 2009)

6.5 Conclusion

Our study is a pilot study with a modest sample size. The main aim of the study was to test the feasibility, effect size and variability of treatment, and provide preliminary data for the design of a larger sample size study.

Furthermore, some analysis of functional MRI data was performed at a non-traditional statistical threshold and therefore our findings should be considered preliminary and inferences should be made with caution, especially relating to the functional connectivity analysis. Indeed, this study is not adequately powered to provide mechanistic explanations to the connectivity changes that were observed in our study.

Nevertheless, our finding of duloxetine being associated with changes in the functional activation patterns in areas of the brain that is known to have relevant function in chronic pain cannot be dismissed out of hand. We feel that our findings lend itself to the growing research on pain in Parkinsons disease in general, and the effects of duloxetine in particular.

Some of the functional connectivity changes observed in our study appears to be consistent with literature pertaining to the areas of the brain thought to be involved in pain processing, although research in this field shows conflicting results and the role of the default mode network in pain processing and the effects of duloxetine may be more complex.

Finally, sample size calculation using the fMRIpower software application may suggest that using resting state whole brain connectivity approach may be inefficient way to detect effects of treatment of duloxetine in Parkinsons disease patients with pain.

Chapter 7: Conclusion

Pain is an important determinant of poor quality of life in Parkinsons disease patients. Yet, the management of pain of Parkinsons disease has oftentimes been poorly executed. Factors contributing to this state of affairs include limitations in the effectiveness of medical therapy.

Duloxetine has gained prominence in the management of pain in a variety of chronic pain conditions. Recent research alludes to its possible use for pain in Parkinsons disease patients but compelling evidence to support this is currently limited.

This research aimed to answer the question whether duloxetine was effective in improving the symptoms of pain in Parkinsons disease patients. Further, we also wanted to determine whether duloxetine had any impact on pain sensitivity in Parkinsons disease patients. Finally, using functional imaging techniques, we wanted to explore how duloxetine affects pain processing.

Using clinical pain measures, psychophysical techniques and functional MRI procedures, this thesis has provided some insights into the gaps in knowledge listed above.

7.1 Key findings and implications

7.1.1 Clinical pain findings

In the clinical pain study, we demonstrated that duloxetine was associated with an improvement in pain symptoms that arose from the affective-motivational dimension of pain. Our findings in this study are important. There is ample evidence supporting the use of duloxetine in a variety of chronic pain conditions. Evidence for duloxetine in Parkinsons disease patients with pain has been less compelling and primarily derived from an open label study and various anecdotal evidence. Indeed, the recently published double blind placebo

controlled trial conducted by Iwaki et al resulted in a negative finding.(Iwaki et al., 2020)

Chronic pain is a multi-faceted and multi-dimensional sensory experience, and can be coloured by a multitude of factors such as attentional states and emotion. Furthermore, specific therapeutic interventions for pain may only modulate a particular dimension of pain.(Finnerup, Sindrup, & Jensen, 2010) Our positive findings relating to changes in affective pain symptoms highlights the importance of careful selection of appropriate outcome measures to ensure that it corresponds to the purported pain dimension being investigated.(Attall et al., 2011)

The findings of this study pose significant clinical implications as it provides the evidence of the efficacy of duloxetine in the management of pain in Parkinsons disease.

7.1.2 Pain sensitivity and task-based functional MRI findings

In this study, we found no statistically significant change in pain thresholds and pain tolerance following duloxetine in Parkinsons disease patients with pain. Additionally, the task-based functional MRI scan did not show any statistically significant difference in brain activation in Parkinsons disease patients with pain following either placebo or duloxetine treatment.

The body of literature relating to pain sensitivity changes in Parkinsons disease patients following drug intervention is severely limited. Our findings echo another study on Parkinsons disease patients with pain that showed no change in pain sensitivity following evoked heat stimuli.(Sung, Vijiaratnam, Chan, Farrell, & Evans, 2018)

Although not statistically significant, we detected an improving trend in the pain threshold of participants following duloxetine. This raises the question of whether duloxetine works by modulating the medial pain pathway that is

involved in the affective-motivational dimension of pain, considering that pain threshold is thought to represent the affective-motivational dimensional of pain.

7.1.3 Pilot resting-state functional scan study findings

In this study, we demonstrated using a relatively liberal statistical threshold that there was an increase in functional connectivity between the default mode network with the insula and the prefrontal cortex in Parkinsons disease patients with pain following duloxetine administration.

The prefrontal cortex and the insula are important constituents of the medial pain pathway responsible for the processing of the affective-motivational dimension of pain.(Ong, Stohler, & Herr, 2019) The resting state scan study was designed as a pilot study and therefore it is difficult to assume generalizability in the general population. Nevertheless, the finding of increased connectivity between the default mode network and regions of the brain involved in affective pain processing provides food for thought.

Finally, the fMRI sample size calculation using fMRIpower software application using our pilot data suggests that using default mode network connectivity may be an inefficient way to measure the effect of duloxetine in Parkinsons disease patients as it involves very subtle changes in connectivity patterns.

7.2 Strengths and weaknesses

We adopted a double blind placebo controlled framework to answer the question regarding the effectiveness of duloxetine in managing symptoms of Parkinsons disease. Thus, the findings from our study can be considered to be more robust as compared to research performed in an open labelled design and case reports.

Although some authorities in the field may consider that the duration of study of 6 weeks to be too brief, previous studies investigating drug effect in studies relating to depression and chronic pain have also adopted the same study duration.

In clinical practice, the prescription of a drug for symptomatic relief i.e. chronic pain usually is of the duration of 1 month to 6 weeks before deeming it to be ineffective. Thus, our decision to adopt the study duration of 6 weeks has real-world applicability.

The advantage of having a short study duration is that it allows the participants to be on the same medication regime from beginning until the end of the study, with no new medication introduced or dosage varied midway. This is one of the strengths of our study as it reduces confounding factors in our study and provides more robust findings on the effectiveness of duloxetine in managing pain symptoms.

A common weakness afflicting all the studies conducted for this thesis is the small sample size. In addition to the reasons detailed in Chapter 4, another factor that may have contributed to the poor recruitment of participants may lie in the study design. The studies that were conducted were designed to minimize the number of study visits for the various outcome measures that included interviews for the clinical pain study, psychophysical procedures for the pain sensitivity study, and imaging for the functional MRI study. This was done due to the limited study funding and personnel to conduct the study visits. Consequently, this resulted in an increase in the time duration to approximately 3 hours for each visit. Parkinsons disease patients with pain can be frail. It is unknown whether this may be a factor in their reluctance to participate as they might feel unable to commit to a study with such an intensive and taxing requirements on their time.

Hopefully, the findings from our study would be able to guide in the design of any future studies to allow more streamlined and targeted research questions with shorter study visit duration.

7.3 Future directions

The studies conducted, as part of the thesis, were not designed to provide a mechanistic explanation for our findings. Nevertheless, some important insights were gained from all the conducted studies. Foremost is the seemingly prominent role of the medial pain pathway, and by extension the affective dimension of pain, with regards to the action of duloxetine for pain in Parkinsons disease.

From the clinical pain study, findings relating to changes in affective pain symptoms should be explored further. This includes performing multi-center trials with a bigger sample size to confirm our findings. Additionally, the role of affective pain in the mechanism of duloxetine should be further clarified. This may come in the form of studies with other outcome measures that can capture changes in the affective pain dimension. Indeed, the question whether the Short-Form McGill Questionnaire is an adequate tool to interrogate the affective dimension of pain in Parkinsons disease needs to be addressed. Pain in Parkinsons disease is complex and a disease-specific pain questionnaire have been developed to reflect this complexity.(Chaudhuri et al., 2015) Given the seemingly important role of the medial pain pathway, the question whether currently available pain questionnaires are able to adequately capture changes in affective pain in Parkinsons disease patients needs to be investigated further.

Another insight from the clinical pain study relates to the purported analgesic effect of duloxetine. Duloxetine is an anti-depressant and its analgesic properties in chronic pain conditions have always been confounded by the alleviation of depressive symptoms and improvement in mood. This is not surprising as the symptoms of pain and depression can co-exist and are inextricably linked.(Von Korff & Simon, 1996) We were unable to draw any conclusion as to whether the analgesic action of duloxetine is independent of its anti-depressant action due to the small sample size. Furthermore, the study duration of 6 weeks can be considered too brief to observe any changes in the depression score.(Machado-Vieira et al., 2010) Further studies with a bigger sample size and with a longer

study duration are needed to confidently answer the question whether improvement in pain symptoms following duloxetine is independent from the changes in mood and affect exerted by the anti-depressant properties of duloxetine.

Further insights on the role of the medial pain pathway were gained from the pain sensitivity study and imaging findings. Although functional MRI confer many advantages over other imaging techniques, criticisms against this method of imaging relates to its low signal to noise ratio.(Logothetis, 2008) Furthermore, this imaging technique is an indirect measure of underlying neuronal activity as it relies on the BOLD signal to detect changes. Further clarification on the role of the medial pain pathway should be performed using more direct imaging methods. For example, PET scan using radio-ligand that assess differences in noradrenaline receptor availability in the brain in Parkinsons disease patients following duloxetine may be a potential approach for future studies to determine the specific regions of the pain matrix that are involved in the modulation of pain.(Sekine et al., 2010; Suhara et al., 2003)

Finally, the importance of a genetic predisposition to pain may explain the various conflicting results in the literature with regards to pain in Parkinsons disease. Specifically, noradrenergic and serotonergic receptor pleomorphisms may play a role in the response to duloxetine in Parkinsons disease patient with pain.(Liu, Zhao, Fan, & Guo, 2019) Going forward, this differential response to duloxetine i.e. responder vs non-responder should be investigated further by performing genetic studies and imaging. Similar work has been done in depressive patients following milnacipran, another serotonin noradrenaline reuptake inhibitor.(Jensen et al., 2014)

7.4 Concluding remarks

The overarching theme of this thesis is the modulation of pain in Parkinsons disease patients.

Our thesis suggests that duloxetine is effective in the management of pain in Parkinsons disease patients. Furthermore, it is possible that this analgesic effect of duloxetine is achieved by modulation of nociceptive signals in the central nervous system.

Previous authorities in the field have suggested that the effect of duloxetine is centred on the brainstem region comprising of the PAG, locus coeruleus and raphe nuclei. From this thesis, our finding on the clinical pain, pain sensitivity and resting state scan appears to suggest that the action of duloxetine may be acting on higher regions of the brain, specifically in areas involved in emotion, mood and affective pain. Further studies are required to confirm our findings.

REFERENCES

Afsharpour, S. (1985). Topographical projections of the cerebral cortex to the subthalamic nucleus. *Journal of Comparative Neurology, 236*(1), 14-28.

Ahlskog, J. E. (2007). Beating a dead horse: dopamine and Parkinson disease. *Neurology, 69*(17), 1701-1711.

Alev, L., Fujikoshi, S., Yoshikawa, A., Enomoto, H., Ishida, M., Tsuji, T., . . . Konno, S. (2017). Duloxetine 60 mg for chronic low back pain: post hoc responder analysis of double-blind, placebo-controlled trials. *Journal of Pain Research, 10*, 1723.

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in Neurosciences, 13*(7), 266-271.

Alexander, G. E., Crutcher, M. D., & DeLong, M. R. (1991). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor,"prefrontal" and "limbic" functions *Progress in Brain Research* (Vol. 85, pp. 119-146): Elsevier.

Allen, N. E., Moloney, N., van Vliet, V., & Canning, C. G. (2015). The Rationale for Exercise in the Management of Pain in Parkinson's Disease. *Journal of Parkinson's Disease*, *5*(2), 229-239.

Allen, N. E., Wong, C. M., Canning, C. G., & Moloney, N. (2016). The association between Parkinson's disease motor impairments and pain. *Pain Medicine, 17*(3), 456-462.

An, J., Le Li, L. W., Su, Y.-A., Wang, Y., Li, K., Zeng, Y., . . . Si, T. (2019). Striatal functional connectivity alterations after two-week antidepressant treatment associated to enduring clinical improvement in major depressive disorder. *Frontiers in Psychiatry, 10*.

Apkarian, A. V., Baliki, M. N., & Geha, P. Y. (2009). Towards a theory of chronic pain. *Progress in Neurobiology, 87*(2), 81-97.

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain, 9*(4), 463-463.

Apkarian, A. V., Sosa, Y., Sonty, S., Levy, R. M., Harden, R. N., Parrish, T. B., & Gitelman, D. R. (2004). Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *Journal of Neuroscience, 24*(46), 10410-10415.

Arendt-Nielsen, L., Brennum, J., Sindrup, S., & Bak, P. (1994). Electrophysiological and psychophysical quantification of temporal summation in the human nociceptive system. *European Journal of Applied Physiology and Occupational Physiology, 68*(3), 266-273.

Argoff, C. (2011). Mechanisms of pain transmission and pharmacologic management. *Current Medical Research and Opinion, 27*(10), 2019-2031.

Arnold, L. M., Lu, Y., Crofford, L. J., Wohlreich, M., Detke, M. J., Iyengar, S., & Goldstein, D. J. (2004). A double‐blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis & Rheumatism, 50*(9), 2974-2984.

Arnold, L. M., Rosen, A., Pritchett, Y. L., D'Souza, D. N., Goldstein, D. J., Iyengar, S., & Wernicke, J. F. (2005). A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain, 119*(1), 5-15.

Ashour, R., & Jankovic, J. (2006). Joint and skeletal deformities in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Movement Disorders, 21*(11), 1856-1863.

Askenasy, J.-J. (2001). Approaching disturbed sleep in late Parkinson's disease: first step toward a proposal for a revised UPDRS. *Parkinsonism & Related Disorders, 8*(2), 123-131.

Attal, N., Cruccu, G., Haanpää, M., Hansson, P., Jensen, T. S., Nurmikko, T., . . . Wiffen, P. (2006). EFNS guidelines on pharmacological treatment of neuropathic pain. *European Journal of Neurology, 13*(11), 1153-1169.

Attall, N., Bouhassira, D., Baron, R., Dostrovsky, J., Dworkin, R. H., Finnerup, N., . . . Rice, A. S. (2011). Assessing symptom profiles in neuropathic pain clinical trials: can it improve outcome? *European Journal of Pain, 15*(5), 441-443.

Baerwald, C., Laufenberg, M., Specht, T., Von Wichert, P., Burmester, G., & Krause, A. (1997). Impaired sympathetic influence on the immune response in patients with rheumatoid arthritis due to lymphocyte subset-specific modulation of beta 2-adrenergic receptors. *British Journal of Rheumatology, 36*(12), 1262-1269.

Baird, C. L., Murawski, M. M., & Wu, J. (2010). Efficacy of guided imagery with relaxation for osteoarthritis symptoms and medication intake. *Pain Management Nursing, 11*(1), 56-65.

Bajic, D., & Proudfit, H. K. (1999). Projections of neurons in the periaqueductal gray to pontine and medullary catecholamine cell groups involved in the modulation of nociception. *Journal of Comparative Neurology, 405*(3), 359-379.

Baliki, M. N., Geha, P. Y., Apkarian, A. V., & Chialvo, D. R. (2008). Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *The Journal of Neuroscience, 28*(6), 1398-1403.

Ballanger, B., Klinger, H., Eche, J., Lerond, J., Vallet, A. E., Le Bars, D., . . . Thobois, S. (2012). Role of serotonergic 1A receptor dysfunction in depression associated with Parkinson's disease. *Movement Disorders, 27*(1), 84-89.

Bandler, R., & Keay, K. A. (1996). Columnar organization in the midbrain periaqueductal gray and the integration of emotional expression *Progress in Brain Research* (Vol. 107, pp. 285-300): Elsevier.

Barbas, H., Saha, S., Rempel-Clower, N., & Ghashghaei, T. (2003). Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. *BMC Neuroscience, 4*(1), 25.

Barbic, F., Perego, F., Canesi, M., Gianni, M., Biagiotti, S., Costantino, G., . . . Furlan, R. (2007). Early abnormalities of vascular and cardiac autonomic control in Parkinson's disease without orthostatic hypotension. *Hypertension, 49*(1), 120-126.

Barili, P., De Carolis, G., Zaccheo, D., & Amenta, F. (1998). Sensitivity to ageing of the limbic dopaminergic system: a review. *Mechanisms of Ageing and Development, 106*(1-2), 57-92.

Baron, M. S., Vitek, J. L., Green, J., Kaneoke, Y., Hashimoto, T., Turner, R. S., . . . Cole, S. A. (1996). Treatment of advanced Parkinson's disease by posterior GPi

pallidotomy: 1-year results of a pilot study. *Annals of Neurology, 40*(3), 355-366.
Barone, P. (2010). Neurotransmission in Parkinson's disease: beyond dopamine. *European Journal of Neurology, 17*(3), 364-376.
Barone, P., Antonini, A., Colosimo, C., Marconi, R., Morgante, L., Avarello, T. P., . . . Ceravolo, R. (2009). The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Movement Disorders, 24*(11), 1641-1649.
Barone, P., Poewe, W., Albrecht, S., Debieuvre, C., Massey, D., Rascol, O., . . . Weintraub, D. (2010). Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *The Lancet Neurology, 9*(6), 573-580.
Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. *Cell, 139*(2), 267-284.
Baskin, D. S., Mehler, W. R., Hosobuchi, Y., Richardson, D. E., Adams, J. E., & Flitter, M. A. (1986). Autopsy analysis of the safety, efficacy and cartography of electrical stimulation of the central gray in humans. *Brain Research, 371*(2), 231-236.
Battelli, L., Black, K. R., & Wray, S. H. (2002). Transcranial magnetic stimulation of visual area V5 in migraine. *Neurology, 58*(7), 1066-1069.
Becerra, L., Morris, S., Bazes, S., Gostic, R., Sherman, S., Gostic, J., . . . Keith, D. (2006). Trigeminal neuropathic pain alters responses in CNS circuits to mechanical (brush) and thermal (cold and heat) stimuli. *Journal of Neuroscience, 26*(42), 10646-10657.
Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2003). General multilevel linear modeling for group analysis in FMRI. *Neuroimage, 20*(2), 1052-1063.
Beecher, H. K. (1946). Pain in men wounded in battle. *Annals of Surgery, 123*(1), 96.
Beiske, A. G., Loge, J. H., Rønningen, A., & Svensson, E. (2009). Pain in Parkinson's disease: Prevalence and characteristics. *Pain, 141*(1), 173-177.
Bellingham, G. A., & Peng, P. W. (2010). Duloxetine: a review of its pharmacology and use in chronic pain management. *Regional Anesthesia & Pain Medicine, 35*(3), 294-303-294-303.
Benarroch, E. E. (2008). Descending monoaminergic pain modulation: bidirectional control and clinical relevance. *Neurology, 71*(3), 217-221.
Benedetti, F., Vighetti, S., Ricco, C., Lagna, E., Bergamasco, B., Pinessi, L., & Rainero, I. (1999). Pain threshold and tolerance in Alzheimer's disease. *Pain, 80*(1-2), 377-382.
Bennett, M. (2001). The LANSS Pain Scale: the Leeds assessment of neuropathic symptoms and signs. *Pain, 92*(1-2), 147-157.
Bernard, J., Huang, G., & Besson, J. (1992). Nucleus centralis of the amygdala and the globus pallidus ventralis: electrophysiological evidence for an involvement in pain processes. *Journal of Neurophysiology, 68*(2), 551-569.
Bhattacharjee, S., Talbot, J., & Vijayashankar, P. (2017). Dopamine D3 receptor Ser9Gly variant is associated with impulse control disorders in Parkinson's disease patients. *Parkinsonism & Related Disorders, 34*, 69-70.
Bingel, U., & Tracey, I. (2008). Imaging CNS modulation of pain in humans. *Physiology, 23*(6), 371-380.

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo‐planar MRI. *Magnetic Resonance in Medicine, 34*(4), 537-541.

Bleakman, D., Alt, A., & Nisenbaum, E. S. (2006). *Glutamate receptors and pain.* Paper presented at the Seminars in cell & Developmental Biology.

Boecker, H., Ceballos-Baumann, A., Bartenstein, P., Weindl, A., Siebner, H., Fassbender, T., . . . Conrad, B. (1999). Sensory processing in Parkinson's and Huntington's disease: Investigations with 3D H215O-PET. *Brain, 122*(9), 1651-1665.

Boileau, I., Warsh, J. J., Guttman, M., Saint‐Cyr, J. A., McCluskey, T., Rusjan, P., . . . Kish, S. J. (2008). Elevated serotonin transporter binding in depressed patients with Parkinson's disease: a preliminary PET study with [11C] DASB. *Movement Disorders, 23*(12), 1776-1780.

Bonnet, A.-M. (2000). Involvement of non-dopaminergic pathways in Parkinson's disease. *CNS Drugs, 13*(5), 351-364.

Boonstra, A. M., Preuper, H. R. S., Balk, G. A., & Stewart, R. E. (2014). Cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. *Pain, 155*(12), 2545-2550.

Bouhassira, D., Attal, N., Alchaar, H., Boureau, F., Brochet, B., Bruxelle, J., . . . Grun-Overdyking, A. (2005). Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain, 114*(1-2), 29-36.

Braak, H., Braak, E., Yilmazer, D., de Vos, R. A., Jansen, E. N., Bohl, J., & Jellinger, K. (1994). Amygdala pathology in Parkinson's disease. *Acta Neuropathologica, 88*(6), 493-500.

Braak, H., Braak, E., Yilmazer, D., Schultz, C., & Jansen, E. (1995). Nigral and extranigral pathology in Parkinson's disease. *Journal of Neural Transmission. Supplementum, 46*, 15-31.

Braak, H., Del Tredici, K., Rüb, U., de Vos, R. A., Steur, E. N. J., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of Aging, 24*(2), 197-211.

Braak, H., Sastre, M., Bohl, J. R., de Vos, R. A., & Del Tredici, K. (2007). Parkinson's disease: lesions in dorsal horn layer I, involvement of parasympathetic and sympathetic pre-and postganglionic neurons. *Acta Neuropathologica, 113*(4), 421-429.

Braz, J. M., Nassar, M. A., Wood, J. N., & Basbaum, A. I. (2005). Parallel "pain" pathways arise from subpopulations of primary afferent nociceptor. *Neuron, 47*(6), 787-793.

Brefel-Courbon, C., Grolleau, S., Thalamas, C., Bourrel, R., Allaria-Lapierre, V., Loï, R., . . . Lapeyre-Mestre, M. (2009). Comparison of chronic analgesic drugs prevalence in Parkinson's disease, other chronic diseases and the general population. *Pain, 141*(1), 14-18.

Brefel-Courbon, C., Ory-Magne, F., Thalamas, C., Payoux, P., & Rascol, O. (2013). Nociceptive brain activation in patients with neuropathic pain related to Parkinson's disease. *Parkinsonism & Related Disorders, 19*(5), 548-552.

Brefel-Courbon, C., Payoux, P., Thalamas, C., Ory, F., Quelven, I., Chollet, F., . . . Rascol, O. (2005). Effect of levodopa on pain threshold in Parkinson's

disease: a clinical and positron emission tomography study. *Movement Disorders, 20*(12), 1557-1563.

Broetz, D., Eichner, M., Gasser, T., Weller, M., & Steinbach, J. P. (2007). Radicular and nonradicular back pain in Parkinson's disease: a controlled study. *Movement Disorders, 22*(6), 853-856.

Buckner, R. L., Andrews‐Hanna, J. R., & Schacter, D. L. (2008). The brain's default network. *Annals of the New York Academy of Sciences, 1124*(1), 1-38.

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., . . . Morris, J. C. (2005). Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *Journal of Neuroscience, 25*(34), 7709-7717.

Budai, D., Harasawa, I., & Fields, H. L. (1998). Midbrain periaqueductal gray (PAG) inhibits nociceptive inputs to sacral dorsal horn nociceptive neurons through α2-adrenergic receptors. *Journal of Neurophysiology, 80*(5), 2244-2254.

Button, K. S., Ioannidis, J. P., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S., & Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience, 14*(5), 365-376.

Bunge, S. A., Ochsner, K. N., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (2001). Prefrontal regions involved in keeping information in and out of mind. *Brain, 124*(10), 2074-2086.

Carpenter, M. B., Nakano, K., & Kim, R. (1976). Nigrothalamic projections in the monkey demonstrated by autoradiographic technics. *Journal of Comparative Neurology, 165*(4), 401-415.

Cauda, F., Sacco, K., Duca, S., Cocito, D., D'Agata, F., Geminiani, G. C., & Canavero, S. (2009). Altered resting state in diabetic neuropathic pain. *PLoS One, 4*(2), e4542.

Cavalieri, T. A. (2005). Management of pain in older adults. *The Journal of the American Osteopathic Association, 105*(3_suppl), 12S-17S.

Chappell, A. S., Desaiah, D., Liu-Seifert, H., Zhang, S., Skljarevski, V., Belenkov, Y., & Brown, J. P. (2011). A Double-blind, Randomized, Placebo-controlled Study of the Efficacy and Safety of Duloxetine for the Treatment of Chronic Pain Due to Osteoarthritis of the Knee. *Pain Practice, 11*(1), 33-41

Chappell, A. S., Ossanna, M. J., Liu-Seifert, H., Iyengar, S., Skljarevski, V., Li, L. C., . . . Collins, H. (2009). Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain, 146*(3), 253-260.

Chaudhuri, K. R., Rizos, A., Trenkwalder, C., Rascol, O., Pal, S., Martino, D., . . . Kessel, B. (2015). King's Parkinson's disease pain scale, the first scale for pain in PD: an international validation. *Movement Disorders, 30*(12), 1623-1631.

Chaudhuri, K. R., & Schapira, A. H. (2009). Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *The Lancet Neurology, 8*(5), 464-474.

Chen, A. C., Niddam, D. M., & Arendt-Nielsen, L. (2001). Contact heat evoked potentials as a valid means to study nociceptive pathways in human subjects. *Neuroscience Letters, 316*(2), 79-82.

Chen, J. (2011). History of pain theories. *Neuroscience bulletin, 27*(5), 343.

Cherkassky, V. L., Kana, R. K., Keller, T. A., & Just, M. A. (2006). Functional connectivity in a baseline resting-state network in autism. *Neuroreport, 17*(16), 1687-1690.

Choi, S.-M., Kim, B. C., Jung, H.-J., Yoon, G.-J., Kang, K. W., Choi, K.-H., . . . Kim, M.-K. (2017). Impact of pain and pain subtypes on the quality of life of patients with Parkinson's disease. *Journal of Clinical Neuroscience, 45*, 105-109.

Chou, R., Turner, J. A., Devine, E. B., Hansen, R. N., Sullivan, S. D., Blazina, I., . . . Deyo, R. A. (2015). The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of Internal Medicine, 162*(4), 276-286.

Chudler, E. H. (1998). Response properties of neurons in the caudate–putamen and globus pallidus to noxious and non-noxious thermal stimulation in anesthetized rats. *Brain Research, 812*(1-2), 283-288.

Chudler, E. H., & Lu, Y. (2008). Nociceptive behavioral responses to chemical, thermal and mechanical stimulation after unilateral, intrastriatal administration of 6-hydroxydopamine. *Brain Research, 1213*, 41-47.

Chudler, E. H., Sugiyama, K., & Dong, W. K. (1995). Multisensory convergence and integration in the neostriatum and globus pallidus of the rat. *Brain Research, 674*(1), 33-45.

Clark, A. (2013). Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behavioral and Brain Sciences, 36*(3), 181-204.

Cleeland, C., & Ryan, K. (1994). Pain assessment: global use of the Brief Pain Inventory. *Annals, Academy of Medicine, Singapore*.

Coffeen, U., López‐Avila, A., Ortega‐Legaspi, J. M., Del Ángel, R., López‐Muñoz, F. J., & Pellicer, F. (2008). Dopamine receptors in the anterior insular cortex modulate long‐term nociception in the rat. *European Journal of Pain, 12*(5), 535-543.

Colder, B. (2011). Emulation as an integrating principle for cognition. *Frontiers in Human Neuroscience, 5*, 54.

Colder, B. (2015). The basal ganglia select the expected sensory input used for predictive coding. *Frontiers in Computational Neuroscience, 9*, 119.

Cole, L. J., Farrell, M. J., Duff, E. P., Barber, J. B., Egan, G. F., & Gibson, S. J. (2006). Pain sensitivity and fMRI pain-related brain activity in Alzheimer's disease. *Brain, 129*(11), 2957-2965.

Collins, S. L., Moore, R. A., & McQuay, H. J. (1997). The visual analogue pain intensity scale: what is moderate pain in millimetres? *Pain, 72*(1-2), 95-97.

Conn, P. J., Battaglia, G., Marino, M. J., & Nicoletti, F. (2005). Metabotropic glutamate receptors in the basal ganglia motor circuit. *Nature Reviews Neuroscience, 6*(10), 787.

Conte, A., Khan, N., Defazio, G., Rothwell, J. C., & Berardelli, A. (2013). Pathophysiology of somatosensory abnormalities in Parkinson disease. *Nature Reviews Neurology, 9*(12), 687.

Conturo, T. E., Lori, N. F., Cull, T. S., Akbudak, E., Snyder, A. Z., Shimony, J. S., . . . Raichle, M. E. (1999). Tracking neuronal fiber pathways in the living human brain. *Proceedings of the National Academy of Sciences, 96*(18), 10422-10427.

Costigan, M., & Woolf, C. J. (2000). Pain: molecular mechanisms. *The Journal of Pain, 1*(3), 35-44.

Craig, A. (1995). Distribution of brainstem projections from spinal lamina I neurons in the cat and the monkey. *Journal of Comparative Neurology, 361*(2), 225-248.

Dang, Y., Zhao, Y., Xing, B., Zhao, X., Huo, F., Tang, J., . . . Chen, T. (2010). The role of dopamine receptors in ventrolateral orbital cortex-evoked anti-nociception in a rat model of neuropathic pain. *Neuroscience, 169*(4), 1872-1880.

de la Cruz Pérez, S. (2017). Effectiveness of aquatic therapy for the control of pain and increased functionality in people with Parkinson's disease: a randomized clinical trial. *European Journal of Physical and Rehabilitation Medicine, 53*(6), 825-832.

de Lau, L. M. L., & Breteler, M. M. B. (2006). Epidemiology of Parkinson's disease. *The Lancet Neurology, 5*(6), 525-535. doi:https://doi.org/10.1016/S1474-4422(06)70471-9

Defazio, G., Berardelli, A., Fabbrini, G., Martino, D., Fincati, E., Fiaschi, A., . . . Tinazzi, M. (2008). Pain as a nonmotor symptom of Parkinson disease: evidence from a case-control study. *Arch Neurol, 65*(9), 1191-1194.

Defazio, G., Gigante, A., Mancino, P., & Tinazzi, M. (2013). The epidemiology of pain in Parkinson's disease. *Journal of Neural Transmission, 120*(4), 583-586.

Del Sorbo, F., & Albanese, A. (2012). Clinical management of pain and fatigue in Parkinson's disease. *Parkinsonism & Related Disorders, 18*, S233-S236.

Delaveau, P., Salgado-Pineda, P., Fossati, P., Witjas, T., Azulay, J.-P., & Blin, O. (2010). Dopaminergic modulation of the default mode network in Parkinson's disease. *European Neuropsychopharmacology, 20*(11), 784-792.

Dellapina, E., Gerdelat‐Mas, A., Ory‐Magne, F., Pourcel, L., Galitzky, M., Calvas, F.,….Brefel-Courbon, C. (2011). Apomorphine effect on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Movement Disorders, 26*(1), 153-157.

Dellapina, E., Pellaprat, J., Adel, D., Llido, J., Harroch, E., Martini, J. B., . . . Payoux, P. (2019). Dopaminergic denervation using [123 I]-FPCIT and pain in Parkinson's disease: a correlation study. *Journal of Neural Transmission, 126*(3), 279-287.

Deloitte (2015). Living with Parkinson's disease. *An Updated Economic Analysis 2014. Canberra: Parkinsons Australia Inc., Deloitte Access Economics.*

DeLong, M. R. (1990). Primate models of movement disorders of basal ganglia origin. *Trends in Neurosciences, 13*(7), 281-285.

Dey, P., & Ray, A. (1982). Anterior cerebellum as a site for morphine analgesia and post-stimulation analgesia. *Indian J Physiol Pharmacol, 26*(1), 3-12.

Djaldetti, R., Shifrin, A., Rogowski, Z., Sprecher, E., Melamed, E., & Yarnitsky, D. (2004). Quantitative measurement of pain sensation in patients with Parkinson disease. *Neurology, 62*(12), 2171-2175.

Djaldetti, R., Yust-Katz, S., Kolianov, V., Melamed, E., & Dabby, R. (2007). The effect of duloxetine on primary pain symptoms in Parkinson disease. *Clinical Neuropharmacology, 30*(4), 201-205.

Doder, M., Rabiner, E., Turjanski, N., Lees, A., & Brooks, D. (2000). Brain serotonin 5HT1A receptors in Parkinson's disease with and without depression measured by positron emission tomography with 11C-WAY 10635. *Movement Disorders, 15*(Suppl 3), 213.

Donoyama, N., & Ohkoshi, N. (2012). Effects of traditional Japanese massage therapy on various symptoms in patients with Parkinson's disease: a case-series study. *The Journal of Alternative and Complementary Medicine, 18*(3), 294-299.

Dorsey, E., Sherer, T., Okun, M. S., & Bloem, B. R. (2018). The emerging evidence of the Parkinson pandemic. *Journal of Parkinson's Disease, 8*(s1), S3-S8.

Draganski, B., Kherif, F., Klöppel, S., Cook, P. A., Alexander, D. C., Parker, G. J., . . . Frackowiak, R. S. (2008). Evidence for segregated and integrative connectivity patterns in the human basal ganglia. *Journal of Neuroscience, 28*(28), 7143-7152.

Duerden, E. G., & Albanese, M. C. (2013). Localisation of pain related brain activation: A meta-analysis of neuroimaging data. *Human Brain Mapping, 34*(1), 109-149.

Durnez, J., Degryse, J., Moerkerke, B., Seurinck, R., Sochat, V., Poldrack, R., & Nichols, T. (2016). Power and sample size calculations for fMRI studies based on the prevalence of active peaks. *BioRxiv*, 049429.

Edwards, R. R., Bingham III, C. O., Bathon, J., & Haythornthwaite, J. A. (2006). Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. *Arthritis Care & Research: Official Journal of the American College of Rheumatology, 55*(2), 325-332.

Ehrt, U., Larsen, J. P., & Aarsland, D. (2009). Pain and its relationship to depression in Parkinson disease. *The American Journal of Geriatric Psychiatry, 17*(4), 269-275.

Eippert, F., Finsterbusch, J., Bingel, U., & Büchel, C. (2009). Direct evidence for spinal cord involvement in placebo analgesia. *Science, 326*(5951), 404-404.

Engels, G., Weeda, W. D., Vlaar, A. M., Weinstein, H. C., & Scherder, E. J. (2016). Clinical Pain and Neuropsychological Functioning in Parkinson's Disease: Are They Related? *Parkinson's Disease, 2016*.

Ertas, M., Sagduyu, A., Arac, N., Uludag, B., & Ertekin, C. (1998). Use of levodopa to relieve pain from painful symmetrical diabetic polyneuropathy. *Pain, 75*(2-3), 257-259.

Factor, S. A., Brown, D. L., & Molho, E. S. (2000). Subcutaneous apomorphine injections as a treatment for intractable pain in Parkinson's disease. *Movement Disorders, 15*(1), 167-169.

Fahn, S., & Elton, R. (1987). UPDRS program members. Unified Parkinsons disease rating scale. *Recent Developments in Parkinson's disease, 2*, 153-163.

Fahn, S., Keiburtz, K., & Tanner, C. M. (2005). Levodopa and the Progression of Parkinson's Disease. *The New England Journal of Medicine, 352*(13), 1386.

Farrar, J. T., Young Jr, J. P., LaMoreaux, L., Werth, J. L., & Poole, R. M. (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain, 94*(2), 149-158

Fava, M. (2003). The role of the serotonergic and noradrenergic neurotransmitter systems in the treatment of psychological and physical symptoms of depression. *The Journal of Clinical Psychiatry*, *64*(13), 26-29.

Fertleman, C. R., Baker, M. D., Parker, K. A., Moffatt, S., Elmslie, F. V., Abrahamsen, B., . . . Gardiner, R. M. (2006). SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. *Neuron, 52*(5), 767-774.

Fields, H. (1999). Central nervous system mechanisms of pain modulation. *Textbook of pain*, Churchill Livingston Press.

Finnerup, N. B., Sindrup, S. H., & Jensen, T. S. (2010). The evidence for pharmacological treatment of neuropathic pain. *Pain, 150*(3), 573-581.

Fisher, B. E., Li, Q., Nacca, A., Salem, G. J., Song, J., Yip, J., . . . Petzinger, G. M. (2013). Treadmill exercise elevates striatal dopamine D2 receptor binding potential in patients with early Parkinson's disease. *Neuroreport, 24*(10), 509-514.

Fisher, B. E., Petzinger, G. M., Nixon, K., Hogg, E., Bremmer, S., Meshul, C. K., & Jakowec, M. W. (2004). Exercise induced behavioural recovery and neuroplasticity in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned mouse basal ganglia. *Journal of Neuroscience Research, 77*(3), 378-390.

Ford, B. (1998). Pain in Parkinson's disease. *Clinical Neuroscience, 5*(2), 63.

Ford, B. (2010). Pain in Parkinson's disease. *Movement Disorders, 25*(S1), S98-S103

Ford, B., Louis, E. D., Greene, P., & Fahn, S. (1996). Oral and genital pain syndromes in Parkinson's disease. *Movement Disorders, 11*(4), 421-426.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience, 8*(9), 700-711.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences, 102*(27), 9673-9678.

Fox, S. H., Katzenschlager, R., Lim, S. Y., Ravina, B., Seppi, K., Coelho, M., . . . Sampaio, C. (2011). The Movement Disorder Society evidence‐based medicine review update: treatments for the motor symptoms of Parkinson's disease. *Movement Disorders, 26*(S3), S2-S41.

Frankel, J., Lees, A., Kempster, P., & Stern, G. (1990). Subcutaneous apomorphine in the treatment of Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 53*(2), 96-101.

Fransen, M., Nairn, L., Winstanley, J., Lam, P., & Edmonds, J. (2007). Physical activity for osteoarthritis management: a randomized controlled clinical trial evaluating hydrotherapy or Tai Chi classes. *Arthritis Care & Research, 57*(3), 407-414.

Freynhagen, R., Baron, R., Gockel, U., & Tölle, T. R. (2006). Pain DETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Current Medical Research and Opinion, 22*(10), 1911-1920.

Friston, K. (2012). Ten ironic rules for non-statistical reviewers. *Neuroimage, 61*(4), 1300-1310.
Fu, C. H., Costafreda, S. G., Sankar, A., Adams, T. M., Rasenick, M. M., Liu, P., . . . Marangell, L. B. (2015). Multimodal functional and structural neuroimaging investigation of major depressive disorder following treatment with duloxetine. *BMC Psychiatry, 15*(1), 82.
Garpenstrand, H., Ekblom, J., Forslund, K., Rylander, G., & Oreland, L. (2000). Platelet monoamine oxidase activity is related to MAOB intron 13 genotype. *Journal of Neural Transmission, 107*(5), 523-530.
Garrity, A. G., Pearlson, G. D., McKiernan, K., Lloyd, D., Kiehl, K. A., & Calhoun, V. D. (2007). Aberrant "default mode" functional connectivity in schizophrenia. *American Journal of Psychiatry, 164*(3), 450-457.
Gerdelat-Mas, A., Simonetta-Moreau, M., Thalamas, C., Ory-Magne, F., Slaoui, T., Rascol, O., & Brefel-Courbon, C. (2007). Levodopa raises objective pain threshold in Parkinson's disease: a RIII reflex study. *Journal of Neurology, Neurosurgery & Psychiatry, 78*(10), 1140-1142.
Goldstein, D. J., Lu, Y., Detke, M. J., Lee, T. C., & Iyengar, S. (2005). Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain, 116*(1), 109-118.
Gostin, L. O., Hodge, J. G., & Noe, S. A. (2017). Reframing the opioid epidemic as a national emergency. *JAMA, 318*(16), 1539-1540.
Gracely, R. (1999). Pain measurement. *Acta Anaesthesiologica Scandinavica, 43*(9), 897-908.
Gracely, R., Geisser, M., Giesecke, T., Grant, M., Petzke, F., Williams, D., & Clauw, D. (2004). Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain, 127*(4), 835-843.
Gracely, R. H., Lota, L., Walter, D. J., & Dubner, R. (1988). A multiple random staircase method of psychophysical pain assessment. *Pain, 32*(1), 55-63.
Grafton, K. V., Foster, N. E., & Wright, C. C. (2005). Test-retest reliability of the Short-Form McGill Pain Questionnaire: assessment of intraclass correlation coefficients and limits of agreement in patients with osteoarthritis. *The Clinical Journal of Pain, 21*(1), 73-82.
Graven‐Nielsen, T., Jansson, Y., Segerdahl, M., Kristensen, J. D., Mense, S., Arendt‐Nielsen, L., & Sollevi, A. (2003). Experimental pain by ischaemic contractions compared with pain by intramuscular infusions of adenosine and hypertonic saline. *European Journal of Pain, 7*(1), 93-102.
Graybiel, A. M. (1984). Neurochemically specified subsystems in the basal ganglia *Functions of the basal ganglia* (Vol. 107, pp. 114-149): Wiley Online Library.
Green, C. R., Wheeler, J. R., LaPorte, F., Marchant, B., & Guerrero, E. (2002). How well is chronic pain managed? Who does it well? *Pain Medicine, 3*(1), 56-65.
Greenbaum, L., Tegeder, I., Barhum, Y., Melamed, E., Roditi, Y., & Djaldetti, R. (2012). Contribution of genetic variants to pain susceptibility in P arkinson disease. *European Journal of Pain, 16*(9), 1243-1250.
Grotle, M., Brox, J. I., & Vøllestad, N. K. (2004). Concurrent comparison of responsiveness in pain and functional status measurements used for patients with low back pain. *Spine, 29*(21), E492-E501.

Gupta, S., Nihalani, N., & Masand, P. (2007). Duloxetine: review of its pharmacology, and therapeutic use in depression and other psychiatric disorders. *Annals of Clinical Psychiatry, 19*(2), 125-132.
Gupta, Y., Chugh, A., & Seth, S. (1989). Opposing effect of apomorphine on antinociceptive activityfx of morphine: A dose-dependent phenomenon. *Pain, 36*(2), 263-269.
Gustin, S., Wrigley, P., Youssef, A., McIndoe, L., Wilcox, S., Rae, C., . . . Henderson, L. (2014). Thalamic activity and biochemical changes in individuals with neuropathic pain after spinal cord injury. *Pain, 155*(5), 1027-1036.
Gustin, S. M., Peck, C. C., Wilcox, S. L., Nash, P. G., Murray, G. M., & Henderson, L. A. (2011). Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes. *Journal of Neuroscience, 31*(16), 5956-5964.
Haber, S. N. (2003). The primate basal ganglia: parallel and integrative networks. *Journal of Chemical Neuroanatomy, 26*(4), 317-330.
Haber, S. N., Fudge, J. L., & McFarland, N. R. (2000). Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *Journal of Neuroscience, 20*(6), 2369-2382.
Hadjistavropoulos, T., & Craig, K. D. (2004). *Pain: psychological perspectives*: Psychology Press.
Hagelberg, N., Forssell, H., Aalto, S., Rinne, J. O., Scheinin, H., Taiminen, T., . . . Jääskeläinen, S. K. (2003). Altered dopamine D2 receptor binding in atypical facial pain. *Pain, 106*(1), 43-48.
Hagelberg, N., Jääskeläinen, S. K., Martikainen, I. K., Mansikka, H., Forssell, H., Scheinin, H., . . . Pertovaara, A. (2004). Striatal dopamine D2 receptors in modulation of pain in humans: a review. *European journal of Pharmacology, 500*(1), 187-192.
Hagell, P., & Brundin, L. (2009). Towards an understanding of fatigue in Parkinson disease. *Journal of Neurology, Neurosurgery & Psychiatry, 80*(5), 489-492.
Hamilton, J. P., & Gotlib, I. H. (2008). Neural substrates of increased memory sensitivity for negative stimuli in major depression. *Biological Psychiatry, 63*(12), 1155-1162.
Hämmerlein, A., Derendorf, H., & Lowenthal, D. T. (1998). Pharmacokinetic and pharmacodynamic changes in the elderly. *Clinical Pharmacokinetics, 35*(1), 49-64.
Harrison, B. J., Yücel, M., Pujol, J., & Pantelis, C. (2007). Task-induced deactivation of midline cortical regions in schizophrenia assessed with fMRI. *Schizophrenia Research, 91*(1-3), 82-86.
HÅvard Loge, J., & Kaasa, S. (1998). Short form 36 (SF-36) health survey: normative data from the general Norwegian population. *Scandinavian Journal of Social Medicine, 26*(4), 250-258.
Hawkes, C. H., Del Tredici, K., & Braak, H. (2010). A timeline for Parkinson's disease. *Parkinsonism & Related Disorders, 16*(2), 79-84.
Heinricher, M., Morgan, M., Tortorici, V., & Fields, H. (1994). Disinhibition of off-cells and antinociception produced by an opioid action within the rostral ventromedial medulla. *Neuroscience, 63*(1), 279-288.

Hentall, I. D., Mesigil, R., Pinzon, A., & Noga, B. R. (2003). Temporal and spatial profiles of pontine-evoked monoamine release in the rat's spinal cord. *Journal of Neurophysiology, 89*(6), 2943-2951.

Herbert, H., & Saper, C. B. (1992). Organization of medullary adrenergic and noradrenergic projections to the periaqueductal gray matter in the rat. *Journal of Comparative Neurology, 315*(1), 34-52.

Holman, A., & Myers, R. (2004). *Treatment of fibromyalgia syndrome with the dopamine 3 receptor agonist pramipexole: A double-blinded, randomized, placebo controlled trial.* Paper presented at the Arthritis and Rheumatism.

Holman, A. J., & Myers, R. R. (2005). A randomized, double‐blind, placebo‐controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. *Arthritis & Rheumatism, 52*(8), 2495-2505.

Holmes, C., Cunningham, C., Zotova, E., Woolford, J., Dean, C., Kerr, S. u., . . . Perry, V. (2009). Systemic inflammation and disease progression in Alzheimer disease. *Neurology, 73*(10), 768-774.

Honey, C. R., Stoessl, A. J., Tsui, J. K., Schulzer, M., & Calne, D. B. (1999). Unilateral pallidotomy for reduction of parkinsonian pain. *Journal of Neurosurgery, 91*(2), 198-201.

Honig, H., Antonini, A., Martinez‐Martin, P., Forgacs, I., Faye, G. C., Fox, T., . . . Odin, P. (2009). Intrajejunal levodopa infusion in Parkinson's disease: a pilot multicenter study of effects on nonmotor symptoms and quality of life. *Movement Disorders, 24*(10), 1468-1474.

Hornung, J.-P. (2003). The human raphe nuclei and the serotonergic system. *Journal of Chemical Neuroanatomy, 26*(4), 331-343.

Hudson, J. I., Wohlreich, M. M., Kajdasz, D. K., Mallinckrodt, C. H., Watkin, J. G., & Martynov, O. V. (2005). Safety and tolerability of duloxetine in the treatment of major depressive disorder: analysis of pooled data from eight placebo-controlled clinical trials. *Human Psychopharmacology: Clinical and Experimental, 20*(5), 327-341.

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery & Psychiatry, 55*(3), 181-184.

Hulsebosch, C. E., & Coggeshall, R. E. (1981). Quantitation of sprouting of dorsal root axons. *Science, 213*(4511), 1020-1021.

Huse, D. M., Schulman, K., Orsini, L., Castelli‐Haley, J., Kennedy, S., & Lenhart, G. (2005). Burden of illness in Parkinson's disease. *Movement Disorders, 20*(11), 1449-1454.

Huskisson, E. C. (1974). Measurement of pain. *The Lancet, 304*(7889), 1127-1131.

Hyland, N. P., & Cryan, J. F. (2010). A gut feeling about GABA: focus on GABAB receptors. *Frontiers in Pharmacology, 1*, 124.

Ichesco, E., Puiu, T., Hampson, J., Kairys, A., Clauw, D., Harte, S., . . . Schmidt‐Wilcke, T. (2016). Altered fMRI resting‐state connectivity in individuals with fibromyalgia on acute pain stimulation. *European Journal of Pain, 20*(7), 1079-1089.

Ilinsky, I., Jouandet, M., & Goldman‐Rakic, P. (1985). Organization of the nigrothalamocortical system in the rhesus monkey. *Journal of Comparative Neurology, 236*(3), 315-330.

Inturrisi, C. E. (2002). Clinical pharmacology of opioids for pain. *The Clinical Journal of Pain, 18*(4), S3-S13.

Iwaki, H., Ando, R., Tada, S., Nishikawa, N., Tsujii, T., Yamanishi, Y., . . . Nomoto, M. (2020). A double-blind, randomized controlled trial of duloxetine for pain in Parkinson's disease. *Journal of the Neurological Sciences*, 116833.

Iwata, K., Fukuoka, T., Kondo, E., Tsuboi, Y., Tashiro, A., Noguchi, K., . . . Kanda, K. (2002). Plastic changes in nociceptive transmission of the rat spinal cord with advancing age. *Journal of Neurophysiology, 87*(2), 1086-1093.

Iyengar, S., Webster, A. A., Hemrick-Luecke, S. K., Xu, J. Y., & Simmons, R. M. A. (2004). Efficacy of duloxetine, a potent and balanced serotonin-norepinephrine reuptake inhibitor in persistent pain models in rats. *Journal of Pharmacology and Experimental Therapeutics, 311*(2), 576-584.

Jaaskelainen, S. K., Rinne, J. O., Forssell, H., Tenovuo, O., Kaasinen, V., Sonninen, P., & Bergman, J. (2001). Role of the dopaminergic system in chronic pain -- a fluorodopa-PET study. *Pain, 90*(3), 257-260.

Jellinger, K. (1999). Post mortem studies in Parkinson's disease—is it possible to detect brain areas for specific symptoms? *Diagnosis and Treatment of Parkinson's Disease—State of the Art* (pp. 1-29): Springer.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17*(2), 825-841.

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis, 5*(2), 143-156.

Jensen, K. B., Petzke, F., Carville, S., Choy, E., Fransson, P., Gracely, R. H., . . . Ingvar, M. (2014). Segregating the cerebral mechanisms of antidepressants and placebo in fibromyalgia. *The Journal of Pain, 15*(12), 1328-1337.

Jensen-Dahm, C., Werner, M. U., Dahl, J. B., Jensen, T. S., Ballegaard, M., Hejl, A.-M., & Waldemar, G. (2014). Quantitative sensory testing and pain tolerance in patients with mild to moderate Alzheimer disease compared to healthy control subjects. *Pain, 155*(8), 1439-1445.

Ji, R.-R., Kohno, T., Moore, K. A., & Woolf, C. J. (2003). Central sensitization and LTP: do pain and memory share similar mechanisms? *Trends in Neurosciences, 26*(12), 696-705.

Joel, D. (2001). Open interconnected model of basal ganglia‐thalamocortical circuitry and its relevance to the clinical syndrome of Huntington's disease. *Movement Disorders, 16*(3), 407-423.

Joel, D., & Weiner, I. (1994). The organization of the basal ganglia-thalamocortical circuits: open interconnected rather than closed segregated. *Neuroscience, 63*(2), 363-379.

Jung, Y. J., Kim, H.-J., Jeon, B. S., Park, H., Lee, W.-W., & Paek, S. H. (2015). An 8-year follow-up on the effect of subthalamic nucleus deep brain stimulation on pain in Parkinson disease. *JAMA Neurology, 72*(5), 504-510.

Kaji, R. (2001). Basal ganglia as a sensory gating devise for motor control. *Journal of Medical Investigation, 48*(3/4), 142-146.

Kaji, R., Shibasaki, H., & Kimura, J. (1995). Writer's cramp: a disorder of motor subroutine? *Annals of Neurology, 38*(6), 837-838.

Kalaitzakis, M., Graeber, M., Gentleman, S., & Pearce, R. (2008). The dorsal motor nucleus of the vagus is not an obligatory trigger site of Parkinson's disease: a critical analysis of α - synuclein staging. *Neuropathology and Applied Neurobiology, 34*(3), 284-295.

Karlsen, K. H., Tandberg, E., Årsland, D., & Larsen, J. P. (2000). Health related quality of life in Parkinson's disease: a prospective longitudinal study. *Journal of Neurology, Neurosurgery & Psychiatry, 69*(5), 584-589.

Kennedy, D. P., Redcay, E., & Courchesne, E. (2006). Failing to deactivate: resting functional abnormalities in autism. *Proceedings of the National Academy of Sciences, 103*(21), 8275-8280.

Khan, H., & Stroman, P. (2015). Inter-individual differences in pain processing investigated by functional magnetic resonance imaging of the brainstem and spinal cord. *Neuroscience, 307*, 231-241.

Khan, S. A., Keaser, M. L., Meiller, T. F., & Seminowicz, D. A. (2014). Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. *Pain, 155*(8), 1472-1480.

Kim, J.-H., Choi, S.-H., Jang, J. H., Lee, D.-H., Lee, K.-J., Lee, W. J., . . . Kang, D.-H. (2017). Impaired insula functional connectivity associated with persistent pain perception in patients with complex regional pain syndrome. *PLoS One, 12*(7).

Kodama, M., Kasahara, T., Hyodo, M., Aono, K., Sugaya, M., Koyama, Y., . . . Masakado, Y. (2011). Effect of low-frequency repetitive transcranial magnetic stimulation combined with physical therapy on L-dopa-induced painful off-period dystonia in Parkinson's disease. *American Journal of Physical Medicine & Rehabilitation, 90*(2), 150-155.

Koltzenburg, M., Lundberg, L. E., & Torebjörk, H. E. (1992). Dynamic and static components of mechanical hyperalgesia in human hairy skin. *Pain, 51*(2), 207-219.

Koltzenburg, M., Torebjörk, H. E., & Wahren, L. K. (1994). Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain. *Brain, 117*(3), 579-591.

Kong, J., Loggia, M. L., Zyloney, C., Tu, P., LaViolette, P., & Gollub, R. L. (2010). Exploring the brain in pain: activations, deactivations and their relation. *Pain, 148*(2), 257-267.

Kosek, E., Ekholm, J., & Hansson, P. (1999). Pressure pain thresholds in different tissues in one body region. The influence of skin sensitivity in pressure algometry. *Scandinavian Journal of Rehabilitation Medicine, 31*(2), 89-93.

Kowal, S. L., Dall, T. M., Chakrabarti, R., Storm, M. V., & Jain, A. (2013). The current and projected economic burden of Parkinson's disease in the United States. *Movement Disorders, 28*(3), 311-318.

Krajcovicova, L., Mikl, M., Marecek, R., & Rektorova, I. (2012). The default mode network integrity in patients with Parkinson's disease is levodopa equivalent dose-dependent. *Journal of Neural Transmission, 119*(4), 443-454.

Kriegeskorte, N., Simmons, W. K., Bellgowan, P. S., & Baker, C. I. (2009). Circular analysis in systems neuroscience: the dangers of double dipping. *Nature Neuroscience, 12*(5), 535.

Krummenacher, P., Candia, V., Folkers, G., Schedlowski, M., & Schönbächler, G. (2010). Prefrontal cortex modulates placebo analgesia. *Pain, 148*(3), 368-374.

Kucyi, A., Salomons, T. V., & Davis, K. D. (2013). Mind wandering away from pain dynamically engages antinociceptive and default mode brain networks. *Proceedings of the National Academy of Sciences, 110*(46), 18692-18697.

Lai, C.-H., & Hsu, Y.-Y. (2011). A subtle grey-matter increase in first-episode, drug-naive major depressive disorder with panic disorder after 6 weeks' duloxetine therapy. *International Journal of Neuropsychopharmacology, 14*(2), 225-235.

Lai, C.-H., & Wu, Y.-T. (2012). Frontal regional homogeneity increased and temporal regional homogeneity decreased after remission of first-episode drug-naive major depressive disorder with panic disorder patients under duloxetine therapy for 6 weeks. *Journal of Affective Disorders, 136*(3), 453-458.

Laitinen, L. V., Bergenheim, A. T., & Hariz, M. I. (1992). Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *Journal of Neurosurgery, 76*(1), 53-61.

Landerholml, Å. H., & Hansson, P. T. (2011). Mechanisms of dynamic mechanical allodynia and dysesthesia in patients with peripheral and central neuropathic pain. *European Journal of Pain, 15*(5), 498-503.

Lange, K. W., Kornhuber, J., & Riederer, P. (1997). Dopamine/glutamate interactions in Parkinson's disease. *Neuroscience & Biobehavioral Reviews, 21*(4), 393-400.

Langford, L. A., & Schmidt, R. F. (1983). Afferent and efferent axons in the medial and posterior articular nerves of the cat. *The Anatomical Record, 206*(1), 71-78.

Lannfelt, L., Sokoloff, P., Martres, M.-P., Pilon, C., Giros, B., Jönsson, E., . . . Schwartz, J.-C. (1992). Amino acid substitution in the dopamine D_3 receptor as a useful polymorphism for investigating psychiatric disorders. *Psychiatric Genetics*, *2*(4), 249-256.

Lavoie, B., Coˆte, P.-Y., & Parent, A. (1992). Immunohistochemical study of the basal ganglia in normal and parkinsonian monkeys. *Advances in Neurology, 58*, 115-121.

Le Bars, D. (2002). The whole body receptive field of dorsal horn multireceptive neurones. *Brain Research Reviews, 40*(1-3), 29-44.

Lee, M. A., Walker, R. W., Hildreth, T. J., & Prentice, W. M. (2006). A Survey of Pain in Idiopathic Parkinson's Disease. *Journal of Pain and Symptom Management, 32*(5), 462-469.

Lefaucher, J., Debray, S., & Jarry, G. (2001). Nd: YAG Laser Evoked Potentials. *Muscle and Nerve*, 496-500.

Li, D., Song, X., Huang, H., Huang, H., & Ye, Z. (2018). Association of Parkinson's disease-related pain with plasma interleukin-1, interleukin-6, interleukin-10, and tumour necrosis factor-α. *Neuroscience Letters, 683*, 181-184.

Li, L. W., Harris, R. E., Tsodikov, A., Struble, L., & Murphy, S. L. (2018). Self‐Acupressure for Older Adults With Symptomatic Knee Osteoarthritis: A Randomized Controlled Trial. *Arthritis Care & Research, 70*(2), 221-229.

Li, W., Chen, Y., Yin, B., & Zhang, L. (2014). Pain in Parkinson's disease associated with COMT gene polymorphisms. *Behavioural Neurology,* ID 304203.

Lim, S. Y., Farrell, M. J., & Evans, A. H. (2011). Parkinson's disease and pain—Nondopaminergic mechanisms are likely to be important too. *Movement Disorders, 26*(7), 1353-1354.

Lim, S. Y., Farrell, M. J., Gibson, S. J., Helme, R. D., Lang, A. E., & Evans, A. H. (2008). Do dyskinesia and pain share common pathophysiological mechanisms in Parkinson's disease? *Movement Disorders, 23*(12), 1689-1695.

Lin, J. J., Alfandre, D., & Moore, C. (2007). Physician attitudes toward opioid prescribing for patients with persistent noncancer pain. *The Clinical Journal of Pain, 23*(9), 799-803.

Lin, M., Wu, J., Chandra, A., & Tsay, B. (1981). Activation of striatal dopamine receptors induces pain inhibition in rats. *Journal of Neural Transmission, 51*(3-4), 213-222.

Linton, S. (2005). *Understanding pain for better clinical practice: a psychological perspective* (Vol. 16): Elsevier Health Sciences.

Liu, Y., Zhao, J., Fan, X., & Guo, W. (2019). Dysfunction in serotonergic and noradrenergic systems and somatic symptoms in psychiatric disorders. *Frontiers in Psychiatry, 10*, 286.

Llorca-Torralba, M., Borges, G., Neto, F., Mico, J. A., & Berrocoso, E. (2016). Noradrenergic locus coeruleus pathways in pain modulation. *Neuroscience, 338*, 93-113.

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature, 453*(7197), 869-878.

Loher, T. J., Burgunder, J.-M., Weber, S., Sommerhalder, R., & Krauss, J. K. (2002). Effect of chronic pallidal deep brain stimulation on off period dystonia and sensory symptoms in advanced Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 73*(4), 395-399.

Löhle, M., Mangone, G., Wolz, M., Beuthien‐Baumann, B., Oehme, L., van den Hoff, J., . . . Storch, A. (2018). Functional monoamine oxidase B gene intron 13 polymorphism predicts putaminal dopamine turnover in de novo Parkinson's disease. *Movement Disorders, 33*(9), 1496-1501.

López-Solà, M., Pujol, J., Hernández-Ribas, R., Harrison, B. J., Contreras-Rodríguez, O., Soriano-Mas, C., . . . Vallejo, J. (2010). Effects of duloxetine treatment on brain response to painful stimulation in major depressive disorder. *Neuropsychopharmacology, 35*(11), 2305-2317.

López-Solà, M., Pujol, J., Hernández-Ribas, R., Harrison, B. J., Ortiz, H., Soriano-Mas, C., . . . Cardoner, N. (2010). Dynamic assessment of the right lateral frontal cortex response to painful stimulation. *Neuroimage, 50*(3), 1177-1187.

Lunn, M. P., Hughes, R. A., & Wiffen, P. J. (2014). Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database of Systematic Reviews*(1).

Luppi, P.-H., Gervasoni, D., Verret, L., Goutagny, R., Peyron, C., Salvert, D., . . . Fort, P. (2006). Paradoxical (REM) sleep genesis: the switch from an aminergic–cholinergic to a GABAergic–glutamatergic hypothesis. *Journal of Physiology, 100*(5-6), 271-283.

Machado-Vieira, R., Baumann, J., Wheeler-Castillo, C., Latov, D., Henter, I. D., Salvadore, G., & Zarate, C. A. (2010). The timing of antidepressant effects: a comparison of diverse pharmacological and somatic treatments. *Pharmaceuticals, 3*(1), 19-41.

Madeo, G., Schirinzi, T., Natoli, S., Pierantozzi, M., Stefani, A., Dauri, M., & Pisani, A. (2015). Efficacy and safety profile of prolonged release oxycodone in combination with naloxone (OXN PR) in Parkinson's disease patients with chronic pain. *Journal of Neurology, 262*(9), 2164-2170.

Magnusson, J. E., & Fisher, K. (2000). The involvement of dopamine in nociception: the role of D1 and D2 receptors in the dorsolateral striatum. *Brain Research, 855*(2), 260-266.

Mak, M. K., Wong-Yu, I. S., Shen, X., & Chung, C. L. (2017). Long-term effects of exercise and physical therapy in people with Parkinson disease. *Nature Reviews Neurology, 13*(11), 689.

Malinen, S., Vartiainen, N., Hlushchuk, Y., Koskinen, M., Ramkumar, P., Forss, N., . . . Hari, R. (2010). Aberrant temporal and spatial brain activity during rest in patients with chronic pain. *Proceedings of the National Academy of Sciences, 107*(14), 6493-6497.

Marangell, L. B., Clauw, D. J., Choy, E., Wang, F., Shoemaker, S., Bradley, L., . . . Wohlreich, M. M. (2011). Comparative pain and mood effects in patients with comorbid fibromyalgia and major depressive disorder: secondary analyses of four pooled randomized controlled trials of duloxetine. *Pain, 152*(1), 31-37.

Márkus, Z., Eödegh, G., Paróczy, Z., Benedek, G., & Nagy, A. (2008). Modality distribution of sensory neurons in the feline caudate nucleus and the substantia nigra. *Acta Biologica Hungarica, 59*(3), 269-279.

Marsala, S. Z., Tinazzi, M., Vitaliani, R., Recchia, S., Fabris, F., Marchini, C., . . . Macerollo, A. (2011). Spontaneous pain, pain threshold, and pain tolerance in Parkinson's disease. *Journal of Neurology, 258*(4), 627-633.

Martinez-Martin, P., Rojo-Abuin, J. M., Rizos, A., Rodriguez-Blazquez, C., Trenkwalder, C., Perkins, L., . . . Chaudhuri, K. R. (2017). Distribution and impact on quality of life of the pain modalities assessed by the King's Parkinson's disease pain scale. *npj Parkinson's Disease, 3*(1), 8.

Mayer, D. J., & Price, D. D. (1976). Central nervous system mechanisms of analgesia. *Pain, 2*(4), 379-404.

Mayhew, S. D., Hylands-White, N., Porcaro, C., Derbyshire, S. W., & Bagshaw, A. P. (2013). Intrinsic variability in the human response to pain is assembled from multiple, dynamic brain processes. *Neuroimage, 75*, 68-78.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS - ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34*(7), 939-939.

Meldrum, B. S. (2000). Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *The Journal of Nutrition, 130*(4), 1007S-1015S.

Meldrum, M. L. (2003). A capsule history of pain management. *JAMA, 290*(18), 2470-2475.

Melzack, R. (1987). The short-form McGill pain questionnaire. *Pain, 30*(2), 191-197.

Melzack, R. (1990). Phantom limbs and the concept of a neuromatrix. *Trends in Neurosciences, 13*(3), 88-92.

Melzack, R., & Wall, P. D. (1965). Pain mechanisms: a new theory. *Science, 150*(3699), 971-979.

Mendlin, A., Martín, F. J., Rueter, L. E., & Jacobs, B. L. (1996). Neuronal release of serotonin in the cerebellum of behaving rats: an in vivo microdialysis study. *Journal of Neurochemistry, 67*(2), 617-622.

Middleton, F. A., & Strick, P. L. (2001). Cerebellar projections to the prefrontal cortex of the primate. *Journal of Neuroscience, 21*(2), 700-712.

Mitchell, L. A., MacDonald, R. A., & Brodie, E. E. (2004). Temperature and the cold pressor test. *The Journal of Pain, 5*(4), 233-237.

Mixcoatl‐Zecuatl, T., & Jolivalt, C. (2011). A spinal mechanism of action for duloxetine in a rat model of painful diabetic neuropathy. *British Journal of Pharmacology, 164*(1), 159-169.

Morgan, M. J., & Franklin, K. B. (1991). Dopamine receptor subtypes and formalin test analgesia. *Pharmacology Biochemistry and Behavior, 40*(2), 317-322.

Moulin, D., Boulanger, A., Clark, A., Clarke, H., Dao, T., Finley, G., . . . Morley-Forster, P. (2014). Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. *Pain Research and Management, 19*(6), 328-335.

Müller, T., Muhlack, S., & Woitalla, D. (2011). Pain perception, pain drug therapy and health status in patients with Parkinson's disease. *Neuroepidemiology, 37*(3-4), 183-187.

Mumford, J. A. (2012). A power calculation guide for fMRI studies. *Social Cognitive and Affective Neuroscience, 7*(6), 738-742.

Mumford, J. A., & Nichols, T. E. (2008). Power calculation for group fMRI studies accounting for arbitrary design and temporal autocorrelation. *Neuroimage, 39*(1), 261-268.

Nackley, A. G., Tan, K. S., Fecho, K., Flood, P., Diatchenko, L., & Maixner, W. (2007). Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both β2-and β3-adrenergic receptors. *Pain, 128*(3), 199-208.

Nagy, A., Eördegh, G., Paróczy, Z., Márkus, Z., & Benedek, G. (2006). Multisensory integration in the basal ganglia. *European Journal of Neuroscience, 24*(3), 917-924.

Nahimi, A., Sommerauer, M., Kinnerup, M. B., Østergaard, K., Wintherdahl, M., Jacobsen, J., . . . Borghammer, P. (2018). Noradrenergic Deficits in Parkinson Disease Imaged with 11C-MeNER. *Journal of Nuclear Medicine, 59*(4), 659-664.

Napadow, V., LaCount, L., Park, K., As‐Sanie, S., Clauw, D. J., & Harris, R. E. (2010). Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis & Rheumatism, 62*(8), 2545-2555.

Nebe, A., & Ebersbach, G. (2009). Pain intensity on and off levodopa in patients with Parkinson's disease. *Movement Disorders, 24*(8), 1233-1237.

Nègre‐Pagès, L., Regragui, W., Bouhassira, D., Grandjean, H., & Rascol, O. (2008). Chronic pain in Parkinson's disease: The cross‐sectional French DoPaMiP survey. *Movement Disorders, 23*(10), 1361-1369.

Nitzan-Luques, A., Minert, A., Devor, M., & Tal, M. (2013). Dynamic genotype-selective "phenotypic switching" of CGRP expression contributes to differential neuropathic pain phenotype. *Experimental Neurology, 250*, 194-204.

Nolano, M., Provitera, V., Estraneo, A., Selim, M. M., Caporaso, G., Stancanelli, A., . . . Santoro, L. (2008). Sensory deficit in Parkinson's disease: evidence of a cutaneous denervation. *Brain, 131*(7), 1903-1911.

Nussbaum, R. L., & Ellis, C. E. (2003). Alzheimer's Disease and Parkinson's Disease. *New England Journal of Medicine, 348*(14), 1356-1364.

Nutt, D. J. (2008). Relationship of neurotransmitters to the symptoms of major depressive disorder. *The Journal of Clinical Psychiatry, 69*, 4-7.

O'Brien, J. A., Ward, A., Michels, S. L., Tzivelekis, S., & Brandt, N. (2009). Economic burden associated with Parkinson disease. *Drug Benefit Trends 21*(6), 179-190.

O'Sullivan, S. S., Williams, D. R., Gallagher, D. A., Massey, L. A., Silveira - Moriyama, L., & Lees, A. J. (2008). Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. *Movement Disorders, 23*(1), 101-106.

Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., & Ugurbil, K. (1992). Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences, 89*(13), 5951-5955.

Ong, W.-Y., Stohler, C. S., & Herr, D. R. (2019). Role of the prefrontal cortex in pain processing. *Molecular Neurobiology, 56*(2), 1137-1166.

Ortiz, J., Heinricher, M., & Selden, N. (2007). Noradrenergic agonist administration into the central nucleus of the amygdala increases the tail-flick latency in lightly anesthetized rats. *Neuroscience, 148*(3), 737-743.

Oshima, H., Katayama, Y., Morishita, T., Sumi, K., Otaka, T., Kobayashi, K., . . . Yamamoto, T. (2012). Subthalamic nucleus stimulation for attenuation of pain related to Parkinson disease. *Journal of Neurosurgery, 116*(1), 99-106.

Ossewaarde, L., Verkes, R. J., Hermans, E. J., Kooijman, S. C., Urner, M., Tendolkar, I., . . . Fernández, G. (2011). Two-week administration of the combined serotonin-noradrenaline reuptake inhibitor duloxetine augments functioning of mesolimbic incentive processing circuits. *Biological Psychiatry, 70*(6), 568-574.

Ozturk, E. A., Gundogdu, I., Kocer, B., Comoglu, S., & Cakci, A. (2017). Chronic pain in Parkinson's disease: Frequency, characteristics, independent factors, and relationship with health-related quality of life. *Journal of Back and Musculoskeletal Rehabilitation, 30*(1), 101-108.

Pacchetti, C., Albani, G., Martignoni, E., Godi, L., Alfonsi, E., & Nappi, G. (1995). “Off” painful dystonia in Parkinson's disease treated with botulinum toxin. *Movement Disorders, 10*(3), 333-336.

Parkkinen, L., Pirttilä, T., & Alafuzoff, I. (2008). Applicability of current staging/categorization of α-synuclein pathology and their clinical relevance. *Acta Neuropathologica, 115*(4), 399-407.

Pauling, L., & Coryell, C. D. (1936). The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. *Proceedings of the National Academy of Sciences, 22*(4), 210-216.

Pellaprat, J., Ory-Magne, F., Canivet, C., Simonetta-Moreau, M., Lotterie, J.-A., Radji, F., . . . Brefel-Courbon, C. (2014). Deep brain stimulation of the subthalamic nucleus improves pain in Parkinson's disease. *Parkinsonism & Related Disorders, 20*(6), 662-664.

Perahia, D. G., Pritchett, Y. L., Desaiah, D., & Raskin, J. (2006). Efficacy of duloxetine in painful symptoms: an analgesic or antidepressant effect? *International Clinical Psychopharmacology, 21*(6), 311-317.

Perez-Lloret, S., Rey, M. V., Dellapina, E., Pellaprat, J., Brefel-Courbon, C., & Rascol, O. (2012). Emerging analgesic drugs for Parkinson's disease. *Expert Opinion on Emerging Drugs, 17*(2), 157-171.

Perl, E. R. (2007). Ideas about pain, a historical view. *Nature Reviews Neuroscience, 8*(1), 71.

Pertovaara, A. (2013). The noradrenergic pain regulation system: a potential target for pain therapy. *European Journal of Pharmacology, 716*(1-3), 2-7.

Pertovaara, A., & Wei, H. (2008). Dual influence of the striatum on neuropathic hypersensitivity. *Pain, 137*(1), 50-59.

Peto, V., Jenkinson, C., Fitzpatrick, R., & Greenhall, R. (1995). The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Quality of Life Research, 4*(3), 241-248.

Petzinger, G. M., Holschneider, D., Fisher, B., McEwen, S., Kintz, N., Halliday, M., . . . Jakowec, M. (2015). The effects of exercise on dopamine neurotransmission in Parkinson's disease: targeting neuroplasticity to modulate basal ganglia circuitry. *Brain Plasticity, 1*(1), 29-39.

Peyron, R., Faillenot, I., Pomares, F., Le Bars, D., Garcia‐Larrea, L., & Laurent, B. (2013). Mechanical allodynia in neuropathic pain. Where are the brain representations located? A positron emission tomography (PET) study. *European Journal of Pain, 17*(9), 1327-1337.

Peyron, R., & Fauchon, C. (2019). Functional imaging of pain. *Revue Neurologique, 175*(1-2), 38-45.

Peyron, R., Laurent, B., & Garcia-Larrea, L. (2000). Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiologie Clinique, 30*(5), 263-288.

Phelps, M. E., Hoffman, E. J., Mullani, N. A., & Ter-Pogossian, M. M. (1975). Application of annihilation coincidence detection to transaxial reconstruction tomography. *Journal of Nuclear Medicine, 16*(3), 210-224.

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biological Psychiatry, 54*(5), 515-528.

Politis, M. (2014). Neuroimaging in Parkinson disease: from research setting to clinical practice. *Nature Reviews Neurology, 10*(12), 708.

Politis, M., & Niccolini, F. (2015). Serotonin in Parkinson's disease. *Behavioural Brain Research, 277*, 136-145.

Politis, M., Wu, K., Loane, C., Quinn, N. P., Brooks, D. J., Oertel, W. H., . . . Piccini, P. (2012). Serotonin neuron loss and nonmotor symptoms continue in Parkinson's patients treated with dopamine grafts. *Science Translational Medicine, 4*(128), 128-141.

Politis, M., Wu, K., Loane, C., Turkheimer, F., Molloy, S., Brooks, D., & Piccini, P. (2010). Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. *Neurology, 75*(21), 1920-1927.

Politis, M., Wu, K., Molloy, S., G. Bain, P., Chaudhuri, K. R., & Piccini, P. (2010). Parkinson's disease symptoms: the patient's perspective. *Movement Disorders, 25*(11), 1646-1651.

Pollack, A. E. (2001). Anatomy, physiology, and pharmacology of the basal ganglia. *Neurologic Clinics, 19*(3), 523-534.

Polli, A., Weis, L., Biundo, R., Thacker, M., Turolla, A., Koutsikos, K., . . . Antonini, A. (2016). Anatomical and functional correlates of persistent pain in Parkinson's disease. *Movement Disorders, 31*(12), 1854-1864.

Potvin, S., Larouche, A., Normand, E., de Souza, J. B., Gaumond, I., Grignon, S., & Marchand, S. (2009). DRD3 Ser9Gly polymorphism is related to thermal pain perception and modulation in chronic widespread pain patients and healthy controls. *The Journal of Pain, 10*(9), 969-975.

Proudfit, H. (1992). Behavioural pharmacology of noradrenergic descending system. *Towards the use of noradrenergic agonists for the treatment of pain*, 119-137, Elsevier Press.

Quinn, N., Lang, A., Koller, W., & Marsden, C. (1986). Painful Parkinson's disease. *The Lancet, 327*(8494), 1366-1369.

Quittenbaum, B. H., & Grahn, B. (2004). Quality of life and pain in Parkinson's disease: a controlled cross-sectional study. *Parkinsonism & Related Disorders, 10*(3), 129-136.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, 98*(2), 676-682.

Rainville, P. (2002). Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology, 12*(2), 195-204.

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., & Bushnell, M. C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science, 277*(5328), 968-971.

Rainville, P., Hofbauer, R. K., Paus, T., Duncan, G. H., Bushnell, M. C., & Price, D. D. (1999). Cerebral mechanisms of hypnotic induction and suggestion. *Journal of Cognitive Neuroscience, 11*(1), 110-125.

Raja, S. N., Carr, D. B., Cohen, M., Finnerup, N. B., Flor, H., Gibson, S., . . . Sluka, K. A. (2020). The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain*, *161*(9), 1976-1982.

Rana, A. Q., Kabir, A., Jesudasan, M., Siddiqui, I., & Khondker, S. (2013). Pain in Parkinson's disease: analysis and literature review. *Clinical Neurology and Neurosurgery, 115*(11), 2313-2317.

Rascol, O., Zesiewicz, T., Chaudhuri, K. R., Asgharnejad, M., Surmann, E., Dohin, E., . . . Bauer, L. (2016). A Randomized Controlled Exploratory Pilot Study to Evaluate the Effect of Rotigotine Transdermal Patch on Parkinson's Disease–Associated Chronic Pain. *The Journal of Clinical Pharmacology, 56*(7), 852-861.

Raskin, J., Pritchett, Y. L., Wang, F., D'Souza, D. N., Waninger, A. L., Iyengar, S., & Wernicke, J. F. (2005). A double‐blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Medicine, 6*(5), 346-356.

Raskin, N. H., Hosobuchi, Y., & Lamb, S. (1987). Headache may arise from perturbation of brain. *Headache, 27*(8), 416-420.

Reichmann, H. (2010). Clinical criteria for the diagnosis of Parkinson's disease. *Neurodegenerative Diseases, 7*(5), 284-290.

Rempe, T., Wolff, S., Riedel, C., Baron, R., Stroman, P. W., Jansen, O., & Gierthmühlen, J. (2014). Spinal fMRI reveals decreased descending inhibition during secondary mechanical hyperalgesia. *PLoS One, 9*(11).

Rempe, T., Wolff, S., Riedel, C., Baron, R., Stroman, P. W., Jansen, O., & Gierthmühlen, J. (2015). Spinal and supraspinal processing of thermal stimuli: an fMRI study. *Journal of Magnetic Resonance Imaging, 41*(4), 1046-1055.

Remy, P., Doder, M., Lees, A., Turjanski, N., & Brooks, D. (2005). Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain, 128*(6), 1314-1322.

Reuter, I., Mehnert, S., Leone, P., Kaps, M., Oechsner, M., & Engelhardt, M. (2011). Effects of a flexibility and relaxation programme, walking, and nordic walking on Parkinson's disease. *Journal of Aging Research, 2011*.

Rey, R., Wallace, L. E., Cadden, J., Cadden, S., & Brieger, G. H. (1995). *The History of Pain*: Springer.

Rietdijk, C. D., Perez-Pardo, P., Garssen, J., van Wezel, R. J., & Kraneveld, A. D. (2017). Exploring Braak's hypothesis of Parkinson's disease. *Frontiers in Neurology, 8*, 37.

Riley, D., Lang, A., Blair, R., Birnbaum, A., & Reid, B. (1989). Frozen shoulder and other shoulder disturbances in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 52*(1), 63-66.

Rodrigues de Paula, F., Teixeira‐Salmela, L. F., Coelho de Morais Faria, C. D., Rocha de Brito, P., & Cardoso, F. (2006). Impact of an exercise program on physical, emotional, and social aspects of quality of life of individuals with Parkinson's disease. *Movement Disorders, 21*(8), 1073-1077.

Rodriguez, M., Obeso, J., & Olanow, C. W. (1998). Subthalamic nucleus‐mediated excitotoxicity in Parkinson's disease: a target for neuroprotection. *Annals of Neurology, 44*(S1 1), S175-S188.

Rommelfanger, K., & Weinshenker, D. (2007). Norepinephrine: the redheaded stepchild of Parkinson's disease. *Biochemical Pharmacology, 74*(2), 177-190.

Rowbotham, M. C. (2001). What is a 'clinically meaningful'reduction in pain? *Pain, 94*(2), 131-132.

Rüb, U., Del Tredici, K., Schultz, C., Ghebremedhin, E., De Vos, R., Steur, E. J., & Braak, H. (2002). Parkinson's disease: the thalamic components of the limbic loop are severely impaired by α-synuclein immunopositive inclusion body pathology. *Neurobiology of Aging, 23*(2), 245-254.

Rudd, R. A., Aleshire, N., Zibbell, J. E., & Gladden, R. M. (2016). Increases in drug and opioid overdose deaths—United States, 2000–2014. *American Journal of Transplantation, 16*(4), 1323-1327.

Ruscheweyh, R., Kühnel, M., Filippopulos, F., Blum, B., Eggert, T., & Straube, A. (2014). Altered experimental pain perception after cerebellar infarction. *Pain, 155*(7), 1303-1312.

Russell, I. J., Mease, P. J., Smith, T. R., Kajdasz, D. K., Wohlreich, M. M., Detke, M. J., . . . Arnold, L. M. (2008). Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain, 136*(3), 432-444.

Saab, C., & Willis, W. (2002). Cerebellar stimulation modulates the intensity of a visceral nociceptive reflex in the rat. *Experimental Brain Research, 146*(1), 117-121.

Saab, C. Y., & Willis, W. D. (2003). The cerebellum: organization, functions and its role in nociception. *Brain Research Reviews, 42*(1), 85-95.

Saadé, N. E., Atweh, S. F., Bahuth, N. B., & Jabbur, S. J. (1997). Augmentation of nociceptive reflexes and chronic deafferentation pain by chemical lesions of either dopaminergic terminals or midbrain dopaminergic neurons. *Brain Research, 751*(1), 1-12.

Saadé, N. E., Shbeir, S. A., Atweh, S. F., & Jabbur, S. J. (1996). Effects of cerebral cortical and striatal lesions on autotomy following peripheral neurectomy in rats. *Physiology & Behavior, 60*(2), 559-566.

Santos‐García, D., & De la Fuente‐Fernández, R. (2015). Factors contributing to caregivers' stress and burden in Parkinson's disease. *Acta Neurologica Scandinavica, 131*(4), 203-210.

Säterö, P., Klingenstierna, U., Karlsson, T., & Olausson, B. (2000). Pain threshold measurements with cutaneous argon laser, comparing a forced choice and a method of limits. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 24*(3), 397-407.

Sawada, H., Oeda, T., Umemura, A., Tomita, S., Kohsaka, M., Park, K., . . . Sugiyama, H. (2015). Baseline C-reactive protein levels and life prognosis in Parkinson disease. *PLoS One, 10*(7).

Scherder, E., Wolters, E., Polman, C., Sergeant, J., & Swaab, D. (2005). Pain in Parkinson's disease and multiple sclerosis: its relation to the medial and lateral pain systems. *Neuroscience & Biobehavioral Reviews, 29*(7), 1047-1056.

Scherder, E. J., Sergeant, J. A., & Swaab, D. F. (2003). Pain processing in dementia and its relation to neuropathology. *The Lancet Neurology, 2*(11), 677-686.

Schestatsky, P., Kumru, H., Valls-Sole, J., Valldeoriola, F., Marti, M. J., Tolosa, E., & Chaves, M. L. (2007). Neurophysiologic study of central pain in patients with Parkinson disease. *Neurology, 69*(23), 2162-2169.

Schrag, A., Jahanshahi, M., & Quinn, N. (2000). What contributes to quality of life in patients with Parkinson's disease? *Journal of Neurology, Neurosurgery & Psychiatry, 69*(3), 308-312.

Schrepf, A., Harper, D. E., Harte, S. E., Wang, H., Ichesco, E., Hampson, J. P., . . . Harris, R. E. (2016). Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study. *Pain, 157*(10), 2217.

Schukro, R. P., Oehmke, M. J., Geroldinger, A., Heinze, G., Kress, H.-G., & Pramhas, S. (2016). Efficacy of Duloxetine in Chronic Low Back Pain with a Neuropathic ComponentA Randomized, Double-blind, Placebo-controlled Crossover Trial. *Anesthesiology, 124*(1), 150-158.

Scott, J., & Huskisson, E. (1976). Graphic representation of pain. *Pain, 2*(2), 175-184.

Scotter, E. L., Abood, M. E., & Glass, M. (2010). The endocannabinoid system as a target for the treatment of neurodegenerative disease. *British Journal of Pharmacology, 160*(3), 480-498.

Sekine, M., Arakawa, R., Ito, H., Okumura, M., Sasaki, T., Takahashi, H., . . . Suhara, T. (2010). Norepinephrine transporter occupancy by antidepressant in

human brain using positron emission tomography with (S, S)-[18 F] FMeNER-D 2. *Psychopharmacology, 210*(3), 331-336.
Selemon, L., & Goldman-Rakic, P. (1985). Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *Journal of Neuroscience, 5*(3), 776-794.
Serý, O., Hrazdilova, O., Didden, W., Klenerová, V., Staif, R., & Znojil, V. (2006). The association of monoamine oxidase B functional polymorphism with postoperative pain intensity. *Neuro Endocrinol Lett, 27*.
Sharabi, Y., Imrich, R., Holmes, C., Pechnik, S., & Goldstein, D. S. (2008). Generalized and neurotransmitter‐selective noradrenergic denervation in Parkinson's disease with orthostatic hypotension. *Movement Disorders, 23*(12), 1725-1732.
Sheikh, J. I., & Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clinical Gerontologist 5*(1-2), 165-173.
Sheline, Y. I., Mintun, M. A., Moerlein, S. M., & Snyder, A. Z. (2002). Greater loss of 5-HT2A receptors in midlife than in late life. *American Journal of Psychiatry, 159*(3), 430-435.
Shen, X., Wong-Yu, I. S., & Mak, M. K. (2016). Effects of exercise on falls, balance, and gait ability in Parkinson's disease: a meta-analysis. *Neurorehabilitation and Neural Repair, 30*(6), 512-527.
Shulman, L. M., Wen, X., Weiner, W. J., Bateman, D., Minagar, A., Duncan, R., & Konefal, J. (2002). Acupuncture therapy for the symptoms of Parkinson's disease. *Movement Disorders, 17*(4), 799-802.
Siegel, P., & Wepsic, J. G. (1974). Alteration of nociception by stimulation of cerebellar structures in the monkey. *Physiology & Behavior, 13*(2), 189-194.
Silverdale, M. A., Kobylecki, C., Kass-Iliyya, L., Martinez-Martin, P., Lawton, M., Cotterill, S., . . . Williams, N. (2018). A detailed clinical study of pain in 1957 participants with early/moderate Parkinson's disease. *Parkinsonism & Related Disorders, 56*, 27-32.
Skelly, A. C., Chou, R., Dettori, J. R., Turner, J. A., Friedly, J. L., Rundell, S. D., . . . Kantner, S. (2020). Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update. *Comparative Effectiveness Review 227.* Rockville MD
Skljarevski, V., Desaiah, D., Liu-Seifert, H., Zhang, Q., Chappell, A. S., Detke, M. J., . . . Backonja, M. (2010). Efficacy and safety of duloxetine in patients with chronic low back pain. *Spine, 35*(13), E578-E585.
Skljarevski, V., Ossanna, M., Liu-Seifert, H., Zhang, Q., Chappell, A., Iyengar, S., . . . Backonja, M. (2009). A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain. *European Journal of Neurology, 16*(9), 1041-1048.
Skljarevski, V., Ramadan N. (2002) The nociceptive flexion reflex in humans. *Pain, 96,* 3-8.
Skljarevski, V., Zhang, S., Desaiah, D., Alaka, K. J., Palacios, S., Miazgowski, T., & Patrick, K. (2010). Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. *The Journal of Pain, 11*(12), 1282-1290.

Skogar, Ö., Fall, P.-A., Hallgren, G., Bringer, B., Carlsson, M., Lennartsson, U., . . . Lökk, J. (2012). Parkinson's disease patients' subjective descriptions of characteristics of chronic pain, sleeping patterns and health-related quality of life. *Neuropsychiatric Disease and Treatment, 8*, 435.

Slonimski, M., Abram, S. E., & Zuniga, R. E. (2004). Intrathecal baclofen in pain management. *Regional Anaesthesia and Pain Medicine, 29*(3), 269-276.

Smith, C. (2010). *Levodopa dose equivalency: A systematic review.* Paper presented at the Annual PD MED Collaborator's Meeting.

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17*(3), 143-155.

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., . . . Matthews, P. M. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage, 31*(4), 1487-1505.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., . . . Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23* (Suppl 1), S208-219.

Strand, L. I., Ljunggren, A. E., Bogen, B., Ask, T., & Johnsen, T. B. (2008). The Short-Form McGill Pain Questionnaire as an outcome measure: test–retest reliability and responsiveness to change. *European Journal of Pain, 12*(7), 917-925.

Stubhaug, A., & Breivik, H. (1997). Longterm treatment of chronic neuropathic pain with the NMDA (N‐methyl‐D‐aspartate) receptor antagonist ketamine. *Acta Anaesthesiologica Scandinavica, 41*(3), 329-331.

Stuginski-Barbosa, J., Rodrigues, G., Bigal, M., & Speciali, J. (2008). Burning mouth syndrome responsive to pramipexol. *The journal of Headache and Pain, 9*(1), 43-45.

Suhara, T., Takano, A., Sudo, Y., Ichimiya, T., Inoue, M., Yasuno, F., . . . Okubo, Y. (2003). High levels of serotonin transporter occupancy with low-dose clomipramine in comparative occupancy study with fluvoxamine using positron emission tomography. *Archives of General Psychiatry, 60*(4), 386-391.

Sung, S., Vijiaratnam, N., Chan, D. W. C., Farrell, M., & Evans, A. H. (2018a). Pain sensitivity in Parkinson's disease: Systematic review and meta-analysis. *Parkinsonism & Related Disorders, 48*, 17-27.

Sung, S., Vijiaratnam, N., Chan, D. W. C., Farrell, M., & Evans, A. H. (2018b). Parkinson disease: A systemic review of pain sensitivities and its association with clinical pain and response to dopaminergic stimulation. *Journal of the Neurological Sciences, 395*, 172-206.

Svensson, M., Lexell, J., & Deierborg, T. (2015). Effects of physical exercise on neuroinflammation, neuroplasticity, neurodegeneration, and behavior: what we can learn from animal models in clinical settings. *Neurorehabilitation and Neural Repair, 29*(6), 577-589.

Tagliazucchi, E., Balenzuela, P., Fraiman, D., & Chialvo, D. R. (2010). Brain resting state is disrupted in chronic back pain patients. *Neuroscience Letters, 485*(1), 26-31.

Takeda, R., Ikeda, T., Tsuda, F., Abe, H., Hashiguchi, H., Ishida, Y., & Nishimori, T. (2005). Unilateral lesions of mesostriatal dopaminergic pathway alters

the withdrawal response of the rat hindpaw to mechanical stimulation. *Neuroscience Research, 52*(1), 31-36.
Talbot, J. D., Marrett, S., Evans, A. C., Meyer, E., Bushnell, M. C., & Duncan, G. H. (1991). Multiple representations of pain in human cerebral cortex. *Science, 251*(4999), 1355-1358.
Tan, Y., Tan, J., Deng, J., Cui, W., He, H., Yang, F., . . . Zhang, X. (2015). Alteration of basal ganglia and right frontoparietal network in early drug-naive Parkinson's disease during heat pain stimuli and resting state. *Frontiers in Human Neuroscience, 9*, 467.
Tang, S. K., Tse, M. M. Y., Leung, S. F., & Fotis, T. (2019). The effectiveness, suitability, and sustainability of non-pharmacological methods of managing pain in community-dwelling older adults: a systematic review. *BMC Public Health, 19*(1), 1488.
Tashev, R., Belcheva, S., Milenov, K., & Belcheva, I. (2001). Antinociceptive effect of somatostatin microinjected into caudate putamen. *Peptides, 22*(7), 1079-1083.
Tendolkar, I., Van Wingen, G., Urner, M., Verkes, R. J., & Fernández, G. (2011). Short-term duloxetine administration affects neural correlates of mood-congruent memory. *Neuropsychopharmacology, 36*(11), 2266-2275.
Tessitore, A., Esposito, F., Vitale, C., Santangelo, G., Amboni, M., Russo, A., . . . Tedeschi, G. (2012). Default-mode network connectivity in cognitively unimpaired patients with Parkinson disease. *Neurology, 79*(23), 2226-2232.
Thompson, T., Gallop, K., Correll, C. U., Carvalho, A. F., Veronese, N., Wright, E., & Stubbs, B. (2017). Pain perception in Parkinson's disease: A systematic review and meta-analysis of experimental studies. *Ageing Research Reviews, 35*, 74-86.
Thulborn, K. R., Waterton, J. C., Matthews, P. M., & Radda, G. K. (1982). Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. *Biochimica et Biophysica Acta (BBA)-General Subjects, 714*(2), 265-270.
Tinazzi, M., Del Vesco, C., Fincati, E., Ottaviani, S., Smania, N., Moretto, G., . . . Defazio, G. (2006). Pain and motor complications in Parkinson's disease. *Journal of Neurology, Neurosurgery, & Psychiatry, 77*(7), 822-825.
Tomlinson, C. L., Patel, S., Meek, C., Herd, C. P., Clarke, C. E., Stowe, R., . . . Wheatley, K. (2012). Physiotherapy intervention in Parkinson's disease: systematic review and meta-analysis. *bmj, 345*, e5004.
Torebjörk, E. (1993). Human microneurography and intraneural microstimulation in the study of neuropathic pain. *Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine, 16*(10), 1063-1065.
Towheed, T., Maxwell, L., Judd, M., Catton, M., Hochberg, M. C., & Wells, G. A. (2006). Acetaminophen for osteoarthritis. *Cochrane Database of Systematic Reviews*(1).
Toy, W. A., Petzinger, G. M., Leyshon, B. J., Akopian, G. K., Walsh, J. P., Hoffman, M. V., . . . Jakowec, M. W. (2014). Treadmill exercise reverses dendritic spine loss in direct and indirect striatal medium spiny neurons in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. *Neurobiology of Disease, 63*, 201-209.

Treede, R.-D., Kenshalo, D. R., Gracely, R. H., & Jones, A. K. (1999). The cortical representation of pain. *Pain, 79*(2-3), 105-111.
Trenkwalder, C., Chaudhuri, K. R., Martinez-Martin, P., Rascol, O., Ehret, R., Vališ, M., . . . Reimer, K. (2015). Prolonged-release oxycodone–naloxone for treatment of severe pain in patients with Parkinson's disease (PANDA): a double-blind, randomised, placebo-controlled trial. *The Lancet Neurology, 14*(12), 1161-1170.
Turner, B. O., Paul, E. J., Miller, M. B., & Barbey, A. K. (2018). Small sample sizes reduce the replicability of task-based fMRI studies. *Communications Biology, 1*(1), 1-10.
Tysnes, O. B., Müller, B., & Larsen, J. (2010). Are dysautonomic and sensory symptoms present in early Parkinson′s disease? *Acta Neurologica Scandinavica, 122*, 72-77.
Ultenius, C., Linderoth, B., Meyerson, B. A., & Wallin, J. (2006). Spinal NMDA receptor phosphorylation correlates with the presence of neuropathic signs following peripheral nerve injury in the rat. *Neuroscience Letters, 399*(1), 85-90.
Urakami, K., Takahashi, K., Matsushima, E., Sano, K., Nishikawa, S., & Takao, T. (1990). The threshold of pain and neurotransmitter's change on pain in Parkinson's disease. *Psychiatry and Clinical Neurosciences, 44*(3), 589-593.
Usunoff, K., Romansky, K., Malinov, G., Ivanov, D., Blagov, Z., & Galabov, G. (1982). Electron microscopic evidence for the existence of a corticonigral tract in the cat. *Journal fur Hirnforschung, 23*(1), 23-29.
Vachon-Presseau, E., Tétreault, P., Petre, B., Huang, L., Berger, S. E., Torbey, S., . . . Griffith, J. W. (2016). Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain, 139*(7), 1958-1970.
Valdes, A. M., Abhishek, A., Muir, K., Zhang, W., Maciewicz, R. A., & Doherty, M. (2017). Association of beta‐blocker use with less prevalent joint pain and lower opioid requirement in people with osteoarthritis. *Arthritis Care & Research, 69*(7), 1076-1081.
Valet, M., Sprenger, T., Boecker, H., Willoch, F., Rummeny, E., Conrad, B., . . . Tolle, T. R. (2004). Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain—an fMRI analysis. *Pain, 109*(3), 399-408.
Valkovic, P., Minar, M., Singliarova, H., Harsany, J., Hanakova, M., Martinkova, J., & Benetin, J. (2015). Pain in parkinson s disease: A cross-sectional study of its prevalence, types, and relationship to depression and quality of life. *PLoS One, 10*(8), e0136541.
Vallbo, Å., & Hagbarth, K.-E. (1968). Activity from skin mechanoreceptors recorded percutaneously in awake human subjects. *Experimental Neurology, 21*(3), 270-289.
van Eimeren, T., Monchi, O., Ballanger, B., & Strafella, A. P. (2009). Dysfunction of the default mode network in Parkinson disease: a functional magnetic resonance imaging study. *Archives of Neurology, 66*(7), 877-883.
Van Marle, H. J., Tendolkar, I., Urner, M., Verkes, R. J., Fernández, G., & Van Wingen, G. (2011). Subchronic duloxetine administration alters the extended amygdala circuitry in healthy individuals. *Neuroimage, 55*(2), 825-831.

Van Wingen, G. A., Tendolkar, I., Urner, M., van Marle, H. J., Denys, D., Verkes, R.-J., & Fernández, G. (2014). Short-term antidepressant administration reduces default mode and task-positive network connectivity in healthy individuals during rest. *Neuroimage, 88*, 47-53.

Vaught, J., Pelley, K., Costa, L., Setler, P., & Enna, S. (1985). A comparison of the antinociceptive responses to the GABA-receptor agonists THIP and baclofen. *Neuropharmacology, 24*(3), 211-216.

Vogt, B. A., Berger, G. R., & Derbyshire, S. W. (2003). Structural and functional dichotomy of human midcingulate cortex. *European Journal of Neuroscience, 18*(11), 3134-3144.

von Campenhausen, S., Bornschein, B., Wick, R., Bötzel, K., Sampaio, C., Poewe, W., . . . Dodel, R. (2005). Prevalence and incidence of Parkinson's disease in Europe. *European Neuropsychopharmacology, 15*(4), 473-490.

Von Korff, M., & Simon, G. (1996). The relationship between pain and depression. *The British Journal of Psychiatry, 168*(S30), 101-108.

von Trott, P., Wiedemann, A. M., Lüdtke, R., Reißhauer, A., Willich, S. N., & Witt, C. M. (2009). Qigong and exercise therapy for elderly patients with chronic neck pain (QIBANE): a randomized controlled study. *The Journal of Pain, 10*(5), 501-508.

Vranken, J., Hollmann, M., Van Der Vegt, M., Kruis, M., Heesen, M., Vos, K., . . . Dijkgraaf, M. (2011). Duloxetine in patients with central neuropathic pain caused by spinal cord injury or stroke: a randomized, double-blind, placebo-controlled trial. *Pain, 152*(2), 267-273.

Vul, E., Harris, C., Winkielman, P., & Pashler, H. (2009). Puzzlingly high correlations in fMRI studies of emotion, personality, and social cognition. *Perspectives on Psychological Science, 4*(3), 274-290.

Vyden, J., MF, G., Callis, G., Laks, M., & H, W. (1971). Effect of propranolol on peripheral hemodynamics in rheumatoid arthritis. *Arthritis and Rheumatism* 14(3), 420.

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., . . . Cohen, J. D. (2004). Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science, 303*(5661), 1162-1167.

Wang, L., An, J., Gao, H. M., Zhang, P., Chen, C., Li, K., . . . Si, T. M. (2019). Duloxetine effects on striatal resting‐state functional connectivity in patients with major depressive disorder. *Human Brain Mapping*, *40*(11), 3338-3346.

Wasner, G., & Deuschl, G. (2012). Pains in Parkinson disease—many syndromes under one umbrella. *Nature Reviews Neurology, 8*(5), 284-294.

Watanabe, M., Maemura, K., Kanbara, K., Tamayama, T., & Hayasaki, H. (2002). GABA and GABA receptors in the central nervous system and other organs *International Review of Cytology* (Vol. 213, pp. 1-47): Elsevier.

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology, 54*(6), 1063.

Wegman, A., van der Windt, D., van Tulder, M., Stalman, W., & de Vries, T. (2004). Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines. *The Journal of Rheumatology, 31*(2), 344-354.

Weidner, C., Schmelz, M., Schmidt, R., Hammarberg, B., Ørstavik, K., Hilliges, M., . . . Handwerker, H. O. (2002). Neural signal processing: the underestimated

contribution of peripheral human C-fibers. *Journal of Neuroscience, 22*(15), 6704-6712.
Wernicke, J. F., Gahimer, J., Yalcin, I., Wulster-Radcliffe, M., & Viktrup, L. (2005). Safety and adverse event profile of duloxetine. *Expert Opinion on Drug Safety, 4*(6), 987-993.
Wernicke, J., Pritchett, Y., D'souza, D., Waninger, A., Tran, P., Iyengar, S., & Raskin, J. (2006). A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology, 67*(8), 1411-1420.
Wiech, K., Ploner, M., & Tracey, I. (2008). Neurocognitive aspects of pain perception. *Trends in Cognitive Sciences, 12*(8), 306-313.
Willer, J. C. (1977). Comparative study of perceived pain and nociceptive flexion reflex in man. *Pain, 3*(1), 69-80.
Willis Jr, W., Zhang, X., Honda, C., & Giesler Jr, G. (2001). Projections from the marginal zone and deep dorsal horn to the ventrobasal nuclei of the primate thalamus. *Pain, 92*(1-2), 267-276.
Willis, W., & Westlund, K. (1997). Neuroanatomy of the pain system and of the pathways that modulate pain. *Journal of Clinical Neurophysiology, 14*(1), 2-31.
Wood, P. B., Schweinhardt, P., Jaeger, E., Dagher, A., Hakyemez, H., Rabiner, E. A., . . . Chizh, B. A. (2007). Fibromyalgia patients show an abnormal dopamine response to pain. *European Journal of Neuroscience, 25*(12), 3576-3582.
Woolf, C. J. (1983). Evidence for a central component of post-injury pain hypersensitivity. *Nature, 306*(5944), 686-688.
Woolrich, M. W., Behrens, T. E., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for FMRI group analysis using Bayesian inference. *Neuroimage, 21*(4), 1732-1747.
Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1992). A three-dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow & Metabolism, 12*(6), 900-918.
Yam, M. F., Loh, Y. C., Tan, C. S., Khadijah Adam, S., Abdul Manan, N., & Basir, R. (2018). General pathways of pain sensation and the major neurotransmitters involved in pain regulation. *International Journal of Molecular Sciences, 19*(8), 2164.
Yang, Y., Wang, Y., Li, S., Xu, Z., Li, H., Ma, L., . . . Fan, Z. (2004). Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. *Journal of Medical Genetics, 41*(3), 171-174.
Yao, N., Shek‐Kwan Chang, R., Cheung, C., Pang, S., Lau, K. K., Suckling, J., . . . Chua, S. E. (2014). The default mode network is disrupted in Parkinson's disease with visual hallucinations. *Human Brain Mapping, 35*(11), 5658-5666.
Yarkoni, T. (2009). Big correlations in little studies: Inflated fMRI correlations reflect low statistical power—Commentary on Vul et al.(2009). *Perspectives on Psychological Science, 4*(3), 294-298.
Yelnik, J. (2008). Modeling the organization of the basal ganglia. *Revue Neurologique, 164*(12), 969-976.
Young, A. B., Penney, J. B., Dauth, G. W., Bromberg, M. B., & Gilman, S. (1983). Glutamate or aspartate as a possible neurotransmitter of cerebral corticofugal fibers in the monkey. *Neurology, 33*(11), 1513-1513.

Zarow, C., Lyness, S. A., Mortimer, J. A., & Chui, H. C. (2003). Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. *Archives of Neurology, 60*(3), 337-341.

Zeitz, K. P., Guy, N., Malmberg, A. B., Dirajlal, S., Martin, W. J., Sun, L., . . . Basbaum, A. I. (2002). The 5-HT3 subtype of serotonin receptor contributes to nociceptive processing via a novel subset of myelinated and unmyelinated nociceptors. *Journal of Neuroscience, 22*(3), 1010-1019.

Zhang, C., Yang, S.-W., Guo, Y.-G., Qiao, J.-T., & Dafny, N. (1997). Locus coeruleus stimulation modulates the nociceptive response in parafascicular neurons: an analysis of descending and ascending pathways. *Brain Research Bulletin, 42*(4), 273-278.

Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging, 20*(1), 45-57.

Zhao, Y., Tan, L., Li, S., Au, W., Seah, S., Lau, P., . . . Wee, H. (2011). Economic burden of Parkinson's disease in Singapore. *European Journal of Neurology, 18*(3), 519-526.

Zhi, Y., Yuan, Y., Si, Q., Wang, M., Shen, Y., Wang, L., . . . Zhang, K. (2019). The Association between DRD3 Ser9Gly Polymorphism and Depression Severity in Parkinson's Disease. *Parkinson's Disease,* ID 1642087.

Zhou, Y., Liang, M., Tian, L., Wang, K., Hao, Y., Liu, H., . . . Jiang, T. (2007). Functional disintegration in paranoid schizophrenia using resting-state fMRI. *Schizophrenia Research, 97*(1-3), 194-205.

Ziegler, E., Magerl, W., Meyer, R., & Treede, R.-D. (1999). Secondary hyperalgesia to punctate mechanical stimuli: central sensitization to A-fibre nociceptor input. *Brain, 122*(12), 2245-2257.

Zigmond, M. J., & Smeyne, R. J. (2014). Exercise: is it a neuroprotective and if so, how does it work? *Parkinsonism & Related Disorders, 20*, S123-S127.

Zis, P., Grünewald, R. A., Chaudhuri, R. K., & Hadjivassiliou, M. (2017). Peripheral neuropathy in idiopathic Parkinson's disease: a systematic review. *Journal of the Neurological Sciences, 378*, 204-209.

Zubieta, J.-K., Bueller, J. A., Jackson, L. R., Scott, D. J., Xu, Y., Koeppe, R. A., . . . Stohler, C. S. (2005). Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. *Journal of Neuroscience, 25*(34), 7754-7762.

Zubieta, J.-K., Heitzeg, M. M., Smith, Y. R., Bueller, J. A., Xu, K., Xu, Y., . . . Goldman, D. (2003). COMT val158met genotype affects μ-opioid neurotransmitter responses to a pain stressor. *Science, 299*(5610), 1240-1243.

APPENDIX I

Types of pain according to Ford classification (Ford, 2010)

Participant	Musculoskeletal	Radicular	Dystonia	Central	Akathisia
1^			+		
2	*			+	
3	+				
4^#					
5^	*	+			
6		+			
7^		+	*		
8^		+			
9#					
10		+			
11^			+		
12		+			
13	+				
14^#					
15^#					
16#					
17	+				
18^		+			
19#					
20	+				
21^	*	+	*		*

^, participant on duloxetine; #, information on pain type not collected; +, predominant type of pain, *, non-dominant type of pain.

APPENDIX II

Individual participant scores of pain outcome measures

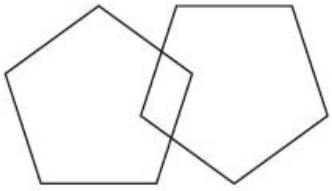
Participants	SFMt1	SFMt2	SFMs1	SFMs2	SFMa1	SFMa2	VAS1	VAS 2
1^	10	13	7	11	3	2	6.5	5.6
2	8	4	4	4	4	0	2.4	5.2
3	8	13	8	9	0	4	4.8	5.9
4^*	10		6		4		5.4	
5^	20	7	14	6	6	1	3.2	5.9
6	9	7	7	6	2	1	3.5	3.2
7^	7	11	6	11	1	0	0.7	2.4
8^	22	21	16	17	6	4	8.2	7.5
9	7	5	5	5	2	0	5.4	4.4
10	13	29	11	22	2	7	1.4	6.4
11^	9	7	4	4	5	3	7.1	6.6
12	18	11	14	9	4	2	2.7	1.5
13	14	8	12	6	2	2	7.8	2.1
14^	10	5	8	5	2	0	5.2	4.0
15^	13	11	10	8	3	3	6.9	6.5
16*	26		17		9		6.7	
17	35	26	25	16	10	10	7.5	7.1
18^	11	9	9	8	2	1	2.9	5.3
19	7	6	7	6	0	0	8.2	7.6
20	2	7	2	6	0	1	1.8	4.8
21^	16	3	13	3	3	0	8.7	2.4

^, participant on duloxetine; * participant withdrawn from study; SFMt1, total score of Short-Form McGill Questionnaire at baseline; SFMt2, total score of Short-Form McGill Questionnaire at study completion; SFMs1, score of the sensory component of Short-Form McGill Questionnaire at baseline; SFMs2, score of the sensory component of Short-Form McGill Questionnaire at study completion; SFMa1, score of the affective component of Short-Form McGill Questionnaire at baseline; SFMa2, score of the affective component of Short-Form McGill Questionnaire at study completion; VAS1, Visual Analogue Score at baseline; VAS2, Visual Analogue Score at study completion.

APPENDIX III

MMSE

		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"
3	( )	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	( )	Read and obey the following: CLOSE YOUR EYES
1	( )	Write a sentence.
1	( )	Copy the design shown.



_____ Total Score

Pain thresholds for mechanical pressure stimuli

Just Noticeable Pain (0.5/10)			**Weak Pain (2.5/10)**			**Moderate Pain (5.5/10)**		
Trial	Weight (kg)	Rating	Trial	Weight (kg)	Rating	Trial	Weight (kg)	Rating
1			**3**			**2**		
7			**5**			**4**		
8			**6**			**9**		
12			**10**			**14**		
13			**11**			**18**		
15			**16**			**20**		
17			**19**			**23**		
21			**22**			**24**		
26			**27**			**25**		
30			**29**			**28**		
Avg			**Avg**			**Avg**		

Pressure RequiredRating of pain (0-10)

JNP_____

MP_____

MDS-UPDRS

1.A	Source of info:			**PART III**	
	PART I		3.4a	Finger tap – R	
1.1	Cognitive impairment		3.4b	Finger tap – L	
1.2	Hallucinations & psychosis		3.5a	Hand movement – R	
1.3	Depressed Mood		3.5b	Hand movement – L	
1.4	Anxious Mood		3.6a	Pronation-supination - R	
1.5	Apathy		3.6b	Pronation-supination – L	
1.6	Features of DDS		3,7a	Toe tapping – R	
1.7	Sleep problems		3.7b	Toe tapping – L	
1.8	Daytime Sleepiness		3.8a	Leg agility – R	
1.9	Pain and other sensations		3.8b	Leg agility – L	
1.10	Urinary problems		3.9	Arising from chair	
1.11	Constipation problems		3.10	Gait	
1.12	Light headedness on standing		3.11	Freezing of gait	
1.13	Fatugue		3.12	Postural stability	
	PART II		3.13	Posture	
2.1	Speech		3.14	Global spontaneity of movement	
2.2	Saliva and drooling		3.15a	Postural tremor – RUL	
2.3	Chewing and Swallowing		3.15b	Postural tremor – LUL	
2.4	Eating Tasks		3.16a	Kinetic tremor – RUL	
2.5	Dressing		3.16b	Kinetic tremor – LUL	
2.6	Hygiene		3.17a	Rest tremor amplitude – RUL	
2.7	Handwriting		3.17b	Rest tremor amplitude – LUL	
2.8	Doing hobbies and other activities		3.17c	Rest tremor amplitude – RLL	
2.9	Turning in bed		3.17d	Rest tremor amplitude – LLL	
2.10	Tremor		3.17e	Rest tremor amplitude – Lip/jaw	
2.11	Getting out of bed		3.18	Constancy of rest tremor	
2.12	Walking and balance			Hoen Yahr Stage	
2.13	Freezing			Were dyskinesia present?	
	PART III			Did dyskinesia affect rating?	
3.1	Speech			**Part IV**	
3.2	Facial expression		4.1	Time spent with dyskinesias	
3.3a	Rigidity - neck		4.2	Functional impact of dyskinesias	
3.3b	Rigidity RUL		4.3	Time spent in OFF state	
3.3c	Rigidity LUL		4.4	Functional impact of fluctuations	
3.3d	Rigidity RLL		4.5	Complexity of motor fluctuations	
3.3e	Rigidity LLL		4.6	Painful OFF state dystonia	

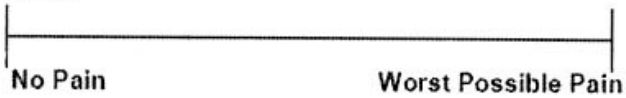
Short Form McGill

Part A: Please describe your pain at the present point in time

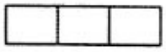
	None (0)	Mild (1)	Moderate (2)	Severe (3)
1. Throbbing				
2. Shooting				
3. Stabbing				
4. Sharp				
5. Cramping				
6. Gnawing				
7. Hot-burning				
8. Aching				
9. Heavy				
10. Tender				
11. Splitting				
12. Tiring-exhausting				
13. Sickening				
14. Fearful				
15. Punishing-cruel				

Part B: Rate your pain during the last week

The following line represents pain of increasing intensity from "no pain" to "worst possible pain". Place a slash (|) across the line in the position that best describes your pain during the past week.



No Pain — Worst Possible Pain



Score in mm
(Investigator's use only)

C. PRESENT PAIN INTENSITY

0 ☐ No pain 1 ☐ Mild 2 ☐ Discomforting
3 ☐ Distressing 4 ☐ Horrible 5 ☐ Excruciating

KING'S PD PAIN SCALE

Patient ID No: _____ **Initials:** _____ **DOB:** _____

This scale is designed to define and accurately describe the different types and the pattern of pain that your patient may have experienced **during the last month** due to his/her Parkinson's disease or related medication.

Each symptom should be scored with respect to

Severity: 0 = None,
1 = Mild (symptoms present but causes little distress or disturbance to patient),
2 = moderate (some distress or disturbance to patient),
3 = Severe (major source of distress or disturbance to patient).

Frequency: 0 = Never,
1 = Rarely (<1/wk),
2 = Often (1/wk),
3 = Frequent (several times per week),
4 = Very Frequent (daily or all the time).

	Severity (0 – 3)	Frequency (0 – 4)	Frequency x Severity
Domain 1: Musculoskeletal Pain			
1. Does the patient experience pain around their joints? (including arthritic pain)	☐	☐	☐
Domain 1 TOTAL SCORE:			☐
Domain 2: Chronic Pain			
2. Does the patient experience pain deep within the body? (A generalised constant, dull, aching pain – *central pain*)	☐	☐	☐
3. Does the patient experience pain related to an internal organ? (For example, pain around the liver, stomach or bowels – visceral pain)	☐	☐	☐
Domain 2 TOTAL SCORE:			☐
Domain 3: Fluctuation-related Pain			
4. Does the patient experience dyskinetic pain? (pain related to abnormal involuntary movements)	☐	☐	☐
5. Does the patient experience "off" period dystonia in a specific region? (in the area of dystonia)	☐	☐	☐
6. Does the patient experience generalised "off"period pain? (pain in whole body or areas distant to dystonia)	☐	☐	☐
Domain 3 TOTAL SCORE:			☐

KING'S PD PAIN SCALE

	Severity (0 – 3)	Frequency (0 – 4)	Frequency x Severity
Domain 4: Nocturnal Pain			
7. Does the patient experience pain related to jerking leg movements during the night (PLM) or an unpleasant burning sensation in the legs which improves with movement (RLS)?	☐	☐	☐
8. Does the patient experience pain related to difficulty turning in bed at night?	☐	☐	☐
		Domain 4 TOTAL SCORE:	☐
Domain 5: Oro-facial Pain			
9. Does the patient experience pain when chewing?	☐	☐	☐
10. Does the patient have pain due to grinding their teeth during the night?	☐	☐	☐
11. Does the patient have burning mouth syndrome?	☐	☐	☐
		Domain 5 TOTAL SCORE:	☐
Domain 6: Discolouration; Oedema/swelling			
12. Does the patient experience a burning pain in their limbs?(often associated with swelling or dopaminergic treatment)	☐	☐	☐
13. Does the patient experience generalised lower abdominal pain?	☐	☐	☐
		Domain 6 TOTAL SCORE:	☐
Domain 7: Radicular Pain			
14. Does the patient experience a shooting pain/ pins and needles down the limbs?	☐	☐	☐
		Domain 7 TOTAL SCORE:	☐
		TOTAL SCORE (all domains):	☐

Comments:

The Geriatric Depression Scale

	Yes	No	
1	☐	☐	Are you basically satisfied with your life?
2	☐	☐	Have you dropped many of your activities and interests?
3	☐	☐	Do you feel that your life is empty?
4	☐	☐	Do you often get bored?
5	☐	☐	Are you hopeful about the future?
6	☐	☐	Are you bothered by thoughts that you can't get out of your head?
7	☐	☐	Are you in good spirits most of the time?
8	☐	☐	Are you afraid that something bad is going to happen to you?
9	☐	☐	Do you feel happy most of the time?
10	☐	☐	Do you feel helpless?
11	☐	☐	Do you often get restless and fidgety?
12	☐	☐	Do you prefer to stay at home, rather than going out and doing new things?
13	☐	☐	Do you frequently worry about the future?
14	☐	☐	Do you feel you have more problems with your memory than most?
15	☐	☐	Do you think it is wonderful to be alive now?
16	☐	☐	Do you often feel downhearted and blue?
17	☐	☐	Do you feel pretty worthless the way you are now?
18	☐	☐	Do you often worry a lot about the past?
19	☐	☐	Do you find life very exciting?
20	☐	☐	Is it hard for you to get started on new projects?
21	☐	☐	Do you feel full of energy?
22	☐	☐	Do you feel that your situation is hopeless?
23	☐	☐	Do you think that most people are better off than you are?
24	☐	☐	Do you frequently get upset over little things?
25	☐	☐	Do you frequently feel like crying?
26	☐	☐	Do you have trouble concentrating?
27	☐	☐	Do you enjoy getting up in the morning?
28	☐	☐	Do you prefer to avoid social gatherings?
29	☐	☐	Is it easy for you to make decisions?
30	☐	☐	Is your mind as clear as it used to be?

PANAS

This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you are feeling this way right now, at this present moment. Use the following scale to record your answers.

1 = Not at all / Very slightly
2 = A little
3 = Moderately
4 = Quite a bit
5 = Extremely

Interested_____Irritable_____
Distressed_____Alert_____
Excited_____Ashamed_____
Upset_____Inspired_____
Strong_____Nervous_____
Guilty_____Determined_____
Scared_____Attentive_____
Hostile_____Jittery_____
Enthusiastic_____Active_____
Proud_____Afraid_____

PDQ39 – Quality of Life Scale

Due to having Parkinson's Disease, how often during the past 30days have you:

Key:0 = never; 1 = rarely; 2 = Sometimes; 3 = Often; 4 = Always or cannot do at all

1. Had difficulty doing the leisure activities you would like to do?___
2. Had difficulty looking after your home, for example, housework, cooking, yard work?___
3. Had difficulty carrying shopping bags?___
4. Had problems walking half a mile?___
5. Had problems walking 100yards (approximately 1 block)?___
6. Had problems getting around the house as easily as you would like?___
7. Had difficulty getting around in public places?___
8. Needed someone else to accompany you when you went out?___
9. Felt frightened or worried about falling in public?___
10. Been confined to the house more than you would like?___
11. Had difficulty showering and bathing?___
12. Had difficulty dressing?___
13. Had difficulty with buttons or shoelaces?___
14. Had problems writing clearly?___
15. Had difficulty cutting up your food?___
16. Had difficulty holding a drink without spilling it?___
17. Felt depressed?___
18. Felt isolated and lonely?___
19. Felt weepy or tearful?___
20. Felt angry or bitter?___
21. Felt anxious?___
22. Felt worried about your future?___
23. Felt you had to hide your Parkinson's from people?___
24. Avoided situations which involve eating or drinking in public?___
25. Felt embarrassed in public?___
26. Felt worried about other people's reaction to you?___
27. Had problems with your close personal relationships?___
28. Received the support you needed from your spouse or partner?___
    (Answer N if you do not have a spouse or partner)
29. Received the support you needed from your family or close friends?___
30. Unexpectedly fallen asleep during the day?___
31. Had problems with your concentration, eg, when reading or watching TV?___
32. Felt your memory was failing?___
33. Had distressing dreams or hallucinations?___
34. Had difficulty speaking?___
35. Felt unable to communicate effectively?___
36. Felt ignored by people?___
37. Had painful muscle cramps or spasms?___
38. Had aches and pains in your joints or body?___
39. Felt uncomfortably hot or cold?___